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Joint Congress of the European Society for Paediatric Endocrinology (ESPE) and the European Society of Endocrinology (ESE) 2025: Connecting Endocrinology Across the Life Course

10–13 May 2025, Copenhagen, Denmark

Connecting Endocrinology Across the Life Course
Joint Congress of ESPE and ESE 2025
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Barlier, Anne
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Guran, Tulay
Höybye, Charlotte
Hubalewska-Dydejczyk, Alicja
Ilias, Ioannis
Jensterle, Mojca
Johannsson, Gudmundur
Kanaka-Gantenbein, Christina
Kandaraki, Eleni
Kjærsgaard, Per
Klee, Philippe
Konrade, Ilze
Korevaar, Tim
Krone, Nils
Krsek, Michal
Laetitia, Martinerie
Le Tissier, Paul
Lefebvre, Hervé
Leger, Juliane
Li, Dong
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Lungu, Adriancatalin
Luque, Raul M.
M. Winter, Elizabeth
MacKenzie, Scott
Macut, Djuro
Maes, Christa
Maiter, Dominique
Makras, Polyzois
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Mantovani, Giovanna
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McElreavey, Ken
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Mendonca, Berenice
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Messina, Maria Francesca
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Miljic, Dragana
Miller, Bradley
Minnetti, Marianna
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Mittag, Jens
Morin-Papunen, Laure
Mortensen, Li Juel
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Mukherjee, Abir
Murray, Philip
Musat, Madalina
Muzsnai, Agota
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Namba, Noriyuki
Neggers, Sebastian
Newell-Price, John
Nicolaides, Nicolas
Niculescu, Dan Alexandru
Niedziela, Marek
Nikolaou, Nikolaos
Nixon, Mark
Nogueiras, Rubén
Nordenström, Anna
Obermayer-Pietsch, Barbara
Olarescu, Nicoleta Cristina
Oliveira, Pedro F:
Olsson, Daniel S.
Ong, Ken K.
Opitz, Robert
Pagotto, Uberto
Pandey, Amit
Papadimitriou, Dimitrios
Patocs, Attila
Pearce, Simon
Pedicelli, Stefania
Peeters, Robin
Pekic Djurdjevic, Sandra
Perez-Rivas, Luis Gustavo
perrild, hans
Perry, Rebecca
Persani, Luca
Perseghin, Gianluca
Peter, Igaz
Pfeifer, Marija
Piekiełko-Witkowska, Agnieszka
Pignatelli, Duarte
Pilgaard, Kasper
Pilz, Stefan
Pohlenz, Joachim
Polak, Michel
Polyzos, Stergios
Popovic, Jadranka
Poutanen, Matti
Power, Deborah
Prasad, Rathi
Prevot, Vincent
Prodam, Flavia
Pruhova, Stepanka
Pyrzak, Beata
Quintos, Jose Bernardo
Radian, Serban
Ragnarsson, Oskar
Rahman, Nafis
Raimann, Adalbert
Rajpert-De Meyts, Ewa
Ramhøj, Louise
Randell, Tabitha
Rauner, Martina
Raverot, Gerald
Reincke, Martin
Rejnmark, Lars
Rey, Rodolfo A.
Richter-Unruh, Annette
Riedl, Stefan
Rizzoti, Karine
Robledo, Mercedes
Rogol, Alan
Roman, Gabriella
Romijn, Hans
Ronchi, Cristina L
Ross, Richard
Ruchala, Marek
Rutten, Elizabeth
Sachs, Laurent
Salerno, Maria Carolina
Samaan, M. Constantine
Santi, Daniele
Saponaro, Federica
Saunders, Philippa
Scaramuzza, Andrea
Schalin-Jantti, Camilla
Schepper Jean, De
Schopohl, Jochen
Schulte, Dominik
Schwarz, Peter
Semler, Jörg
Senniappan, Senthil
Shah, Pratik
Shaikh, M Guftar
Shestakova, Ekaterina
Shestakova, Marina
Shimon, Ilan
Sikjaer, Tanja
Siklar, Zeynep
Simoni, Manuela
Skae, Mars
Skordis, Nicos
Söderlund, Sanni
Soucek, Ondrej
Stalla, Gü nter Karl
Steenblock, Charlotte
Stefanaki, Charikleia
Steichen, Elisabeth
Stimson, Roland
Storbeck, Karl
Street, Maria
Sumnik, Zdenek
Svensson, Jannet
Szinnai, Gabor
Tabarin, Antoine
Tauschmann, Martin
Ten, Svetlana
Tena-Sempere, Manuel
Tenenbaum-rakover, Yardena
Terzolo, Massimo
Theiler-Schwetz, Verena
Theodoropoulou, Marily
Tigas, Stelios
Timmers, Henri
Toledo, Rodrigo
Tomlinson, Jeremy
Toppari, Jorma
Tóth, Miklós
Touraine, Philippe
Trifanescu, Raluca
Tsagarakis, Stylianos
Tsourdi, Elena
Tzanela, Marinella
Uday, Suma
Ugege, Modupe
Underbjerg, Line
Valerio, Giuliana
van den Akker, Erica
van der Lely, Aart Jan
Van Eck, Judith
van Hul, Wim
van Santen, Hanneke
van Trotsenburg, Paul
Vantyghem, Marie-Christine
Vassiliadi, Dimitra
Vila, Greisa
Vilmann, Lea
Visser, Edward
Vlachopapadopoulou, Elpis
Volke, Vallo
Vukovic, Rade
Wasniewska, Malgorzata
Wass, John
Weiss, Ram
Werther, George
Widimsky, Jiri
Wilding, John
Williams, Tracy Ann
Winter, Elizabeth M.
Wirth, Eva
Wit, Jan Maarten
Witchel, Selma
Woelfle, Joachim
Wójcik, Małgorzata
Wong, Sc
Wood, Claire
Wudy, Stefan
Yadav, Sangita
yavropoulou, maria
Yeoh, Phillip
Yildiz, Bulent
Zabuliene, Lina
Zacharin, Margaret
Zandee, Wouter
Zangen, David
Zarkovic, Milos
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CONTENTS

Joint Congress of ESPE and ESE 2025
Connecting Endocrinology Across the Life Course

RAPID COMMUNICATIONS

POSTER PRESENTATIONS

EPOSTER PRESENTATIONS

AUTHOR INDEX

Prize Lectures

Endocrinology Across the Life Course Award

AW1

Abstract Unavailable

DOI: 10.1530/endoabs.110.AW1

The Geoffrey Harris Award Lecture

AW2

Learning from rare diseases: from corticotroph deficiency to corticotroph adenomas

Thierry Brue[1]
[1]Conception Hospital Marseille, France

Founded 3 decades ago, the Genhypopit network, an international consortium to identify genetic causes of hypopituitarism (such as mutations in pituitary transcription factor genes like *POU1F1*, *PROP1* or *LHX3/4*), allowed to decipher several phenotype-genotype correlations in various presentations of congenital pituitary hormone deficiencies. These include congenital isolated **corticotroph deficiency (ACTHD)**, the focus of this presentation. In collaboration with the group of Jacques Drouin (Canada), which discovered Tpit as the main regulator of mouse corticotroph development, we identified in patients referred to this network the first two families with ACTHD caused by mutations of *TPIT*, currently known as *TBX19*, demonstrating its major role in corticotroph function in humans also (Cell 2001). When further characterizing ACTHD patients with or without TBX19 mutations, we recognized in the latter group 3 families with both ACTHD and variable immunodeficiency, an association that we first described as DAVID syndrome (JCEM 2012) and found to be due to *NFKB2* gene mutations (JCEM 2014). Using a model of in vitro differentiation of mature human pituitary cell types from human induced pluripotent stem cells (3D culture of hypothalamo-pituitary organoids with or without pathogenic variations of *NFKB2*), we recently demonstrated the role of this gene in corticotroph differentiation (eLife 2024). Bridging from ACTHD to **Cushing's disease**, we were the first to show that TPIT/TBX19 immunostaining could be used to characterize adenomatous corticotroph cells (JCEM 2003), currently one of the main criteria for defining corticotroph tumors in the WHO classification of pituitary tumors. In terms of pathophysiology of this disease, further collaborative works with the group of J. Drouin led to the involvement of CABLES1 inactivation or Brg1 loss of function, and the roles of cyclin E or Pax7. Recently, in collaboration with Guido Kroemer in Paris, we found that plasma ACBP/DBI - Acyl coenzyme A binding protein that stimulates food intake and lipo-anabolic reactions - was elevated in both patients and mice with Cushing's syndrome. In mice, ACBP/DBI inhibition abolished manifestations of Cushing's syndrome such as weight gain or type 2 diabetes, which opens promising therapeutic avenues (Nature Metab 2024). These studies highlight the role of rare diseases in the identification of important physiological mechanisms and the added value of collaborative work between adult or pediatric specialists and experimental researchers. Hypothalamo-pituitary organoids represent a unique model for several genetically determined pituitary diseases affecting pituitary development and/or proliferation and for the study of developing or mature human pituitary cells.

DOI: 10.1530/endoabs.110.AW2

Andrea Prader Award

AW3

Abstract Unavailable

DOI: 10.1530/endoabs.110.AW3

Research Award

AW5

Abstract Unavailable

DOI: 10.1530/endoabs.110.AW5

The *European Journal of Endocrinology* Award Lecture

AW6

MODY and Beyond: The Changing Face of Monogenic Diabetes

Kashyap Patel[1]
[1]Institute of Biomedical and Clinical Science, University of Exeter, UK

European Journal of Endocrinology Maturity Onset Diabetes of the Young (MODY) is the most common form of monogenic diabetes, where a genetic diagnosis can guide personalised treatment. However, accurate diagnosis depends on testing the right genes. This talk highlights the need to refine gene panels by including genes with strong evidence for MODY and removing those with insufficient support. This ensures more patients receive a correct diagnosis while avoiding misdiagnosis and inappropriate treatment. Optimising the cost-benefit of genetic testing also requires careful patient selection. The talk discusses clinical and familial criteria that increase the likelihood of identifying a monogenic cause of diabetes. Additionally, reduced penetrance—where individuals with pathogenic variants do not develop diabetes—is increasingly recognised in MODY and other monogenic disorders. This has important implications for interpreting genetic results, particularly in unaffected individuals. Emerging evidence suggests that polygenic risk may influence penetrance, challenging the traditional view of MODY as a purely monogenic disease. This talk explores recent findings on the interplay between monogenic and polygenic factors, shedding light on the genetic complexity of MODY. These insights have significant implications for diagnosis, management, and genetic counselling, paving the way for more precise and effective care for patients with MODY and other forms of diabetes.

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Outstanding Clinician Award & The International Outstanding Clinician Award

AW7.1

Abstract Unavailable

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AW7.2

Abstract Unavailable

DOI: 10.1530/endoabs.110.AW7.2

Clinical Endocrinology Journal Foundation Award Lecture

AW8

Tackling adrenocortical cancer: a clinician perspective

Massimo Terzolo[1]
[1]University of Turin - Department of Clinical and Biological Sciences, Italy

During my talk I will address the following issues concerning treatment of patients with adrenocortical carcinoma (ACC):

- Indication of mitotane therapy in the adjuvant setting.
- Indication of mitotane therapy in the advanced disease setting.
- Managing mitotane therapy and the accompanying supportive therapy to improve patient compliance and adherence to treatment.
- The challenges of conducting clinical trials in ACC.
- Future perspectives for personalized treatments.

DOI: 10.1530/endoabs.110.AW8

International Research Award and The *Hormone Research in Paediatrics* Prize

AW9

Abstract Unavailable

DOI: 10.1530/endoabs.110.AW9

European Hormone Medal Award Lecture

AW10

Disorders of thyroid hormone action: insights from human genetics

Krishna Chatterjee
University of Cambridge, Institute of Metabolic Science, Cambridge, United Kingdom

In my lecture, I will present notable contributions of our group in the field of thyroid hormone action. We have defined a multisystem disorder, often presenting in childhood, caused by mutations in SECISBP2, a factor which controls the synthesis of proteins (including deiodinase enzymes) which contain the aminoacid selenocysteine. This syndrome is associated with disordered thyroid hormone metabolism and phenotypes (e.g. muscular dystrophy, azoospermia) due to deficiency of selenoproteins in specific tissues plus features (e.g. photosensitivity, progressive hearing loss, aortic aneurysm) secondary to the lack of selenoenzymes which breakdown reactive oxygen species in cells. This disorder is a unique exemplar of the adverse consequences of oxidative stress in humans. We have discovered diverse mutations in THRB, causing Resistance to Thyroid Hormone (RTH) beta. We were first to discover homologous mutations in THRA causing RTHalpha - a form of congenital hypothyroidism which is underdiagnosed because thyroid function tests are near-normal; we first described and dominant negative mutations in PPARG, causing lipodystrophic insulin resistance. In these disorders, I will show that heterozygous mutant receptors inhibit the function of their normal cellular counterparts in a dominant negative manner - a unifying pathogenetic mechanism in these conditions and some other nuclear receptormediated disorders. Insights gained from the properties of unique receptor mutations and corresponding clinical phenotypes of prismatic cases, have enabled us to elucidate the molecular basis of dominant negative inhibition, informing approaches to treatment of these disorders.

DOI: 10.1530/endoabs.110.AW10

ESPE Young Investigator Awards

AW11

Abstract Unavailable

DOI: 10.1530/endoabs.110.AW11

Jens Sandahl Christiansen Awards

AW12.1

Abstract Unavailable

DOI: 10.1530/endoabs.110.AW12.1

AW12.2

Importance of gut microbiota for the effectiveness of weight loss – role of glucocorticoids

Ana Djordjevic[1]
[1]Institute for Biological Research "Siniša Stanković" - National Institute of the Republic of Serbia, Serbia

The global prevalence of obesity is increasing and there is growing evidence of a link between the gut microbiota and obesity. However, the specific bacterial strains and mechanisms involved in the development and treatment of obesity are not fully understood. We are investigating how probiotics modulate the gut microbiota to improve metabolic health in animal models of obesity and how dietary interventions remodel the gut microbiota to support weight loss in children with obesity. To investigate the role of the gut microbiota in obesity, we analyzed its composition using 16S rRNA gene amplicon sequencing in obese and obesity-resistant mice, while therapeutic effect of probiotics were examined in obese mice. We also examined the changes in the gut microbiota of children with obesity before and after a hypocaloric diet. In obesity-resistant mice, increased *Lactobacillus* abundance was negatively correlated with blood triglycerides, which, together with decreased expression of hepatic and intestinal free fatty acid transporters, suggests a role for the gut microbiota in preventing ectopic lipid accumulation. We have also shown that oral administration of a specific *Lactobacillus* strain to obese mice normalizes their gut microbiota, reduces hepatic steatosis and improves gut barrier integrity (patent pending), suggesting the gut microbiota as a potential therapeutic target. In children with obesity, a linear regression model showed that higher abundance of *Blautia* and *Anaerostipes* correlated with greater weight loss, while higher abundance of *Erysipelotrichaceae* UCG-003 and *Faecalibacterium* was negatively correlated with weight loss efficacy. Based on the above findings and our previous research on glucocorticoids as important mediators in obesity, whose availability and metabolism may be regulated by the activity of the gut microbiota, our future research aims to identify glucocorticoid-metabolizing gut bacteria and elucidate the molecular mechanisms by which they influence gut permeability and adipose tissue metabolism, thus contributing to the alleviation of obesity.

DOI: 10.1530/endoabs.110.AW12.2

Henning Andersen Award Presentations

HA1

JOINT1690

Association between premature ovarian insufficiency and biological aging: evidence from the UK Biobank and NHANES population-based surveys

Jinting Zhou[1], Menglin Fan[1,2], Aaron Aaron M. Lett[3], Qiqi You[1,2], Jingjing Zeng[2], Bo Chen[2], Yucen Wu[3], Hui Xing[1] & Shaoyong Xu[1]
[1]Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science, Department of Endocrinology, Xiangyang, China, 2Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science, Center for Clinical Evidence-Based and Translational Medicine, Xiangyang, China, 3Imperial College London, London, United Kingdom

Background
Premature ovarian insufficiency (POI), defined as menopause occurring before the age of 40 years, causes physiological changes in organs and health disorders. The issue of whether patients with POI have accelerated aging is important but epidemiological studies were lacking. This study aimed to analyze whether POI is associated with accelerated biological aging, and whether menopausal hormone therapy (MHT) in the POI population is associated with reduced biological aging.
Methods
This study analyzed 229,779 female aged 40 years and older from the UK Biobank (2006–2010) and NHANES (1999–2018). Menopause information such as age at menopause, cause of menopause, and use of MHT was collected through

a questionnaire. Biological age acceleration was defined by the Klemera–Doubal method, which was calculated through biomarkers, in reference to chronological ageing. Biological age acceleration >0 was defined as biological aging. Association between POI and biological aging was analyzed using multivariate linear regression and logistic regression models.

Results

In the UK Biobank and NHANES, a total of 6,105 (3.7%) and 1,882 (15.9%) female with POI were recorded, respectively. The results showed participants with POI had an increased risk of biological aging (UK Biobank: OR = 1.50 [95% CI: 1.24- 1.82]; NHANES: OR = 1.20 [95% CI: 1.07- 1.34]) and decrease in leukocyte telomere length (LTL) (UK Biobank: 0.0109 [95% CI: 0.0079- 0.0109]), compared with those without POI. Restricted cubic spline showed linear relationship between age at menopause and biological aging. With every 5-year increase in menopausal age, the risk of biological aging decreased by 11% and 2%, respectively (UK Biobank: OR = 0.89 [95%CI: 0.85- 0.93]; NHANES: OR = 0.98 [95%CI: 0.95- 1.00]). In the UK Biobank, participants with natural and surgical POI had a 48%, 55% increased risk of biological aging compared without POI, respectively. In the NHANES, the risk of biological aging was increased by 17%, 27%, respectively in female with natural and surgical. Participants with POI who underwent MHT had reduced risk of aging compared with those who did not (UK Biobank: OR = 0.63 [95%CI: 0.43- 0.92]; NHANES: OR = 0.75 [95%CI: 0.61- 0.92]).

Conclusion

Female with POI had a significantly increased risk of biological aging compared with those without POI. Participants with POI who received MHT had a reduced risk of aging compared with those who did. This study suggests patients with POI should be informed about the risks of aging and the potential benefits of early MHT.

DOI: 10.1530/endoabs.110.HA1

HA2

JOINT3472

USP8 genotype is associated with recurrence risk in Cushing's disease: an international, retrospective, multicenter cohort study

Qilin Zhang[*1,2], Yixin Cai[2], Ana Paula Abreu[1], Michael Buchfelder[3], Boyuan Yao[2], Felicia A Hanzu[4], Yuyu Liu[2], Jun Thorsteinsdottir[5], Zengyi Ma[2], Jörg Flitsch[6], Shuo Zhang[2], Jürgen Honegger[7], Rona Carroll[1], Hongying Ye[2], Zhaoyun Zhang[2], Ursula Kaiser[1], Martin Reincke[8], Marily Theodoropoulou[8], Yao Zhao[2] & Luis Gustavo Perez-Rivas[*9]

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Background

The recurrence rate of Cushing's disease (CD) after surgery varies between 5–50%. About 30–60% of CD tumors carry somatic *USP8* variants. Prior studies on small cohorts have reported opposite association between *USP8* variants and recurrence. Here, we analyzed *USP8* genotype and recurrence risk in a large, international cohort of patients with postoperative remission and long follow-up.

Methods

Retrospective analysis across seven neuroendocrine centers from China, Europe, and the U.S. All patients had *USP8* genotype, demographic, clinical, biochemical, and follow-up data. Patients with prior pituitary intervention or bilateral adrenalectomy were excluded. We estimated the recurrence risk with Kaplan-Meier curve, long-rank test, and Cox regression.

Results

Among 435 patients (82.8% female; median follow-up: 5.61 years), *USP8* variants were identified in 195 (44.8%) tumors. Variants were more prevalent in younger ($P<0.001$) and female ($P<0.001$) patients and were associated with a lower incidence of cavernous sinus invasion ($P=0.021$) and reduced post-operative cortisol levels ($P=0.004$). Of these, 371 initially reached post-op remission, but 71 recurred during follow-up. *USP8* variants significantly increased recurrence risk in microadenomas (HR 2.36, $P=0.025$), while in macroadenomas, no significant association was observed (HR 0.58, $P=0.126$). Stratification by *USP8* genotype and tumor size produced four subgroups. However, due to similar recurrence risks (HR 1.08, $P=0.824$) and comparable clinical characteristics between *USP8* variant microadenomas and macroadenomas, these two variant subgroups were merged into a single category, resulting in three distinct categories: wild-type microadenomas, *USP8* variant adenomas, and wild-type macroadenomas, with 5-year cumulative recurrence rates of 6.45%, 12.53%, and 31.16%, respectively. The log-rank test revealed significant differences in recurrence risk among these 3 categories ($P<0.001$). Further evaluation of postoperative 1-week nadir cortisol levels showed category-specific recurrence risks. For wild-type microadenomas, cortisol levels ≥ 2 μg/dl were associated with increased recurrence risk (HR 7.26, $P=0.016$). In *USP8* variant adenomas, recurrence risk was elevated only at cortisol levels ≥ 5 μg/dl (HR 6.11, $P<0.001$). Postoperative cortisol levels were not significantly associated with recurrence in wild-type macroadenomas. We further identified additional, varied factors associated with recurrence risk across the three categories.

Conclusions

USP8 genotype, combined with tumor size, is associated with different risk of recurrence in CD. This study highlights the heterogeneity of CD recurrence patterns and underscores the importance of combining tumor size and somatic *USP8* genotype to guide follow-up strategies.

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Plenary Lectures

PL1

Abstract Unavailable

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PL2

Abstract Unavailable

DOI: 10.1530/endoabs.110.PL2

PL3

Thyroid Cancer Across the Lifespan: Similar yet Different

Steven Waguespack[1]
[1]The University of Texas MD Anderson Cancer Center, USA

Both follicular cell- and C cell-derived thyroid carcinomas affect patients of all ages. Although similar in many aspects across the lifespan, there are also significant differences in cancer pathogenesis, clinical behavior, and management depending on the age at diagnosis. This plenary will provide an up-to-date overview of thyroid cancer across the age continuum, including cutting-edge advances in research and therapy.

DOI: 10.1530/endoabs.110.PL3

PL4

Adverse effects of endocrine disrupting chemicals though life course

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Endocrine disrupting chemicals (EDCs) are natural or human-made chemicals that can interfere with the synthesis, secretion, transport, binding, action or elimination of natural hormones in the body. They are found in numerous household and industrial products and we are therefore all exposed to a cocktail of these chemicals through food, indoor air and dust, personal care products and clothing. EDCs are measurable in serum or urine from almost all. Exposure to even low doses of EDCs at vulnerable time windows during fetal life and early childhood, when the organs are rapidly developing have long-term impact on future health and disease. Examples on adverse health effects will be provided from the Odense Child Cohort, in which 2500 pregnant women were enrolled from 2010-12 in early pregnancy and serum and urine samples were collected. Their offspring are being followed through the age of 18 years with extensive repeatedly collected information from both questionnaires, biological sampling and clinical examinations in order to study the importance of EDCs exposure on metabolic syndrome, immune system, reproduction, growth pattern and neuropsychological development. We have measured perfluroalkyl substances (PFAS), phthalates, phenols, parabens and pesticides in serum and urine from more than 7000 mothers and children and have information on anogenital distance, weight and height and blood pressure, language development, asthma and allergy, infections, antibodies towards infections, ADHD, IQ, DXA, VO2 max and puberty.

Bullet points

- Endocrine disrupting chemicals (EDCs) can interfere with hormones in the body
- We are all exposed to EDCs
- Fetus and child are vulnerable to EDC exposure
- EDC exposure during development have long term implications for health and disease
- In the Odense Child Cohort we have measured EDCs in serum and urine from more than 7000 mothers and children
- Maternal EDC exposure is associated with metabolic syndrome, immune system, reproduction, growth pattern and neuropsychological development in the offspring

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PL6

Unlocking the secrets of exercise: A pathway to enhanced insulin sensitivity and metabolism in type 2 diabetes

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Skeletal muscle is a central player in locomotion and systemic metabolism, particularly in glucose regulation. Type 2 diabetes and obesity are associated with insulin resistance and muscle dysfunction, often exacerbated by sarcopenic obesity. Exercise is a proven intervention to counteract these declines, yet the molecular mechanisms underlying its benefits remain incompletely understood. Emerging research highlights the dynamic and time-dependent molecular responses in skeletal muscle following exercise, including waves of transcriptional, proteomic, and metabolic changes. Integration of multi-omics approaches is revealing new insights into how skeletal muscle interacts with other organs to maintain energy homeostasis. However, individual variability in exercise responses underscores the need for precision exercise strategies tailored to genetic, epigenetic, environmental, and phenotypic factors. By mapping the molecular landscape of exercise adaptation, researchers aim to identify therapeutic targets to enhance insulin sensitivity, prevent metabolic dysfunction, and inform personalized interventions. Despite ongoing challenges, understanding the intricate biology of exercise holds promise for innovative strategies to combat Type 2 diabetes and related disorders, supporting the mantra that "exercise is medicine."

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Symposia

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S3.2

Transition for Prader Willi Syndrome

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Prader-Willi syndrome (PWS) is a complex neurodevelopmental genetic disorder with a specific trajectory leading to early obesity with hyperphagia, psychiatric disturbances, endocrine and metabolic disorder. Global incidence is approximately 1 in 20,000 births in Europe. PWS is usually diagnosed early in life and then managed by pediatric teams. Transition is defined as "a process of organized and coordinated change of adolescents and young adults with a chronic medical condition from a pediatric system of care to the adult system of care". Transition is a process, whereas ‘transfer’ is the actual moment of the first appointment at adult care. A European endocrinologist expert group examined in 2015 the gap in metabolic and endocrine care of patients during transition (2). They highlighted the necessity of multidisciplinary collaboration across health sectors for endocrine diseases, the need for pediatric and adult endocrinologists to work together, early involvement of adolescents in their disease, and also of parents in the transition process. The transition of patients with PWS from adolescence to adult life is particularly challenging for medical care because of multiple comorbidities and specific skills required for the medical team but also management of behavioral problems that may preclude socialization. This period of profound changes is thus prone to disruptions, the main risks being the worsening of the medical situation and losing the follow-up of patients. The MTG5 “Growth and obesity” of the EndoERN organized a webinar on 16th of November 2021 and convened experts of the disease to address the transition of care in PWS. Speakers brought their knowledge of this peculiar period on psychiatric and endocrinological aspects but also examined the complementary points of view as pediatricians and adult specialists. The experience of parents and patients was also presented. In this presentation I will show the adaptations our team made based on our long term experience to optimize the transition of care of adolescents to young adults with PWS and the challenges to face to give them the best chance of having a satisfactory quality of life.

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S4.2

A data-based campaign on reducing exposure to Endocrine Disruptors in mother-infant dyads: the Life Milch Project

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The Life MILCH project -"Mother and Infant dyads: Lowering the impact of endocrine disrupting chemicals in milk for a Healthy Life" (www.lifemilch.eu) is a pilot study aimed at reducing the impact of environmental endocrine disruptors (EDs) on human health by assessing exposure and effects on mother-child pairs, with breastmilk as a main biomarker of exposure. The first screening phase of the project on 500 mother-child pairs enrolled in three different Italian locations, showed significant associations between mothers' lifestyle and diet and ED levels in maternal urine, breastmilk, and infant urine samples at different timepoints (1, 3, 6, 12 months of age), and identified possible main sources of maternal exposure to EDs to establish a risk assessment model. Based on this evidence-driven model, the project has developed a specific prevention/awareness campaign and interventions for reducing maternal exposure to EDs. Our hypothesis is that a change in food habits and lifestyle would reduce the levels of specific EDs in the mothers, their breastmilk and, consequently, in the infants. These prevention activities were carried out in the three project locations and with three specific targets: first involving pregnant woman and breastfeeding mothers, and then woman of childbearing age and health professionals. The efficacy of the prevention campaign and intervention was assessed by a subsequent biomonitoring of ED levels in the breast milk of 150 women who have participated in the campaign during pregnancy/nursing, including an assessment of their infants' ED exposure levels and development at 6 months of age (second screening – currently ongoing). Finally, we will compare the results obtained in the 2nd screening with those obtained in the 1st screening to clarify whether specific interventions could effectively reduce and prevent exposure to some EDs. (LIFE18 ENV/IT/000460).

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S5.2

Management of bone fragilty and osteoporosis in children and adolescence

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Osteoporosis, a skeletal disorder with bone fragility, is rare in children and adolescents. The diagnosis is based on low BMD (Z-score $<$-2.0, appropriately adjusted for height and skeletal maturity) and a fracture history indicative of higher-than-normal bone fragility. Compared with primary osteoporosis (various genetic forms), secondary osteoporosis is more common and poses major treatment challenges in various pediatric subspecialties. Many chronic diseases and their treatment can impair childhood bone mass development and lead to osteoporosis. In the absence of a known chronic disease, fragility fractures and low BMD should prompt extensive screening for secondary causes. Genetic skeletal fragility disorders should be considered when no secondary cause can be identified. Management consists of treatment of the underlying illness and optimizing calcium and vitamin D intake and physical activity. Treatment with bone-active medication should be considered on a personalized basis, depending on the severity of osteoporosis and the underlying disease and its anticipated prognosis versus the absence of evidence of anti-fracture efficacy and potential harmful effects of pharmacotherapies. Only few large-scale studies with pharmacological treatment have been performed in childhood osteoporosis and most of them had BMD and not fractures as a primary outcome. When treatment of the underlying cause is not possible or effective and fracture risk appears high, antiresorptive drugs should be considered. Treatment with bisphosphonates has been shown to improve BMD in several underlying conditions but data on fracture prevention are mostly lacking. Rebound hypercalcemia after denosumab use limits its benefits in children. Anti-sclerostin antibody and other osteoanabolic treatments will hopefully in the future be available for selected pediatric patient groups. The management of children and adolescents with osteoporosis and fragility fractures requires a patient-centered multidisciplinary approach.

Key learning points

- Secondary osteoporosis has emerged as an important pediatric disease and involves all pediatric subspecialties.
- Evaluation of skeletal health should be part of chronic illness management for early diagnosis and timely treatment of pediatric osteoporosis.
- Pharmacotherapy, usually antiresorptives, needs to be determined on individual basis, considering the severity of osteoporosis, the underlying disease and its anticipated prognosis.
- Treatment options are limited and their efficacy inadequately established.
- There is need for osteoanabolic treatment options both in primary and secondary childhood osteoporosis.

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S5.3

Novel therapies in osteogenesis imperfecta

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For a period of nearly 2 decades the use of intravenous bisphosphonates was the only recommended medical treatment for children and adults with osteogenesis imperfecta (OI). In adults some small trials using PTH have been performed showing some osteoanabolic effect. During the last 10 years short acting antiresorptive agents like denosumab have been investigated. Due to the severe rebound after cessation of the treatment and fluctuations in calcium levels this strategy is not recommended. All antiresorptive agents increase bone mass by accumulating "old bone" which has a poor quality due to the structural collagen defect in most patients. Osteoanabolic agents like anti sclerostin antibodies or TGF-beta increase activity of osteoblasts and produce new collagen, which needs to be mineralized. Trials are currently on the way but it will remain unclear how long the treatment needs to be given and what happens after stopping the treatment. In adults a trial assessing the effect of PTH and zoledronic acid is currently performed pathing the way to a sequential therapy of osteoanabolic and antiresorptive treatments in the future. However, all these treatments will not correct the structural collagen defect. A first trial with embryonic mesenchymal stem cells has shown that this approach is safe in children with OI. These stem cells will produce normal collagen and might be able to replace the structural impaired bone in the patients. This might be a treatment alternative in the future while a gene therapy, correcting the mutation, is still not on the horizon currently. In addition to these drugs, the care for patients with OI will remain an interdisciplinary challenge which require surgeons, physiotherapist, pain nurses and many other specialists to provide a treatment adapted to the individual patient with this heterogenous disease.

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S6.2

Current Challenges and New Perspectives in Cyclic Cushing's Syndrome

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Variability is common, if not omnipresent, in cortisol excess. So-called "cyclic Cushing's syndrome" (cCS) refers to a subset of patients in whom periods of glucocorticoid excess (peaks) spontaneously alternate with periods of low or normal cortisol concentrations (troughs). cCS is marked by diagnostic errors, and possibly poorer outcomes. In this talk, I will provide an overview of different cortisol secretion kinetics, with a particular focus on the diagnostic challenges encountered in both adult and pediatric patients. Drawing on new data from our international patient cohort – collected from expert centers worldwide – I will offer practical guidance for improving diagnosis and patient care. Using case-based examples, I will highlight common diagnostic pitfalls and how to avoid them. I will present novel findings on cortisol secretion patterns and explore associated clinical and biochemical outcomes in patients with cCS. Finally, I will discuss potential underlying mechanisms of cyclicity and offer an outlook on ongoing and future research directions.

Key questions addressed in this talk

- *To cycle or not to cycle*:(How) can we distinguish cortisol variability from true cyclic Cushing's syndrome?
- What are the main diagnostic pitfalls in cyclic Cushing's syndrome, and how can we avoid them?
- What is the optimal treatment approach for patients with (suspected) cyclic Cushing's syndrome?
- Is cyclicity unique to the corticotroph axis, and what mechanisms might explain it?

What are the future directions of research on cyclic Cushing's syndrome?

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S7.3

Population screening of early stage Type 1 diabetes

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One of the most important advances in type 1 diabetes (T1D) research has been the identification of a long incubation period, starting months to years prior to the appearance of disease symptoms and progressing in a complete asymptomatic way. This pre-symptomatic phase can be recognized by the detection in the blood of autoantibodies against multiple islet antigens, including GAD, insulin, IA-2 and ZnT8. In children and adolescents the detection of two or more among these autoantibodies is highly predictive of future clinical T1D, approaching nearly certainty within 10-15 years. The pre-symptomatic disease staging and risk estimate of further progression is based on the assessment of glucose status: Stage 1, associated with normoglycemia; Stage 2, associated with dysglycemia; Stage 3, associated with hyperglycemia and need to start insulin therapy (corresponding to clinical T1D). These stages have been recently assigned the ICD-10 codes E10.A1, E10.A2 and E10.9, respectively. Therefore, measurement of islet autoantibodies has been increasingly adopted as the basic tool for screening programs, implemented initially in families and other cohorts of genetically predisposed individuals, and then more and more in the general population of pediatric ages. The identification of T1D at an early pre-symptomatic stage has several clinical benefits: opportunity for education and monitoring of at risk individuals to support a smooth transition to clinical diabetes and insulin therapy; reduction of the incidence of diabetic ketoacidosis and minimization of clinical manifestations at onset; potential access to disease modifying treatments (e.g. Teplizumab) and clinical trials. Conversely, the impact of screening the general population for T1D need to be assessed for ethical, psychological, socioeconomic and financial aspects. Particularly, anxiety and distress related to screening have been reported in association with communication to families of significant risk of future T1D. The new and growing discipline of pre-symptomatic/early T1D needs in depth investigations and overarching approaches such as that accomplished by EDENT1FI, a large European consortium conducting: screening children from the general population; evaluating the associated psychological impact and providing support and education to families; implementing protocols for monitoring and follow up of at risk people; and proving information and opportunities for disease modifying therapies.

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S9.2

Novel targets and sequential therapies in neuroendocrine neoplasms

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Neuroendocrine tumors (NENs) are a diverse group of malignancies characterized by diverse clinical behaviors and responses to treatment. Despite significant advances in therapies, there is still an urgent need for new therapeutic targets and optimized sequential treatment strategies to improve patient outcomes. Recent developments in NEN treatment are discussed, focusing on innovative approaches such as molecular targeting, peptide receptor radionuclide therapy (PRRT), and combinations of available therapeutic approaches. Current therapeutic options, including somatostatin analogs, targeted therapies, chemotherapy, and PRRT, were reviewed while investigating their efficacy and limitations. It also highlights the potential of emerging molecular targets, including mTOR inhibitors, angiogenesis regulators, and epigenetic modulators, which offer hope for better disease control. An essential aspect of modern NEN treatment is the sequencing of therapy to maximize survival and reduce toxicity. Clinical evidence supporting rational choice of first-line and subsequent therapies was evaluated. Advances in PRRT were also highlighted, such as alpha- and beta-emitting radionuclides, combination regimens, and new radiopharmaceuticals. In conclusion, the role of precision medicine, a cutting-edge approach, and the importance of genomic and transcriptomic profiling in guiding the choice of therapy is emphasized. It addresses challenges such as resistance to treatment, the need for extended clinical trials, and integrating multidisciplinary care models. Ultimately, there is a need for continuous research and international collaboration to refine NEN treatment paradigms and improve patient outcomes.

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S10.1

Molecular basis of short stature

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In this talk, we will describe the spectrum of genetic variants that affect height. We will differentiate between common genetic variants identified by genome-wide association studies which have very small effects on height versus rare genetic variants with larger effects causing monogenic causes of short stature. We will then review two specific genetic causes of short stature, mutations in the ACAN gene and NPR2 gene. These genes both affect growth at the growth plate. We will discuss clinical trials of agents targeting these genetic defects and pathways. We will then explore the utility of genetic testing in identifying an etiology of short stature in the clinical setting.

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S11.3

Intratumoral glucocorticoid secretion in adrenocortical carcinoma and its implication for CAR-T cell targeting

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Glucocorticoids (GC) confer a profound immunosuppressive effect and are extensively used in autoimmune diseases and cancer therapy for their anti-inflammatory properties. However, this mechanism is also exploited by multiple endocrine and non-endocrine cancers that secrete GCs either by active production or metabolite recycling to modulate immune-recognition and –therapy. In this talk, the speaker will provide data on adrenocortical carcinoma (ACC) as perfect exemplary cancer entity to explore the impact of autocrine GC signaling in hormonally active cancers on cancer progression as well as the expression of cancer antigens that can be targeted with CAR-T cell immunotherapy. He will further provide transcriptomic and mechanistic insights in ACC tumor biology, will show how cancer antigens can be modulated to increase CAR-T cell recognition thresholds by GC signaling and demonstrates clinically relevant intratumoral biomarkers for GC secretion and disease progression in ACC. While GC secretion negatively affects conventional CAR-T cell efficacy the presenter will provide further selective T cell engineering capabilities to alleviate the detrimental effects on T cell efficacy on the one hand, while exploiting the exalted GC driven cancer antigen expression on the other. He will provide data that show how GC-resistant CAR-T cells exceed autocrine GC cancer signaling for effective immunotherapeutic targeting while inducing complete and sustained remission in steroidogenic ACC mouse models. Due to the promising curative potency of CAR-T cells in preclinical ACC mouse models, ROR1 CAR-T cells will enter

phase I clinical trial at our center, where we will assess safety and tolerability of ACC-directed CAR-T cells in human ACC patients.
Key findings
- Autocrine glucocorticoid (GC) cancer signaling induces cancer progression and antigen expression that can be targeted with genetically modified CAR-T cells.
- ROR1 is an extracellular oncogenic protein that is a suitable CAR-T cell target which further acts as new biomarker for intratumoral glucocorticoid secretion due to its tight regulation by GC signaling.
- Glucocorticoid-resistant CAR-T cells exploit autocrine GC signaling for effective CAR-T cell therapeutic targeting while inducing complete and sustained remission in ACC bearing mice.
  ROR1 CAR-T cells will be evaluated in human ACC patients in phase I clinical trial.

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S11.4

Testicular adrenal rest tumors in congenital adrenal hyperplasia: clinical, biochemical, and molecular aspects

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With advancements in diagnosis and treatment, most patients with congenital adrenal hyperplasia (CAH) now reach adulthood, and we are increasingly faced with long-term complications. A common complication in both male and female patients with classic CAH is gonadal dysfunction, which can lead to subfertility or infertility. In male patients, gonadal failure may be caused by testicular adrenal rest tumors (TART). These tumors are typically found bilaterally and can obstruct the seminiferous tubules due to their central location within the rete testis, resulting in either oligospermia or azoospermia. Furthermore, TART can cause irreversible damage to the surrounding testicular tissue. Current research indicates that the type and severity of CAH, which are closely associated with genotype, as well as disease duration and poor disease management, are significant factors contributing to the development of TART. However, there are also reports of TART arising in young children and in patients who have good control or milder forms of the disease. Signs of gonadal dysfunction may become apparent already during puberty; therefore, regular endocrine gonadal function assessment and imaging in male patients with CAH should start at an early age. Early detection of TART and optimization of treatment can prevent potentially irreversible gonadal dysfunction and infertility.

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S11.5

Overview of non-CAH forms of primary adrenal insufficiency in childhood

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Primary adrenal insufficiency (PAI) is a relatively rare but life-threatening clinical condition caused by dysfunction or destruction of the adrenal cortex resulting steroid hormones deficiencies, including cortisol and aldosterone. Although rare, PAI is a potentially lethal disease that requires early recognition and treatment. However, symptoms are often unspecific and diagnosis can be difficult, frequently causing a delay in diagnosis. Congenital and acquired causes of PAI can be recognized. Congenital causes, other than CAH, include other defects of steroidogenesis (e.g., congenital lipoid adrenal hyperplasia), conditions of adrenal hypoplasia and ACTH resistance. Acquired causes include autoimmunity, adrenal injury of hemorrhagic, infectious and infiltrative nature, and transient forms (e.g., medical induced PAI). Autoimmune cause is the second most frequent cause of PAI in children after CAH, either as an isolated disease or as a manifestation of polyendocrinopathy. Congenital AI usually presents early in life with signs of adrenal crisis or hypoglycemic seizures. Acquired PAI can have an insidious onset characterized by the slow and progressive onset of nonspecific symptoms, such as anorexia, weight loss, morning sickness or vomiting, and fatigue; this could result in diagnostic delay and danger to the child's life. The finding of these signs and symptoms should alert the physician to the possibility of PAI. The purpose of this talk is to present an overview of the main causes of PAI, other than the better-known congenital adrenal hyperplasia (CAH), in order to highlight epidemiological, clinical, and laboratory features that can lead to a timely diagnosis and appropriate treatment of these conditions.

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S12.3

Safety of GH replacement in adults with hypopituitarism

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Growth hormone deficiency (GHD) observed in adults either presents in childhood and persists into adulthood (childhood-onset GHD [CO-GHD]) or arises in adulthood (adult-onset GHD [AO-GHD]). GHD in adults is most frequently caused by hypothalamic/pituitary lesions, often due to a pituitary adenoma or its associated treatments by surgery or radiotherapy. Adult GHD is linked to a wide spectrum of clinical features, including abnormal body composition, reduced bone mineral density, decreased muscle strength and exercise capacity, unfavorable metabolic profile, and impaired physiological well-being and quality of life. Data from some studies also suggest that hypopituitary patients with untreated GHD may be predisposed to decreased life expectancy due to cardiovascular and cerebrovascular diseases, although an association between GHD and increased mortality has not been definitively proven. Since recombinant human GH was first introduced in the mid-1980s, clinical studies have shown that GH therapy increased lean body mass and

decreased body fat, improved bone health, enhanced patient-reported quality of life, and reduced total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol in adults with GHD, although its effects on cardiovascular risks and mortality have been inconclusive. Administration of long-term GH replacement in adults with GHD is overall well-tolerated, but concerns regarding potential risks of diabetes mellitus, new malignancy, tumor recurrence, and cardiovascular diseases still remain and will be discussed. Long-term surveillance studies of large cohorts and adequate controls are therefore needed for a better benefit-risk assessment. Finally, GHD across transition period appears as a specific situation which needs to be managed and discussed in a proper way.

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S13.2

Endocrine disruptors affect male reproductive disorders in fetal and early postnatal life

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Male reproductive development depends on normal testicular hormones that induce masculinization in fetal and early postnatal life. Genetic and environmental factors that disrupt reproductive hormone production or action cause congenital reproductive organ defects, such as undescended testes, hypospadias, and short anogenital distance, while in adult life the adverse effects may appear as poor semen quality or testicular germ cell cancer. This spectrum of reproductive disorders has been named testicular dysgenesis syndrome (TDS), and it can present as one or multiple disorders of TDS. Congenital cryptorchidism or hypospadias have been associated with exposure to several endocrine disruptors that can be classified as antiandrogens, dioxin-like or estrogenic compounds. Concomitant exposure to a large mixture of endocrine disruptors raises concern, although exposure levels to single chemicals might seem safe. Legislation to secure chemical safety and international agreements, such as Stockholm convention have made our environment cleaner, but constant emergence of new chemicals poses a challenge to preventive medicine. We are acting often only after the harm has occurred.

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S13.3

The evolutionary pressure on humans and other mammals to be reproductively successful

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Spermatogenesis is crucial for our ability to reproduce. However, it also represents an evolutionary battleground. Genes that emerge during evolution are first expressed in the testis and spermatogenesis heavily depends on the rapidly evolving sex chromosomes. The evolution of spermatogenesis is also reflected by a great variation in testis size among primates and even among our closest relatives – the great apes.To explore the evolution of spermatogenesis we collected testicular specimens and reproductive data on more than 100 species of apes, including all great apes. This extensive resource allows us to assess the efficiency of spermatogenesis among these species quantitatively and to evaluate differences in reproductive hormones. To better understand the molecular processes that affect the evolution of spermatogenesis, we also generated single-nuclei gene-expression data from ~100k testicular cells from 11 species. We identified both evolutionary conserved and divergent patterns of gene expression. Notably, we observed a rapid molecular evolution in late post-meiotic germ cells. In addition, we were able to identify sex-chromosome-specific gene expression in spermatids, indicating recent meiotic drive processes, which are known to impair spermatogenesis. I will highlight our major findings from this extensive dataset and other comparative data on spermatogenesis across primates, with a particular emphasis on human spermatogenesis. The evolution of spermatogenesis can provide valuable insights into the molecular processes critical for its efficiency, potentially shedding light on why human spermatogenesis is relatively poor.

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S14.1

Calcium sensing receptor and its function in health and disease

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The calcium-sensing receptor (CaSR) is a critical modulator of mineral homeostasis. This cell-surface class C G-protein coupled receptor binds extracellular calcium, phosphate and amino acids, and is the target of calcimimetic and calcilytic drugs. The CaSR is expressed on the cell surface as a homodimer and is most highly expressed in the parathyroid glands and the thick ascending limb of the Loop of Henle, where it acts to maintain a near-constancy of circulating calcium concentrations by regulating parathyroid hormone (PTH) secretion and urinary calcium excretion, respectively. The other major calcitropic role of the CaSR involves regulating mammary gland PTH related peptide (PTHrP) secretion during lactation. The importance of the CaSR for calcium homeostasis is highlighted by the identification of germline loss- and gain-of-function CaSR mutations, which cause familial hypocalciuric hypercalcaemia (FHH) and autosomal dominant hypocalcaemia (ADH), respectively, and also by the efficacy of CaSR-targeted drugs for the treatment of parathyroid disorders. The CaSR also has non-calcitropic roles and is highly expressed in pancreatic beta-cells, where it regulates insulin secretion and may also influence glucose homeostasis. In addition, abnormal expression or function of the CaSR is implicated in the pathogenesis of chronic lung diseases and also malignancies such as carcinoma of the breast. This has led to CaSR targeted drugs being evaluated for non-calcitropic disorders. Novel strategies such as utilising inhaled calcilytic drugs for asthma may help to minimize adverse effects arising from inappropriate modulation of the CaSR in calcitropic tissues.

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S14.2

Recent advances in the diagnosis and management of Hypophosphatasia

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Hypophosphatasia (HPP) is a rare inherited metabolic disorder characterized by deficient activity of tissue-nonspecific alkaline phosphatase (TNAP) caused by variants in the ALPL gene. Disease manifestations include: reduced skeletal mineralization, rickets, lung hypoplasia, vitamin B6-dependent neurological manifestations, craniosynostosis, premature loss of deciduous teeth, and muscle pain. The clinical presentation can comprise failure to thrive with muscular hypotonia, delayed motor development, and gait disturbances later in childhood. In adults, pseudofractures are a characteristic indicator of severely compromised enzyme activity. However, non-classical symptoms like generalized musculoskeletal pain, weakness, and fatigue, frequently accompanied by neuropsychiatric and gastrointestinal problems are increasingly recognized as key findings in patients with HPP. The diagnosis is based on clinical manifestations in combination with persistently low alkaline phosphatase (ALP) activity, elevated levels of ALP substrates, specifically inorganic pyrophosphate (PPi), pyridoxal 5'-phosphate (PLP) or urine phosphoethanolamine (PEA), and genetic confirmation of a causative *ALPL* variant. Considering the wide range of manifestations, treatment must be multimodal and tailored to individual needs. The multidisciplinary team for comprehensive management of HPP patients should include expertise to ensure disease state metabolic and musculoskeletal treatment, dental care, neurological and neurosurgical surveillance, pain management, physical therapy, and psychological care. Asfotase alfa as first-in-class enzyme replacement therapy (ERT) for HPP was shown to improve survival, rickets, and functional outcomes in severely affected children. However, we need to know more the effects of the enzyme replacement therapy on emerging manifestations of the disease. The understanding of the pathophysiology behind the diverse clinical manifestations of HPP is instrumental for improving the diagnostic process, working on novel means to substitute enzyme activity, and developing an integrative care of the HPP patient.

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S14.3

Molecular basis of Pseudohypoparthyroidism

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The *GNAS* complex locus on chromosome 20q13.3 encodes the alpha-subunit of the stimulatory G protein (Gsα) and several splice variants thereof. With the exception of the transcriptional start site giving rise to Gsα, at least four *GNAS* regions undergo parent-specific epigenetic changes. Several human disorders are caused by mutations in *GNAS* or adjacent genomic regions. Thus, pseudohypoparathyroidism type Ia (PHP1A) is caused by heterozygous inactivating mutations involving the maternal *GNAS* exons 1-13 that lead to PTH-resistant hypocalcemia and hyperphosphatemia. Affected patients furthermore can present with resistance to TSH and other hormones, and typically develop characteristic abnormalities referred to as Albright's Hereditary Osteodystrophy (AHO). The same or similar mutations on the paternal allele also cause some of these AHO features, but without mineral ion changes, and this disorder is therefore referred to as pseudopseudohypoparathyroidism (PPHP). Other heterozygous mutations on the maternal allele (including deletions, duplications, insertions, and inversions) lead to epigenetic changes at one or several *GNAS* DMRs (Differentially Methylated Regions), thereby causing autosomal dominant pseudohypoparathyroidism type Ib (AD-PHP1B). The genetic defect(s) responsible for sporadic PHP1B (sporPHP1B) remains unknown for most cases, yet characteristic epigenetic changes at the *GNAS* DMRs can be readily detected. Thus, multiple genetic or epigenetic *GNAS* abnormalities impair Gsα function thereby reducing cAMP-dependent signaling events down-stream of various G protein-coupled receptors.

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S15.1

Regulation of HPT-axis in maternal-foetal health - Thyroid and Fertility

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Thyroid autoimmunity (TAI) and thyroid dysfunction are prevalent among women of reproductive age, significantly impacting fertility and pregnancy outcomes. This talk explores the intricate relationship between thyroid health and female reproductive function, emphasizing the role of thyroid hormones in ovarian regulation. The discovery of thyroid-stimulating hormone (TSH) and its receptors on ovarian surface epithelium and oocytes underscores the importance of thyroid hormones in reproductive physiology. While overt hypothyroidism is widely recognized as a risk factor for infertility and adverse pregnancy outcomes, the association between subclinical hypothyroidism (SCH) and infertility remains inconsistent across literature. This inconsistency is partly due to varying TSH cut-offs and a lack of robust prospective studies. The talk will address the current lack of consensus on initiating levothyroxine treatment for SCH to prevent fertility issues, highlighting the methodological limitations and small sample sizes of existing studies. Additionally, the diverse population of women with thyroid autoimmunity and dysfunction, influenced by factors such as age and co-existing health conditions, complicates uniform treatment recommendations. The presentation will delve into thyroid hormone-dependent mechanisms, including ovarian function regulation and endometrial quality, as well as thyroid hormone-independent mechanisms like immunological dysfunction and direct infiltration of reproductive organs by thyroid autoantibodies. Understanding these mechanisms is crucial for developing targeted treatment strategies to improve fertility outcomes in women with TAI. This talk aims to provide a comprehensive overview of the current state of research, identify gaps, and propose directions for future studies.

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S16.1

International Diabetes Transition Recommendations- a joint initiative between ISPAD- ADA- EASD

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Transition from pediatric to adult diabetes care is a critical period associated with increased risk of adverse health outcomes, disengagement from healthcare services, and psychosocial challenges. This consensus report, developed jointly by the International Society for Pediatric and Adolescent Diabetes (ISPAD), the European Association for the Study of Diabetes (EASD), and the American Diabetes Association (ADA), provides recommendations to optimize transition care for young people with diabetes. A systematic review, along with a global survey of 372 healthcare professionals and 146 individuals with diabetes or carers, identified significant variability in transition models, with many lacking structured readiness assessments, dedicated transition personnel, or formal education programs. Only 32.8% of healthcare centers utilized a transition readiness checklist, and less than 25% had structured transition education or dedicated staff to support transition efforts. Identified barriers included poor communication between pediatric and adult teams, lack of psychosocial support, and uncoordinated care transfers.

The consensus framework recommendations outline three key phases of transition:

1. Pre-transition: Early preparation (12–24 months before transfer), structured education, transition readiness assessments, and active family/carer involvement.
2. Transfer of care: Timely scheduling of the first adult care visit, provision of a written medical summary, structured communication between care teams, and encouragement of peer support.
3. Post-transfer: Ongoing assessment of diabetes knowledge and psychosocial well-being, flexible care models (e.g., telehealth, young adult clinics), and education on emergency care management.

Despite limited high-quality evidence on transition outcomes, structured programs have shown improvements in engagement, care satisfaction, and self-management skills. This report underscores the need for adaptable, resource-sensitive strategies tailored to diverse healthcare settings. Future research should evaluate long-term clinical and psychosocial outcomes to further refine best practices. Implementing these global recommendations will help ensure a seamless, supportive transition, ultimately improving long-term health and well-being for young people with diabetes.

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S17.1

Recombinant antibody fragments as new modulators of gonadotropin receptor activity

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G Protein-Coupled Receptors (GPCRs) constitute the most abundant receptor family in the genome and also represent the primary class of therapeutic targets. Gonadotropins and their receptors play a central role in the control of both male and female reproduction. Gonadotropins (i.e. FSH, LH, hCG) are extensively used in assisted reproduction technologies (ART). However, no pharmacological tool allowing to tightly control gonadotropin receptors' activity through competitive antagonism or allosteric modulation is available in clinics. Therefore, some therapeutic needs remain unmet. Despite the tremendous success of antibodies as therapeutic agents, very few therapeutic antibodies targeting GPCRs have been approved to date. VHHs are small antibody fragments derived from the variable domain of heavy-chain antibodies (HcAbs) in camelids. Their small size (12 ~ 15 KDa) combined with their unique structural features (i.e., long CDR3, the ability to interact with concave surfaces, and access to cryptic epitopes that classical immunoglobulins cannot reach) make them intriguing tools for targeting GPCRs. In particular, VHHs have demonstrated their ability to modulate some GPCRs in an allosteric manner and have also proven to be valuable tools in structural biology for this receptor class. We have developed VHHs specific to gonadotropin receptors by phage display from immune and synthetic libraries. The selection and screening processes for identifying high-affinity/selectivity VHHs have been optimized to deal with high attrition rates and identify VHHs with specific pharmacological profiles. We have demonstrated novel biochemical and pharmacological properties of these VHHs that allow the modulation of fertility in mice without using exogenous hormones.

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S20.1

The long-term effects of duchenne muscular dystrophy and its treatment on bone strength

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Duchenne muscular dystrophy (DMD) is a relentlessly progressive dystrophinopathy arising from pathogenic, loss of function variants in the *DMD* gene. Corticosteroid (CS) monotherapy is the mainstay of DMD treatment in many

countries around the world; even dystrophin-targeted treatments such as gene therapy do not relinquish patients from CS. On daily CS therapy, walking is prolonged by two years (with loss of ambulation typically experienced around 14 years of age), and life expectancy is typically extended into the late 20's and early 30's. Daily CS therapy is also characterized by well-known endocrine and bone co-morbidities including excess weight gain, short stature, delayed puberty, adrenal insufficiency, and bone fragility due to osteoporosis. In an effort to attenuate the adverse effects of CS therapy in DMD, regimens alternative to daily CS have been implemented (such as prednisone 10 days on/off); however, this saltatory approach comes at a cost to muscle strength. Recently, a novel steroid (vamorolone) has been studied in DMD. Data to nearly three years post-exposure suggest efficacy parity of high-dose vamorolone relative to classic CS regimens, along with improved growth velocity + serum bone turnover markers, and fewer vertebral fractures. However, excess weight gain, adrenal insufficiency and bone fragility can still occur on vamorolone, necessitating their ongoing, anticipatory prevention. DMD represents a serious secondary osteoporosis condition due to the high frequency of fractures, their devastating consequences, and limited potential for medication-unassisted recovery from osteoporosis. Lower extremity fractures are associated with premature, permanent loss of ambulation, while fat embolism syndrome after long bone injuries has been linked to acute respiratory distress syndrome and unexpected mortality. Vertebral fractures, often silent, occur at an alarmingly high rate in daily, classic CS-treated DMD, necessitating periodic surveillance with lateral spine imaging. Current management strategies centre around early detection of vertebral and non-vertebral fractures, with a single low-trauma vertebral or long bone fracture providing clear rationale for instituting bone protection therapy. At the same time, the high fracture rates of DMD combined with the devastating consequences of bone fragility have sparked interest in osteoporosis treatment *prior* to first fractures. Intravenous bisphosphonates remain the cornerstone of osteoporosis therapy in DMD. In an effort to improve the convenience of osteoporosis treatment and minimize first exposure adverse events, denosumab has been tried in this setting. However, even the low bone turnover of DMD does not protect against the denosumab-induced rebound phenomenon, leading to recommendations against the routine use of this agent in pediatric DMD. Overall, it is recognized that DMD is the ideal setting to consider not only prevention of first-ever fractures but also osteoanabolic agents, given the limitations of bisphosphonate monotherapy in low bone turnover states such as DMD. Strategic planning for primary osteoporosis prevention is currently underway by members of The OPTIMIZE DMD Consortium, an international working group dedicated to education, advocacy and research in endocrine and bone health care for people with DMD.

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S20.2

Transition from boy to man - Puberty/testosterone

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Glucocorticoids reduce inflammation and preserve muscle function in Duchenne muscular dystrophy (DMD) but cause pubertal delay. Consideration of testosterone treatment for the induction of puberty was introduced as part of the International Care Considerations in DMD in 2018 but the timing of this and methods used to induce puberty vary. It also remains unclear what happens to endogenous testosterone levels once testosterone supplementation is stopped, particularly in the context of ongoing GC therapy.
The aims of this session are to understand:
The cause and impact of delayed puberty in DMD
Assessment and treatment of delayed puberty in DMD
Follow-up after pubertal induction in DMD
Conversations surrounding sexual health and fertility in DMD
The causes of pubertal delay in DMD will be summarised and the evidence base for pubertal induction reviewed, which confirms that testosterone is safe and well tolerated in this population and may also be associated with an increase in contractile muscle bulk. The variations in international practice will be highlighted using results from a recent survey and in particular, with respect to ongoing surveillance of hypogonadism after pubertal induction. Finally, the views of young men regarding some of the awkward conversations surrounding sexual health and fertility in DMD will be shared from a recent qualitative study.

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S21.5

Genital Surgery in Disorders of Sex Development

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The European Reference Network on Rare Endocrine Conditions (Endo-ERN) wants to take a cautious and evidence-based position regarding genital surgery in individuals with Disorders/Differences in Sex Development (DSD). Given its focus on rare endocrine conditions, including DSD, Endo-ERN's position aligns with the broader European emphasis on human rights, ethical medical practices, and patient-centred care. ENDO ERN wants to address the ethical, medical, and legal considerations surrounding genital surgery in individuals with DSD in Europe and acknowledges intersex as a part of human diversity while providing clarity in a medical or scientific context. It advocates for a shift towards patient-

centred care that prioritizes the rights and well-being of individuals with DSD, particularly children. Recommendations emphasize deferring non-urgent, irreversible surgeries until the individual can provide informed consent whenever possible, strengthening support systems for families, and promoting a standardized European framework that respects human rights, with clearly defined quality indicators for surgery.

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S23.2

Novel genetic causes for CHI

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Congenital Hyperinsulinism is the most common cause of persistent hypoglycaemia in childhood. The condition is clinically and genetically heterogeneous with over 35 different disease genes identified. Routine screening of these genes in individuals living with congenital hyperinsulinism identifies a pathogenic variant in ~50% of cases. Understanding the genetic cause of an individual's hyperinsulinism is critical as it will help to guide medical management. In recent years, genetic discovery efforts in congenital hyperinsulinism have focussed on screening for germline coding variants within genes known to have an important role in the pancreatic beta-cell. Much less attention has been afforded to the non-coding genome. This is largely because of the difficulties in interpreting the impact of non-coding variants on gene regulation. The Exeter Genomics Laboratory is an international referral centre for congenital hyperinsulinism, having received samples from over 4000 individuals living with this condition for genetic testing. Using state-of-the-art technology, we are improving our understanding of the genetics of this condition, which is leading to new knowledge of the pathways governing insulin secretion and importantly is providing more families with a genetic diagnosis. During this lecture I will show how we have developed methods to identify somatic variants in the known hyperinsulinism genes that are present in the pancreas but have remained undetected in leukocyte DNA. Results will also be presented from our genome sequencing studies which show how non-coding variants that disrupt the regulation of genes not normally expressed within the beta-cells, are a common cause of hyperinsulinism. These findings demonstrate, that for some, hyperinsulinism can present for the first time in adulthood- broadening the phenotypic spectrum associated with some monogenic forms of hyperinsulinism.

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S23.3

What is new in CHI therapeutics - Alpelisib

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Congenital hyperinsulinism (CHI) is a disorder of unregulated insulin secretion, leading to severe and persistent hypoglycemia especially in the newborn period. Mutations in the *ABCC8* and *KCNJ11* genes (which encode the SUR1 and the KIR subunit of KATP channels, respectively) are the commonest genetic cause of CHI. These mutations impair KATP channel function, leading to persistent depolarization of pancreatic beta cells and excessive insulin release. Patients with *ABCC8* or KCNJ11mutations present with severe, medically refractory hypoglycemia, necessitating aggressive interventions such as partial or near-total pancreatectomy. The first line drug therapy for CHI is diazoxide, however most patients with *ABCC8*/*KCNJ11* mutations do not respond. Other treatment options include octreotide (both short and long acting), nifedipine and sirolimus but even with these therapies most patients will continue to have episodes of hypoglycemia. Alpelisib, a selective phosphatidylinositol3-kinase (PI3K) inhibitor plays a crucial role in regulating cell growth, insulin signalling, and glucose metabolism. Originally approved for treating PIK3CA-mutated, hormone receptor-positive advanced breast cancer and overgrowth syndromes, alpelisib has also shown efficacy in managing non-islet-cell tumor hypoglycemia.The major side effect of alpelisib in patients with PIK3CA-mutated, hormone receptor-positive advanced breast cancer is hyperglycemia (with diabetic ketoacidosis reported in a few patients). Given the hyperglycemic effect of alpelisib we describe our observations in three patients with severe genetic forms of CHI where we re-purposed Alpelisib therapy for treating the hypoglycemia. Treatment was initiated at 12.5mg orally daily, with gradual dose adjustments based on clinical responses. Outcome measures included blood glucose variability, frequency of hypoglycemic episodes, need for supplemental feeding, and treatment safety. Alpelisib significantly improved glycemic control, reducing the frequency of hypoglycemic episodes in all three patients. This allowed for the tapering of other medications and in two patients discontinuation of all other medications (diazoxide and octreotide) and facilitated a transition to bolus gastrostomy-tube/oral feeding. No significant adverse effects were reported, growth and weight of all the patients remained normal. These observations suggest that alpelisib may be used for treating patients with CHI who are refracotry to all other forms of medical therapy. Randomized controlled trials are needed to assess its long-term safety and efficacy for CHI.

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S24.2

The relevance of Epigentics variability on Phenotype variation

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Our goal is to elucidate mechanisms underpinning developmental programming of disease. Focusing on non-genetic and non-environmental triggers, we've identified Trim28 and Nnat as novel 'probabilistic' regulators of disease outcomes. Loss-of-function mutations, in either gene triggers a unique developmental phenomenon known as 'polyphenism', in which genetically identical animals take on one of several meta-stable phenotypic programs, during development. These models represent the first formal demonstrations of mammalian polyphenism and carry profound implications for our understanding of the origins of disease risk in that they suggest that each individual may have several preferred multi-trait disease susceptibility states. I will share data that (i) characterize the phenotypic and epigenetic distinctions between these states in mice, in the contexts of cancer, obesity and food-addiction; (ii) first dissections of the mechanisms underpinning the developmental disease susceptibility state decision; (iii) provide evidence for alternate developmental trajectories in humans, including a high-dimensional analyses of monozygotic twin discordance and a panUKBB deconvolution that reveals human obesity endotypes. Collectively, these data alter our understanding of the fundamentals of the origins of metabolic disease heterogeneity.

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S25.2

Senolytics and senomorphics: new treatments on the door?

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Cellular senescence is a stress response marked by the upregulation of anti-apoptotic pathways and loss of cellular function while maintaining an active secretory profile. Senescent pancreatic β-cells contribute to the development of Type 2 Diabetes and secrete a unique senescence-associated secretory phenotype (SASP) with potential effects on surrounding cells. Removing senescent β-cells leads to their functional recovery. scRNASeq analysis of mouse and human islets identified different subpopulations of senescent β-cells based on the expression of two cyclin-dependent kinase inhibitors: *Cdkn1a*$^+$ β-cells had reduced expression of functional and hallmark identity genes. In contrast, *Cdkn2a*$^+$ β-cells had a specific SASP profile. *In vitro*, SASP factors induced senescence and impaired insulin secretion, making senescent cells and its SASP a therapeutic target. JAK inhibitors were used to inhibit SASP secretion (senomorphic effect) and were compared to ABT263, which induced apoptosis in senescent cells (senolytic effect). SASP inhibition was confirmed with proteomic analysis of conditioned media from human β-cells, while senolytic action was shown through morphological analysis. In a mouse high-fat diet model of insulin resistance, senomorphic drugs improved blood glucose levels, increased insulin levels, restored glucose responsiveness, and decreased senescence and SASP genes while restoring the β-cell specific transcriptome. Human islets from donors with and without T2D were treated in vitro with senomorphic drugs, which preferentially decreased the *CDKN1A*$^+$ human subpopulation, increased survival, decreased SASP secretion, and improved GSIS in humans. In conclusion, the non-cell autonomous effects of SASP in β-cells can be pharmacologically inhibited to restore β-cell function and identity.

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S26.1

Genetic determinants of normal pubertal timing

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Pubertal timing varies widely and influences lifelong health. We conducted a multi-ancestry GWAS in ~800,000 women, identifying 1,080 genetic signals for age at menarche (AAM), explaining 11% of trait variance. Extreme polygenic scores correlated with significantly altered puberty timing. Exome-wide analyses in 220,000 women identified rare variants, including in *ZNF483*, which nullified polygenic effects. Functional analyses implicated 665 genes, including *GPR83*, a GPCR enhancing *MC3R* signaling, a key puberty regulator. Shared genetic signals with menopause and DNA damage response genes suggest ovarian reserve integrity may influence pubertal onset. We also identified body size-dependent and independent pathways linking puberty timing to metabolic disease risk. These findings illuminate the genetic architecture of puberty, highlighting interactions between common and rare variants and their impact on reproductive health and disease susceptibility.

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S26.2

Definition of puberty onset in boys - secular changes?

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In clinical practice, the preferred method for assessing pubertal onset in boys is the orchidometer, introduced by Andrea Prader in 1966. Puberty is typically defined as beginning when the testicular size reaches 4 ml. However, several studies suggest that a testicular size of 3 ml is strongly associated with the activation of the hypothalamic-pituitary-gonadal axis and subsequent pubertal development. Recent publications indicate a secular trend toward earlier pubertal onset in girls, but data for boys are more limited. This talk will provide an overview of the physical and hormonal changes during puberty and various methods for assessing the onset and progression of puberty in boys. In addition to the orchidometer, the use of ultrasound for measuring testicular volume will be described, with examples from the Bergen Growth Study 2. The Tanner stages for genital and pubic hair development will be presented, as well as hormone measurements. Furthermore, the literature suggesting the relevance of a testicular size of 3 ml in defining the onset of puberty will be discussed. Lastly, we will address the question of whether secular changes are occurring in the age of pubertal onset in boys.

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S26.3

AMH as reproductive marker in healthy females and Turner syndrome patients from birth to adulthood

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The majority of patients with Turner Syndrome suffer from primary ovarian insufficiency (POI). This is a major concern for the patients and their families. To counsel the patients, we need markers of ovarian activity as well as predictors of POI. At centers offering ovarian cryopreservation, this assessment is essential when selecting relevant candidates for the procedure. AMH is a unique marker of ovarian function. In contrast to inhibin B and estradiol produced by mature ovarian follicles, AMH is produced by granulosa cells surrounding small antral follicles. This characteristic expression pattern is essential for the clinical use of AMH in pediatric endocrinology. In adulthood, POI is characterized by amenorrhea and hypergonadotropic hypogonadism. However, many TS girls are diagnosed prenatally due to ultrasound findings, or in mid childhood due to short stature. Due to central inhibition of the HPG axis, it is a challenge to assess ovarian activity in prepubertal girls. However, ovarian activity in prepubertal girls is not shut down completely. Infant minipuberty is characterized by a transient surge of ovarian activity. Even in mid childhood, there is subtle ovarian activity from small antral follicles growing independently from FSH stimulation. Activity from theses follicles contributes to detectable levels of circulating AMH in all healthy girls. Interestingly, each girl maintains her relative AMH during childhood, and AMH in minipuberty correlates therefore with AMH in adolescence. Based on data of circulating levels of reproductive hormones from infancy to adulthood in healthy females and patients with Turner Syndrome, I will discuss the clinical use of markers and predictors of POI.

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S27.1

The biochemical and clinical significance of 11-oxygenated androgens

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For decades, endocrinology has recognised testosterone and 5α-dihydrotestosterone (DHT) as the only potent androgens in human physiology. However, the discovery of adrenal-derived 11-oxygenated androgens, notably 11-ketotestosterone (11KT), has challenged this established view, leading to a reassessment of the androgen pool. In the last decade, 11-oxygenated androgens have been implicated in several disease states, including polycystic ovary syndrome, congenital adrenal hyperplasia, and castration-resistant prostate cancer. This presentation will provide an overview of the adrenal biosynthesis and peripheral metabolism of 11-oxygenated androgens, including their conversion to 11-oxygenated oestrogens. It will also summarise their emerging roles in human health and disease, highlighting the need to incorporate these androgens into routine steroid profiling, particularly in an era when LC-MS/MS is more accessible.

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S27.2

New therapeutic steroid sparing options for Congenital Adrenal Hyperplasia

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Since the pioneering work of Lawson Wilkins in the 1950s, glucocorticoids have been the cornerstone of therapy for patients with congenital adrenal hyperplasia, particularly classic 21-hydroxylase deficiency (21OHD). Glucocorticoids are used both to replace the cortisol deficiency and to provide the missing negative feedback to the hypothalamic-pituitary-adrenal (HPA) axis, to lower the production of unwanted precursors, which are metabolized to androgens. Substantially higher than physiologic glucocorticoid dosing with late-day dosing is often required to correct the adrenal-derived androgen excess, allow normal growth and development, and maintain fertility. This glucocorticoid exposure, however, leads to long-term complications in adults, such as obesity, mood disorders, bone loss, and cardiometabolic dysfunction. Alterative pharmacologic targets have been explored to reduce glucocorticoid exposure in 21OHD. Crinecerfont, a corticotropin-releasing factor type 1 receptor (CRF1) antagonist was trialed in placebo-controlled studies for children and adults with 21OHD. The pediatric trial showed a reduction in androstenedione (A4) of ~50% after 4 weeks, which allowed glucocorticoid dose reduction of 18%, with ~25% A4 reduction by week 28. In the adult trial, A4 also fell ~50% after 4 weeks, which enabled a 27.3% (17% placebo-controlled) glucocorticoid dose reduction, while maintaining A4 at or below baseline. Additional therapeutics targeting the HPA axis are in trials, particularly atumelnant, an orally administered MC2R (ACTH receptor) antagonist, and Lu AG13909, an antibody to ACTH. These treatments might allow simplified and less toxic glucocorticoid regimens for children and adults with 21OHD, to improve short- and long-term outcomes.

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S27.3

Novel approaches to glucocorticoid replacement

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Despite optimal replacement therapy with corticosteroids, patients with adrenal insufficiency continue to experience reduced quality of life and face elevated risks of mortality and morbidity. A significant challenge lies in our inability to replicate the precise, dynamic secretion patterns of cortisol and aldosterone, coupled with the absence of reliable biomarkers to ensure adequate corticosteroid dosing. Conventional hydrocortisone formulations possess short half-lives (approximately 90 minutes), necessitating multiple daily doses. Recently, extended-release hydrocortisone (ER-HC) formulations have been developed, allowing for once or twice daily administration, which are more user-friendly and have demonstrated beneficial effects. Emerging evidence suggests that subcutaneous administration of hydrocortisone via a pump may offer additional advantages. These recent advancements will be presented and discussed.

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S28.1

Diabetes mellitus and Bone fragility: Pathophysiological aspects

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The incidence of diabetes, a disease characterized by high blood glucose levels, is increasing worldwide. Besides the well-known complications of diabetes including cardiovascular disease, retinopathy, nephropathy, and neuropathy, also bone fragility has recently been recognized as a complication of diabetes. In fact, type 1 diabetes is associated with a 6-fold increase in hip fractures with a marked loss of bone mineral density, while type 2 diabetes is associated with a 1.5-fold increase of hip fractures even in the presence of a higher bone mineral density. In both cases, diabetic bone disease is characterized by a low bone turnover and an increased incorporation of advanced glycation end-products into the collagenous matrix, rendering it stiff and inflexible. Moreover, bone vascularization is reduced in diabetic animals; in particular the number of pro-osteogenic H-type vessels is diminished. Experimental evidence shows that elevated ROS production, senescence, and suppressed Wnt signaling contribute to diabetic bone disease. Suppressed Wnt signaling also stimulates the differentiation of adipocytes in the bone marrow, which contribute to an inflammatory, pro-osteoclastogenic milieu. Finally, several miRNAs are differentially expressed any may contribute to diabetic bone disease

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S28.2

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S29.1

Sleep disturbances in patients with pituitary tumours

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Suprasellar tumors that compress the optic chiasm can lead to disturbances in sleep-wake rhythms, possibly due to damage to the brain's biological clock, the suprachiasmatic nucleus (SCN). Studies have shown that pituitary tumors with suprasellar extension impair circadian regulation and thermoregulation. In patients with a history of optic chiasm compression, there is reduced expression of arginine vasopressin (AVP) in the SCN, while vasoactive intestinal peptide (VIP) levels remain unchanged. This suggests selective impairment of the SCN, which may contribute to sleep disturbances. Additionally, patients with a history of chiasm compression show altered skin temperature regulation. Specifically, these patients exhibit lower proximal skin temperature and an absent association between pre-sleep skin temperature gradient and sleep onset latency, indicating disrupted hypothalamic control of both vigilance and thermoregulation. Furthermore, patients with hypopituitarism and optic chiasm compression demonstrate impaired photosensitive retinal ganglion cell (ipRGC) function, as evidenced by a weaker post-illumination pupil response (PIPR) compared to those without chiasm compression. This diminished PIPR is associated with delayed sleep timing but no significant differences in sleep duration or quality. Taken together, these findings support the hypothesis that damage to the hypothalamus, particularly the SCN and associated nuclei, impairs both circadian rhythms and thermoregulatory functions, contributing to sleep disturbances in patients with pituitary tumors compressing the optic chiasm.

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S29.2

Insufficient sleep in obesity: An eating jet lag

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In contemporary society, modern lifestyles adversely impact our sleep and eating routines, particularly the timing of these activities. For example, the access to artificial light at night enables us to eat and stay awake at almost any time, leading to late sleep onset, short sleep duration, and circadian misalignment. In the general population, the most extreme example of circadian disruption is observed among shift workers. However, even non-shift workers who delay activities face mild circadian misalignment, known as social jet lag. This arises from accumulated sleep debt during the week, prompting extended sleep on weekends and resulting in inconsistent sleep patterns. Social jet lag is a potential risk factor for obesity and unhealthy eating habits, primarily due to insufficient sleep. In addition, our research group has shown that social jet lag is associated with breakfast skipping which could also be associated with circadian misalignment and obesity. Considering the aforementioned, we proposed the eating jet lag as a novel marker to study the irregularity in meal timing and its association with obesity. In this talk, we will explore the complex relationship between circadian misalignment and obesity, emphasizing how social and eating jet lag can lead to metabolic dysregulation and weight gain. Circadian misalignment induced from eating jet lag could have a negative impact on glucose metabolism and insulin sensitivity, increasing obesity risk. By examining these mechanisms, we will discuss the broader implications of eating jet lag in health. Although specific clinical recommendations remain inconclusive, we will discuss strategies to mitigate the adverse effects of sleep deprivation on metabolic health, including promoting regular sleep and meal timing.

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S30.1

Thyroid Hormone Resistance

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The syndromes of Resistance to Thyroid Hormone (RTH) are a group of rare disorders that cause relative tissue resistance to the effect of thyroid hormone (TH). Each syndrome has a genetic basis, unique phenotype, and most have a distinct biochemical profile, but nonetheless they remain difficult to diagnose. In this session, I will focus on the presentation, diagnosis and management of two forms of RTH, in childhood and adulthood. RTH beta is characterised by raised thyroid hormones, non suppressed TSH and variable tissue sensitivity to thyroid hormone, often with thyrotoxic features. RTH alpha, more recently identified, causes profound tissue hypothyroidism, despite normal TH levels. At the end of the talk, the audience will be familiar with the presenting features, typical biochemical profile and underlying pathogenic basis RTH alpha and beta, and will be aware of the therapeutic options available for affected patients.

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S30.2

>50 years of neonatal screening - where do we stand?

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Thyroid hormone (TH) is essential for brain development in utero and during the first two to three years of life. The negative effects of TH deficiency on brain development are irreversible. Early detection of TH deficiency in neonates (congenital hypothyroidism (CH) through newborn screening (NBS)) allows for early treatment, thereby preventing brain damage. Research in the 19th century highlighted the importance of early detection and treatment of CH to prevent growth and mental development issues. Newborn screening began in Buffalo, New York, in 1960 with Dr. Robert Guthrie's blood test for PKU. By the 1970s, the thyroid gland's production of thyroxine (T4) and triiodothyronine (T3) was known, and radioimmunoassay enabled detection of thyroid hormone deficiencies. Screening for CH began in 1973 with the measurement of total T4 in dried blood spots. In 1982, an international conference on neonatal thyroid screening with representatives from 34 countries led to widespread screening. Annually, 7-9 million newborns are screened in industrialized countries. Primary CH affects about 1 in 3800 to 1 in 4000 newborns, mainly due to thyroid dysgenesis (90%). The conference recommended focusing on detecting increased TSH levels and screening premature infants due to often low T4 levels. Currently, worldwide, the majority of NBS programs for CH employ TSH as the primary screening marker although a select few programs still utilize T4 as the primary marker, enabling the detection of both primary and central CH. However, neonatal screening for CH remains challenging, with continuous efforts to improve algorithms by adapting testing protocols, and using reference intervals for screening parameters. New developments, such as machine learning, and DNA-based screening, are being explored to enhance screening performance and reduce the number of false positive referrals. This presentation provides an overview of the aspects of the screening on CH from the start of screening to the present.

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S31.2

Germline variants in non-medullary thyroid cancer'

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Recognizable features of a genetic predisposition to cancer are the development of 1 or more malignancies at an earlier than expected age and/or familiar clustering of cancer. Although nonmedullary thyroid carcinoma (NMTC) meets these characteristics (eg, 16% diagnosed below 35 years, increased risk for a second primary tumour and a 3- to 10-fold increased risk in relatives), most NMTC cases remain genetically unexplained. Familial nonmedullary thyroid cancer constitutes 3% to 9% of all thyroid cancers and is recognized as a distinct clinical entity, with heritability partially attributable to tumour predisposition syndromes such as PTEN hamartoma tumour syndrome, Carney complex, familial adenomatous polyposis, DICER1 syndrome, and Werner syndrome. In addition, genome-wide association studies and family-based case series have suggested a variety of possible associated genes (eg, DIRC3, FOXE1, NRG1, SMAD3, SRGAP1, SRRM2, and TITF-1/NKX2.1). Furthermore, recent studies indicate that NMTC heritability may be partly polygenic. Besides important clinical implications for the index patient, identification of a causative germline variant also facilitates cascade testing and surveillance of relatives, allowing early identification of (pre)malignant conditions. Currently no clear guidelines for genetic testing for NMTC are available. An important unanswered question is whether patients with NMTC should undergo genetic testing and, if so, which type of genetic test (eg, single gene/gene panel/whole exome or genome sequencing) should be performed. Recent genetic screening of a large, unbiased paediatric NMTC cohort detected a relatively high prevalence (13%) of P/LP germline variants in well-known tumour predisposing genes. This prevalence led us to recommend genetic counselling for all patients with childhood NMTC.

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S33.3

Pregnancy following bariatric surgery

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With the rising worldwide incidence of obesity, particularly in the young, bariatric surgery offers an effective method of meaningful and sustained weight loss. So, pregnancy after bariatric surgery is now a common scenario. Most women have good pregnancy outcomes, with reduced rates of pre-eclampsia and gestational diabetes, however, rates of stillbirth and small-for-gestational-age babies are increased,In this talk some unresolved questions in the management of pregnancy after bariatric surgery as the modification of glucose homeostasis, the diagnosis of diabetes,the importance of a strict follow up during pregnancy, the assesment and correction of micronutrient and/or macronutrient deficiencies management of preexisting obesity related complications will be underlined.

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S34.1

Don't mess with my iodine! chemical-induced perturbation in synthesis and metabolism of thyroid hormone impairs brain development

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The complexity of thyroid hormone (TH) signaling pathways presents a myriad of targets for potential interference by environmental contaminants. Many of these sites of action can be detected by alterations in T3 and T4 concentrations in the blood. Iodine is essential for production of TH, severe deficiencies leading to hypothyroidism. Given the importance of TH in brain development, maintaining iodine status is especially critical during pregnancy - pregnant women with iodine deficiency (ID) and their progeny may be particularly susceptible to environmental exposures that impact the TH system. In this presentation, a rodent pregnancy model on perchlorate, an environmental contaminant that interferes with the iodine transport, and iopanoic acid (IOP), a chemical that interferes with TH metabolism will be described. Perchlorate, when combined with dietary ID induces structural defects in developing brain, alters synaptic transmission, and impairs behavioral measures of sensory gating. Reductions in serum TH in the fetus that persist to the first week of life are required to induce these changes, changes that were greatly exacerbated under conditions of ID. *Decreases* in serum TH induced by perchlorate stand in stark contrast to *increases* in serum T4 observed in response to exposure to IOP. IOP blocks deiodinases, enzymes responsible for activating and deactivating TH and maintain optimal receptor-level concentrations for T3-mediated gene transcription. Despite a peripheral state of hyperthyroidism, brain T3 is reduced in the newborn pup and a neuroanatomical defect similar to that reported for perchlorate was present in the brains of offspring. Together, the dissociation of peripheral vs central TH effects by IOP demonstrate the criticality of tissue levels TH while the combined effects of perchlorate and ID underscore the need to consider additional environmental stressors when determining the impact of chemical exposure on brain function. *Does not reflect EPA policy*.

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S34.2

Neurodevelopmental effects of thyroid hormone system disruption – insights from the ATHENA project

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The aim of the ATHENA project was to develop new test methods for detecting thyroid hormone (TH) system disruption. The primary objective of the *in vivo* studies was to identify new sensitive and specific neurodevelopmental endpoints that may serve as reliable indicators for such disruption. Several neurological endpoints were examined in rat offspring exposed to two thyroid peroxidase (TPO) inhibiting substances: the drug methimazole and the pesticide amitrole, followed by studies examining effects from additional substances with different modes of action. Developmental exposure to the two TPO-inhibiting substances induced a range of adverse neurodevelopmental effects, including changes in cortical gene expression, altered motor activity levels, formation of periventricular heterotopia, reduced parvalbumin-positive cells in the cortex and hippocampus, and decreased TH concentrations in the brain. These effects were consistently observed when TH concentrations in serum were reduced by 50% or more during foetal and postnatal development. By including transcriptomic analyses of the hippocampus, the project also aimed to identify candidate biomarker genes that may be more sensitive indicators of TH system disruption than the identified morphological endpoints. Exposure to chemicals affecting the TH system through other modes of action caused variable effects on TH levels. In most cases, the observed TH reductions were not substantial enough to adversely affect the newly identified TH-specific neurological endpoints, indicating that these methods may lack the sensitivity needed to protect human brain development from adverse effects caused by TH system disruptors. In light of these findings, the ATHENA consortium recommends that, in a regulatory context, changes to serum and brain TH concentrations in rodents should be recognized as predictors of adversity in their own right. Overall, the ATHENA project has provided critical insights into the impacts of TH system disruption on brain development and has suggested improved regulatory measures, for better protection of human health.

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S34.3

EDC targets of the thyroid hormone system - HTS and in vivo assays for identification of potential reference compounds'

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The thyroid hormone system (THS) is a main target of endocrine-disrupting chemicals (EDC), natural or human-made chemicals that may interfere with hormonal systems during development, adolescence or adulthood. EDC interference, especially during sensitive developmental windows of susceptibility, may lead to irreversible setpoint changes of hormonal feedback regulation, inadequate function of hormone-regulated processes or predispose to disease development in adulthood or subsequent generations. Human, especially, brain development critically depends on adequate provision of maternal T4, particularly during first trimester fetal thyroid development and maturation, lessons learned from impact of iodide deficiency and genetic disorders affecting development and function of the THS. *In silico*, *in vitro*, *in vivo* test systems and animal experimental models allow the systematic, hypothesis-free or targeted interrogation of potential interference of single or groups of chemicals with relevant functional components of the THS system. ~70 000 low molecular weight chemicals, representing 1/5 of the current chemical universe, were screened for five THS targets (hr DIO1-3, DEHAL1, MCT8) of EDC using non-radioactive high throughput screening assays photometrically detecting iodide by the Sandell-Kolthoff reaction. Identified inhibitors are further prioritized with respect to their potency, target specificity, cytotoxicity and potential biological, medical or environmental relevance. Prioritized chemicals undergo testing in selected (established, validated, novel) *in vitro* test methods (reporter assays, cellular models, organoids) applicable for regulatory purposes by comparison with reference compounds affecting the respective THS target. Top hits are functionally characterized *in vivo* using mechanistically meaningful and biologically-informative experimental models for living organisms, which reflect intact function and regulation of the THS during and/or after completion of development (*Xenopus* amphibian metamorphosis, zebrafish, rodent). Application of 3R principles, development of New Approach Methodologies (NAM), and such data-based focused *in vivo* testing for prioritized relevant chemicals will accelerate EDC characterization, increase hazard-predictive power and chemicals safety for environmental and human health.

References
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S35.2

Genetic regulation of osteoarthritis pathogenesis

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Osteoarthritis causes debilitating pain and disability, resulting in a considerable socioeconomic burden, yet no drugs are available that prevent disease onset or progression. Osteoarthritis is a complex trait, and the currently reported genome-wide associated loci explain only a small proportion of its heritability. We previously developed and validated a rapid-throughput imaging pipeline to detect signs of osteoarthritis in the mouse knee joint. We utilised this pipeline to phenotype mutant mice generated by the International Knockout Mouse Consortium. We identified genes with functional involvement in osteoarthritis pathogenesis, including the homeobox gene *Pitx1* as a potential key regulator of disease progression. Using this pipeline, we were able to functionally characterize human osteoarthritis candidate genes in mouse models. Finally, we utilised this pipeline to phenotype mice with an osteoarthritis-associated polymorphism in the *Dio2* gene and demonstrated a protective role in disease onset, with significant public health implications. This work aims to both accelerate functional gene discovery in osteoarthritis and facilitate drug discovery opportunities for this common, incapacitating chronic disease.

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S36.3

Deficient anterior pituitary with common variable immune deficiency (DAVID syndrome)

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Deficient Anterior pituitary with common Variable Immune Deficiency (DAVID) syndrome results from heterozygous mutations of the nuclear factor kappa-B subunit 2 (*NFKB2*) gene, causing adrenocorticotropic hormone deficiency (ACTHD) and primary hypogammaglobulinemia. Only a few cases of DAVID syndrome have been reported since its first description by our team through the international multicenter GENHYPOPIT network (Quentien MH et al. JCEM 2012). We analyzed 28 cases with ACTH deficiency published from 2012 to 2022 (Mac TT et al. J Neuroendocrinol. 2023). ACTH deficiency was the only hormone deficiency in 79% of patients, but some patients harbored growth hormone (GH) and thyroid stimulating hormone (TSH) deficiencies. The first presenting symptoms were sinus/pulmonary infections (82%, mean age of 3 years) and alopecia (mean age of 4.7 years). ACTH deficiency was the third presenting condition (mean age at diagnosis: 8.6 years). All patients had hypogammaglobulinemia (decreased IgA and IgM levels), and 57% of patients had at least one autoimmune manifestation. Heterozygous mutations at the 3' end of the *NFKB2* gene, coding for the C-terminal domain of the protein, were identified in all cases. While NFKB signaling plays a crucial role in the immune system, its connection to endocrine symptoms is unclear. We established a human disease model to investigate the role of NFKB2 in pituitary development by creating pituitary organoids from CRISPR/Cas9-edited human induced pluripotent stem cells (hiPSCs). Introducing homozygous $TBX19^{K146R/K146R}$ missense pathogenic variant in hiPSC, an allele found in congenital isolated ACTHD, led to a strong reduction of corticotrophs number in pituitary organoids. Then, we characterized the development of organoids harboring $NFKB2^{D865G/D865G}$ mutations found in DAVID patients. $NFKB2^{D865G/D865G}$ mutation acted at different levels of development with mutant organoids displaying changes in the expression of genes involved on pituitary progenitor generation (*HESX1*, *PITX1*, *LHX3*), hypothalamic secreted factors (*BMP4*, *FGF8*, *FGF10*), epithelial-to- mesenchymal transition, lineage precursors development (*TBX19*, *POU1F1*) and corticotrophs terminal differentiation (*PCSK1*, *POMC*), and showed drastic reduction in the number of corticotrophs (Mac TT et al. Elife. 2024). Our results provide strong evidence for the direct role of *NFKB2* mutations in the endocrine phenotype observed in DAVID syndrome patients and demonstrate the role – to be further analyzed - of NFKB2 in pituitary differentiation, especially for the corticotroph lineage.

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S37.1

The genetic spectrum of PA: from monogenic disorders to aldosterone dysregulation in hypertension

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Primary aldosteronism is the most common form of secondary arterial hypertension. Its prevalence increases with the severity of hypertension, reaching up to 25% in patients with treatment resistant hypertension. Due to the difficulty of its diagnosis, only a minority of patients are tested for PA and even less are appropriately treated. Somatic and germline mutations have been identified in a majority of aldosterone producing adenoma and in familial forms of primary aldosteronism. In most cases, genetic abnormalities are found in genes coding for ion channels (*KCNJ5*, *CACNA1D*, *CACNA1H*, *CLCN2*, *SLC30A1*, *MCOLN3*) or pumps (*ATP1A1*, *ATP2B3*). They occur as somatic mutations in aldosterone producing adenoma and as germline mutations in familial forms of the disease. Mutations in these genes affect intracellular ion homeostasis and/or cell membrane potential, leading to increased intracellular calcium concentrations and activation of calcium signalling, the main regulator of aldosterone biosynthesis. Double mutations in *CTNNB1* and *GNAQ/GNA11* have been identified in aldosterone producing adenoma presenting in puberty, pregnancy and menopause, while somatic mutations in *CADM1* in APA have revealed novel mechanisms of regulation of aldosterone biosynthesis. Beyond categorically overt PA, recent evidence suggests a continuum of dysregulated aldosterone production which affects a substantial proportion of patients with hypertension. Genome-wide association studies suggest that common genetic variation may underlie dysregulated aldosterone production in the general population, leading to PA in extreme cases. Remarkably, PA susceptibility loci have been associated with hypertension related traits and are in part shared between unilateral and bilateral forms of PA. This represents a paradigm shift in our understanding of PA, suggesting a genetically determined continuum between dysregulated aldosterone production and PA in hypertension.

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S39.1

Precision medicine in diabetes

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People are all different, and this is no different when we consider people with diabetes, yet the current approaches to management of diabetes tend to treat everyone the same. The field of precision medicine aims to recognise these differences – whether at the level of their phenotype or at the molecular level. Faced with multiple, and increasing, treatment options for diabetes as well as increasing healthcare costs there is a clear need to target therapy to maximise benefit and reduce harm for every patient with diabetes. This talk will discuss advances in precision medicine and pharmacogenetics in diabetes. I will highlight recent work on how phenotypic variation matters, and how this maps to genetic variation, and will provide an overview of how genetic variants alter glycaemic response to commonly used diabetes drugs and how these inform on disease and drug mechanism. I will finish with an overview of iDiabetes – an intelligent diabetes platform that we will be using to implement precision diabetes care in Tayside in 2024.

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S39.3

The impact of rare gene variants in common diabetes and obesity

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The boundary between monogenic and polygenic type 2 diabetes (T2D) or oebsity is more fluid than previously thought. Emerging research has revealed an intermediate oligogenic form of T2D/obesity, which serves as a crucial genetic bridge between these two extremes. In this presentation, I will discuss recent scientific advances supporting the classification of genes involved in oligogenic T2D/obesity. While polygenic T2D/obesity research has significantly advanced our understanding of genetic susceptibility, it has faced limitations in pinpointing direct causal relationships between genetic signals and the molecular mechanisms driving the disease. In contrast, studies on oligogenic T2D/obesity have provided clearer causal links between specific genes and disease risk, uncovering novel therapeutic targets. By recognizing oligogenic T2D/obesity as a distinct genetic entity, we open new avenues for research and precision medicine, moving beyond broad genetic risk scores toward targeted therapeutic interventions.

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S40.2

Central regulation of body weight

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Brain lipid sensing and adaptive response to modern food environment: a culprit in obesogenic environment? While the over-consumption of energy-dense foods is now clearly identified as one of the main causes of obesity, there is a large body of evidence supporting that the development of obesity and related disorders is also the result of an interaction between specific genetic polymorphisms and the modern food environment. High circulating triglyceride (TG) and reward-dysfunction re common hallmark of obesity and obesogenic environment. In the reward dopaminergic circuit, neurons specifically express the lipoprotein lipase (LPL), an enzyme able to hydrolyze TG, suggesting that circulating TG might modulate the activity of dopaminergic and dopaminoceptive neurons. W have discovered that circulating TG act directly onto DA-D2 (DR2) receptors expressing neurons modulating the reinforcing and motivational values of feeding. In humans, we discovered that the neural responses to food cues show a significant correlation between postprandial increases in TG and the presence of Drd2/Taq1A genetic polymorphism. TaqIA is located in the gene that codes for the Ankyrin repeat and kinase domain containing 1 kinase (ANKK1) near the dopamine D2 dopamine receptor (DR2) gene. It affects 30 to 80% of the population and its homozygous expression of the A1 allele correlates with a 30 to 40% reduction of striatal DR2, a typical feature of addiction, over-eating and other psychiatric pathologies. Using genetic approaches, we revealed that Ankk1 loss-of-function in dorsal and ventral striatum leads to alteration in learning, impulsive, and flexible behaviors resembling the endophenotypes described in A1 carriers. We also observed an unsuspected role of ANKK1 in striatal DR2-expressing neurons in the regulation of energy homeostasis and documented differential nutrient partitioning in humans with versus without the A1 allele. Altogether, our data indicates that genetic variant of TaqIA greatly influence how the reward system response to modern food environment and particularly nutritional lipids to control behavior and metabolism.

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SS1.1

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SS1.2

Pharmacological treatment of obesity in adults and its impact on comorbidities

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Pharmacological treatment of obesity is passing through many changes in the last decades; different agents have been approved, and newer options are leaning towards higher efficacy and a more favourable safety profile; however, medications approved for a longer time are still available and useful for many patients. This presentation will focus on the 2024 Update Position Statement of Specialists from the Brazilian Association for the Study of Obesity and Metabolic Syndrome (Abeso) and the Brazilian Society of Endocrinology and Metabolism (SBEM), with the aim of reviewing all the approved medications for the management of obesity in Brazil (sibutramine, orlistat, liraglutide, semaglutide and bupropion/ naltrexone fixed dose), with the addition of tirzepatide. The presentation will focus on efficacy, safety profile and the impact of drugs on different comorbidities.

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SS1.3

Epigenetic memory of fat cells: the role in weight regain

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Reducing body weight to improve metabolic health and other comorbidities is a primary goal in treating obesity. However, maintaining weight loss is a considerable challenge, especially as the body is believed to retain an obesogenic memory via biological imprinting of prior obese states that contributes to the defence of body weight. Yet, overcoming this hurdle to long-term effective treatment is difficult because the molecular mechanisms underpinning this phenomenon remain largely unknown. Here, by using single-nuclei RNA-sequencing, we show that both human and mouse visceral adipose tissue retain a cellular transcriptional memory after appreciable weight loss. Furthermore, we observed that the mouse adipocyte epigenome continues to bear obesity-induced alterations, negatively affecting adipocyte function. In mice adipocytes carrying this obesogenic epigenetic memory respond differently to nutritional stimuli, resulting in accelerated rebound weight gain. We find that the epigenetic memory can explain future transcriptional deregulation in response to further high-fat diet feeding. Together, our data suggests the existence of an obesogenic memory in adipocytes, and likely other cells, largely based on stable epigenetic changes. These changes appear to prime cells to respond in a pathological manner to an obesogenic environment and may contribute to the problematic "yo-yo" effect on body weight observed with dieting. Targeting these changes could potentially improve long-term weight management and health outcomes

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Debate Sessions

D1.1

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D1.2

Metformin is not effective and safe during pregnancy in women with PCOS

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Metformin therapy induces weight loss and improves insulin resistance in women with PCOS. In pregnancy, gestational diabetes mellitus (GDM) is more prevalent in women with PCOS and overweight compared to women without PCOS. Disappointingly, GDM incidence was similar in women with PCOS treated with metformin or placebo, initiated late in 1st trimester. Furthermore, no significant longterm beneficial effect was seen in metabolic health of women treated with metformin versus placebo. Pregnancy is a window of sensitivity in offspring, and metformin may pose a risk, metformin passes placenta and maternal metformin intake results in therapeutic metformin concentrations in umbilical cord blood, hence metformin exposure of offspring is quite high. However, metformin therapy had potentially beneficial, lowering effect on maternal testosterone, in women with PCOS carrying a boy. Testosterone is elevated during healthy pregnancy, but women with PCOS have significantly higher testosterone levels than women without PCOS. Moreover, boys have been reported more susceptible to maternal testosterone regarding risk of neurodevelopmental disorders, autism spectrum disorder, but there is no data on maternal metformin treatment and autism spectrum disorder in PCOS. However, available data regarding metformin and neurodevelopment are not fully reassuring, as metformin therapy in pregnancy may be linked to borderline reduced cognitive function in children. Overall, metformin therapy cannot be recommended for pregnant women with PCOS due to lack of effect and offspring safety concerns, supporting previous guidelines.

Disclosure of interest
None declared

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D2.1

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Meet the Expert Basic Scientist Sessions

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MTEBS3

Breaking down signalling in hypogonadotropic hypogonadism

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Human reproduction is regulated by a small number of hypothalamic neurons secreting the neurohormone GnRH. During development, GnRH neurons migrate from the nasal placode to the hypothalamus by following the terminal nerve to position into the medial preoptic area of the hypothalamus. Once there, GnRH neurons project to the median eminence where the decapeptide is released and transported to the pituitary for the production of gonadotropins, which in turn regulate the production of gonadal sex steroids. Defects in the development or funciton of GnRH neurons lead to hypogonadotropic hypogonadism (HH), a genetic class of disorders due to GnRH deficiency. The genetics of HH is complex and not fully understood with 50% of the cases still unexplained. During the seminar, I will illustrate how Semaphorins, a class of molecules that play key roles during embryonic development and cancer progression, play distinct but essential roles for the correct functioning of the GnRH neuronal system. During the seminar I will also explain how dysfunctional semaphorin signalling can be causing related genetic forms of infertility.

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MTEBS4

Senescence in peadiatric pituitary tumours

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Background
Senescence is a cellular process that is normally associated with ageing. In fact, senescent cells are rare in the tissues of children and young adults. However, our research has shown that adamantinomatous craniopharyngioma (ACP), a clinically aggressive paediatric pituitary tumour, contain cells that express the hallmarks of cellular senescence and senescence associated secretory phenotype (SASP). Moreover, we have hypothesised that these senescent cells, through their SASP, promote tumourigenesis in both mouse and human ACP. To test this hypothesis, we have analysed the effects of the ablation of senescent cells and modulation of their SASP using genetic ACP mouse models and pharmacological approaches.
Methods
Genetic murine ACP models that mimic human ACP (*Hesx1*$^{Cre/+}$; *Ctnnb1*$^{loxex3/+}$ and the inducible adult *Sox2*$^{CreERT2/+}$; *Ctnnb1*$^{loxex3/+}$ models) were used. ACP models were combined with a novel *p21-stop-FDR* mouse model, which expresses a fusion protein of diphtheria toxin receptor (DTR) with a fluorescent mCherry reporter from the *Cdkn1a* (p21) locus. This mouse model can report and ablate p21-expressing cells, including the senescent cluster cells in the ACP models. The ACP models were also combined with a new *R26-stop-mBRF1* model, which allows attenuation of the SASP by degrading the mRNAs of many inflammatory SASP factors. In-vivo survival studies, ex vivo culture and immunohistochemical characterizations were carried out.
Results
Ablation of senescent cluster cells or attenuation of the SASP using genetic mouse models, leads to asignificant reduction in ACP tumour burden and increased mouse survival. In addition to inhibitors of anti-apoptotic proteins, we show that a new senolytic compound targeting the ER-Golgi protein transport machinery can also ablate senescent cluster cells in ACP mouse models ex-vivo.
Conclusion
Our results demonstrate a critical role of senescent cells in ACP tumourigenesis and identify these cells as potential targets for senotherapies.

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MTEBS5

Abstract Unavailable

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MTEBS6

Beta is better: current progress in preserving and restoring beta cell function

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Preserving and restoring beta cell function is a key objective in efforts to modify the progression of type 1 diabetes (T1D). This *Meet the Expert* session will feature a leading expert who will discuss the latest advances in beta cell preservation, regeneration, and replacement therapies. Given the autoimmune nature of T1D, strategies aimed at protecting residual beta cells from immune attack remain crucial. Additionally, regenerative approaches seek to enhance beta cell survival and proliferation through small molecules, gene editing, and reprogramming strategies. Recent progress in stem cell-derived beta-like cells and islet transplantation offers potential solutions for restoring insulin production. Advances in encapsulation technologies and immune evasion strategies aim to improve the long-term survival and function of transplanted cells. Despite these promising developments, challenges remain, including immune rejection, the need for lifelong immunosuppression, and the difficulty of achieving full functional integration of beta cells. In this session, the expert will provide insights into current research, clinical applications, and the future of beta cell-directed therapies in T1D. Attendees will have the opportunity to engage in discussions on the most promising approaches and ongoing clinical trials, as well as the challenges that must be addressed to achieve durable beta cell function and a potential cure for T1D.

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MTEBS7

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Meet the Expert Sessions

MTE1

Fertility matters: exploring the impact of lipodystrophy

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Lipodystrophy syndromes are rare diseases characterized by deficiency of subcutaneous adipose tissue. This may affect the entire body (generalized lipodystrophy) or large portions of the body (partial lipodystrophy). Decreased body fat leads to both low levels of the adipokine leptin, and severe insulin resistance due to ectopic lipid storage. Reproductive consequences of lipodystrophy stem from two distinct mechanisms. In patients with severe leptin deficiency (usually generalized lipodystrophy), low leptin leads to an energy conservation state, resulting in partial hypogonadotropic hypogonadism. In patients with both generalized and partial forms of lipodystrophy, insulin resistance leads to hyperinsulinemia as a compensatory response. High insulin acts on the ovaries to create a phenotype comparable to polycystic ovary syndrome (PCOS), with ovarian enlargement, hyperandrogenism, and anovulatory cycles. Hyperinsulinemia also may lead to excess production of 11-oxygenated androgens by the adrenal glands by upregulating *CYP11B1*. As a consequence of both hypogonadotropic hypogonadism and PCOS, fertility is greatly diminished in women with generalized lipodystrophy and is moderately reduced in women with partial lipodystrophy. Leptin replacement ameliorates both hypogonadotropic hypogonadism and insulin resistance with consequent hyperandrogenism and restores fertility in many women with generalized lipodystrophy. However, pregnancies in women with lipodystrophy have high complication rates, including miscarriage in 34-48%, diabetes (either preexisting or gestational) in over 50%, and preeclampsia in 39-45%. For patients with lipodystrophy in need of contraception or hormone replacement, use of oral estrogens, as in combination oral contraceptive pills, is contraindicated due to the risk of severe hypertriglyceridemia that may precipitate acute pancreatitis. Instead, progestin only or non-hormonal contraceptives are preferred, and transdermal estrogen should be used if estrogen replacement is needed.

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MTE2

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MTE3

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MTE5

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MTE6

Management of ACC during the ages

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Adrenocortical carcinoma (ACC) is a rare but highly aggressive endocrine tumor with a relatively poor prognosis, which depends on disease stage, resection status, and tumor grading. Surgery remains the cornerstone of treatment and the only realistic chance for cure. However, even after complete resection, a significant proportion of patients remain at high risk for recurrence. Beyond surgery, treatment options are limited, with scientific evidence often based on small retrospective studies, leading to considerable uncertainty in clinical decision-making. This lack of robust data is even more pronounced in pediatric patients, whose management is largely extrapolated from studies in adults. Recent guidelines have provided recommendations for the clinical management of ACC, yet the supporting evidence for many of these recommendations remains weak. From a clinical perspective, some critical questions need to be addressed, such as identifying patients who will benefit most from different adjuvant therapies, as well as refining the management of patients with recurrent disease, where treatment strategies remain uncertain. Additionally, managing patients with advanced ACC presents a significant challenge, as responses to the best available systemic therapy, EDP plus mitotane, remain limited. This presentation will explore the current state of ACC management, highlight ongoing challenges, and discuss potential strategies to improve outcomes.

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MTE7

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MTE8

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MTE10

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MTE11

Hot-Topic Osteoanabolic therapies: when to choose what

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Osteoanabolics, i.e., agents that stimulate the osteoblast to form new bone, are the most efficacious among antiosteoporotic regimens and are considered as the spearhead of severe osteoporosis management. Currently available osteoanabolic agents can be divided into molecules that bind and stimulate the receptor type 1 of parathyroid hormone (PTH1R), teriparatide (TPTD) and abaloparatide (ABL), and monoclonal antibodies against sclerostin, with romosozumab (ROMO) to be the only representative of the class in clinical practice. Osteoanabolic agents increase BMD and bone strength while being more effective than antiresorptives in reducing fracture risk in postmenopausal women. Osteoanabolic agents typically serve as a second line therapy in case of antiresorptives' failure. However, they could (and should) also be used as a first line treatment in patients at high fracture risk, given that they perform better when given in treatment-naïve patients and that in patients at very high/imminent fracture risk, a rapid fracture risk reduction is critical to prevent new fractures. Among osteoanabolics, ROMO was more effective than TPTD in increasing BMD in treatment-naïve women and in women previously treated with bisphosphonates but there is no direct comparison of the antifracture benefits of the two agents. In contrast, in a head-to-head comparative study ABL achieved greater BMD increases at the hip than TPTD and led to a greater reduction of major osteoporotic fractures but with no differences in vertebral or non-vertebral fracture risk. There is no direct comparison of ROMO with ABL at present. With PTH1R agonists, stimulation of bone formation is maintained for as long as their administration is continued, the increase of bone formation with ROMO seems to be transient, lasting only for the first few months of treatment, with suppressed bone formation for the remainder of therapy. ROMO might have an advantage over PTH1R agonists in patients with renal insufficiency as well as in patients with hypercalcemia, hypercalciuria or nephrolithiasis, and hyperuricemia. On the opposite, PTH1R agonists may have an advantage over ROMO in low-bone turnover states and in cases of rare complications associated with prolonged bone turnover suppression, such as the osteonecrosis of the jaw and the atypical fractures. ROMO is contraindicated in patients with a history of myocardial infraction or stroke and should be used with caution in patients with cardiovascular risk factors. Among osteoanabolic agents only TPTD is approved for the treatment of male osteoporosis and glucocorticoid-induced osteoporosis. Finally, convenience of administration, reimbursement by national health systems and length of clinical experience may influence the decision of which osteoanabolic agent to use.

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MTE12

Management of endocrinopathies induced by cancer therapy

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Cancer therapies, including chemotherapy, radiation, immune checkpoint inhibitors (ICIs), and targeted agents, can lead to significant endocrine dysfunctions, impacting patient outcomes and quality of life. Endocrinopathies such as hypothyroidism, adrenal insufficiency, diabetes, hypophysitis, and hypogonadism are frequently observed, necessitating early detection and comprehensive management. Thyroid dysfunction, commonly triggered by radiation and ICIs, requires regular thyroid function monitoring and appropriate levothyroxine replacement. Immune-related hypophysitis, often associated with CTLA-4 inhibitors, necessitates hormone replacement, including glucocorticoids, to prevent adrenal crisis. Similarly, ICI-induced adrenalitis warrants prompt glucocorticoid therapy, with stress dosing during acute illness. Cancer therapy-related diabetes, particularly from ICIs and glucocorticoid use, may require insulin therapy and close glucose monitoring. Hypogonadism, resulting from chemotherapy, radiation, or androgen deprivation therapy, should be assessed with hormonal evaluations and managed with hormone replacement where appropriate. Additionally, osteoporosis is a concern in patients receiving androgen deprivation or aromatase inhibitors, necessitating bone mineral density monitoring and interventions such as bisphosphonates or denosumab. Effective management of therapy-induced endocrinopathies involves a multidisciplinary approach integrating oncologists, endocrinologists, and primary care providers. Regular endocrine assessments, individualized hormone replacement, and patient education play pivotal roles in optimizing long-term outcomes. As cancer survival rates improve, proactive identification and management of these endocrine complications are essential to enhancing patient well-being and treatment success.

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MTE13

Management of the child with ambiguous genitalia

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Managing ambiguous genitalia in newborns requires a multidisciplinary approach, involving pediatric endocrinologists, geneticists, neonatologists, urologists, and psychologists. A DSD team provides individualized psychosocial support to families. A structured evaluation is crucial to identify the underlying cause and assess any associated health risks. Initial workup includes clinical, biochemical, and genetic investigations to guide diagnosis. The clinical evaluation includes a thorough history (maternal drug use, family history of disorders/differences of sexual development (DSD), unexplained neonatal deaths) and physical examination (including anogenital measurements). Urgent investigations should rule out life-threatening adrenal insufficiency in cases of suspected congenital adrenal hyperplasia (CAH), requiring immediate glucocorticoid (GC) and mineralocorticoid (MC) therapy. Biochemical tests include measurement of sex steroids, adrenal hormones, gonadotropins, and anti-Müllerian hormone (AMH) to assess gonadal function. Genetic testing, including karyotyping and next-generation sequencing panels, helps determine the molecular diagnosis, guiding management decisions. Treatment of children with adrenal insufficiency requires the immediate initiation of GC and MC replacement. Hormone therapy may also be required for androgen excess or deficiency at follow-up. Sex assignment involves shared decision-making with parents and a DSD team, considering long-term outcomes. Psychological support is essential. Surgical intervention remains controversial and is increasingly delayed to preserve bodily autonomy, with early surgery discouraged unless medically necessary. Long-term care consists of lifelong follow-up to ensure hormonal balance, fertility potential, and psychosocial well-being. Support from DSD network teams helps families navigate challenges, fostering acceptance and inclusivity. A comprehensive, ethical, and individualized approach ensures the best outcomes for children with ambiguous genitalia. In this MTE, the management of two teaching cases, one manifesting at birth and one presenting in prepuberty, will be discussed.

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MTE14

Diagnosing and managing AVP excess

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Hyponatremia often presents significant challenges in both its differential diagnosis and management. This presentation will address key concepts and recent developments to assist clinicians in overcoming these challenges. Pathophysiologically, hyponatremia is marked by an excess of arginine vasopressin (AVP), which can be "appropriate" in response to hypovolemia or "inappropriate" due to underlying conditions, medications, or other triggers. The most common cause of inappropriate AVP secretion is the syndrome of inappropriate antidiuresis (SIAD). This presentation will offer a practical diagnostic approach to hyponatremia, aiming to differentiate its various underlying causes, including SIAD. In terms of treatment, the key distinction is whether hyponatremia is acute and symptomatic—requiring immediate intervention with hypertonic saline—or chronic, where overcorrection must be avoided to prevent osmotic demyelination. The management of chronic hyponatremia should focus on the underlying cause while also addressing the water excess. Fluid restriction remains the first-line treatment for SIAD, although additional therapies are often needed to promote free water excretion. Recent years have seen the emergence of new treatment options, such as oral urea, high-protein diets, SGLT2 inhibitors, and tolvaptan. This presentation will review the scientific evidence supporting these developments and provide practical guidance for clinicians on how to implement them.

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MTE15

Abstract Unavailable

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MTE16

Hormone treatment in transgender teenagers

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An increasing number of transgender adolescents seek hormone treatment because they wish to align their body with their gender identity in order to reduce gender dysphoria. Medical care for adolescents should be offered by a multidisciplinary team, including mental health professionals as well as medical specialists. First a psychological and clinical assessment is performed, followed by counselling about medical treatment options and alternatives and their benefits and risks. The possible impact of treatment on fertility and options for fertility preservation are important topics in counselling. Several treatment options exist to suppress sex hormones and to induce sex characteristics consistent with gender identity. Care should be tailored to the specific needs of the adolescent. Current guidelines on hormone treatment and treatment monitoring will be reviewed. The transition from paediatric to adult care is an important phase to ensure adolescents receive appropriate long-term follow-up. This phase also requires attention to topics such as education, employment, relationships and sexual functioning. Transgender care, especially for adolescents, has become the subject of political and societal debate. Reviews have concluded there is a lack of high-quality evidence in this area. An increasing body of outcome data of hormonal treatment for transgender adolescents is available from observational studies, including data on mental health, development of secondary sex characteristics, growth and adult height, body composition, bone mineral accrual, and treatment continuation/discontinuation. However, long-term data are still limited. Therefore care is ideally combined with collection of data for research purposes.

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MTE17

Management of Adrenal incidentaloma

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Definition
Adrenal incidentalomas are masses found on imaging performed for reasons other than investigating adrenal pathology.
Prevalence
Rare in childhood Prevalence increases with age - around 10% of the population aged >70y have adrenal incidentaloma.
Aetiology
Most are benign adrenocortical adenoma, but there is a wide differential for unilateral and bilateral lesions. In children any adrenal mass is likely to be clinically relevant and require investigation and intervention.
Investigation:has two main aims:
1. *Is the lesion(s) benign?* Imaging with non-contrast CT is the most reliable means to determine is a lesion is a benign adrenocortical adenoma, but if indeterminate an interval follow up scan may be needed. Urine steroid metabolomics holds promise to assist in the discrimination between benign and malignant disease. Clearly malignant lesions need urgent investigation and management. Biopsy is infrequently needed
2. *Is the lesion(s) hormonally functioning?* Examination of the patient may reveal features of hormonal hypersecretion. For unilateral adrenocortical adenoma the 1mg overnight dexamethasone suppression test is used to establish if there is Mild Autonomous Cortisol Secretion (MACS) and if the patient is hypertensive additionally a plasma renin to aldosterone ratio assessed. For all other masses assessment of these parameters and plasma or urinary metanephrines is also needed. For bilateral lesions consistent with hyperplasia, screening with 17 hydroxyprogesterone is also needed. If bilateral metastases or infiltrative disease is suspected urgent assessment of cortisol reserve is needed.
Management
Unilateral benign lesions causing clinically apparent hormonal excess usually require resection by minimally invasive surgery by an expert surgeon. Surgery for MACS may be indicated where basal ACTH is suppressed there are clear co-morbidities that can be driven by cortisol – e.g. hypertension, diabetes mellitus. Benefit is likely to be greater in younger patients. Malignant and indeterminant disease need careful multi-disciplinary discussion to discuss surgical approach and adjuvant therapies.

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MTE18

Type 1 diabetes in athletes

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Introduction
Exercising benefits individuals with type 1 diabetes (T1D) by improving overall health, glycemic control, and body composition. However, managing blood glucose fluctuations during and after exercising remains a significant challenge, preventing many individuals with T1D from meeting the recommended physical activity level of 30 minutes per day. In particular, the fear of hypoglycemia leads to reduced physical activity.
Aim
The objectives of this session are to equip the audience with essential knowledge on exercise physiology in athletes with T1D and provide the participants with the latest recommendations for optimizing blood glucose management during exercise. Additionally, I will share insights into our clinic supporting athletes with T1D in training and competition, helping them perform at their highest potential.
Methods
To address these challenges, the *Clinic for Athletes with Type 1 Diabetes* was established in 2019 at Steno Diabetes Center Aarhus, Denmark. Our clinic's goal is to power athletes with T1D compete on par with their peers without diabetes by refining their diabetes management strategies for training and competition. In doing so, we also support them optimize their athletic performance.
Results
Our "Plan, Do, Study, Act" (PDSA) change model will be presented. Moreover, baseline and follow-up data will be reported on diabetes-related metrics from our athletes, including time-in-range and HbA1c, as well as patient-reported outcomes (PROs) such as WHO-5, SF-12, PAID, patient involvement in treatment, and the HFS-II Short Form (behavior and worry).
Conclusion
Our preliminary findings indicate that athletes in our clinical program reported a reduction in diabetes-related distress and fear of hypoglycemia, while we observed improvements in glycemic control. Furthermore, this talk outlines a method for implementing clinical guidelines for both recreational and elite athletes with T1D.

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Pre-Congress Courses

PCC1.1

Introduction: Case Mentimeter

Jens Pedersen[1] & Lena Bjergved Sigurd[1]
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This pre-congress thyroid ultrasound course is designed for trained endocrinologists seeking to refine their skills in thyroid imaging and intervention. The course will cover how to perform a thyroid ultrasound, how to assess and grade thyroid nodules, and how to conduct a fine needle aspiration biopsy (FNAB). Additionally, the course will introduce minimally invasive techniques for managing thyroid pathology. The program will include case presentations, expert-led lectures, and a hands-on training session to ensure practical skill development.

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PCC1.2

Abstract Unavailable

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PCC1.3

Sonographic assessment of the thyroid gland, diffuse thyroid illness including autoimmune disease

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Thyroid ultrasound is a highly valuable tool for assessment of the thyroid volume, texture, echogenicity, and nodule evaluation and risk stratification. The method is preferably performed by the decision-making clinician. Due to the superficial location of the thyroid gland in the neck, the resolution of the ultrasound images is very high, and even small lesions in the thyroid can be detected. If a large part of the thyroid extends into the thorax, as can be seen in older individuals, this hinders a complete thyroid ultrasound examination. Thyroid autoimmunity, whether reflecting presence of autoimmune thyroiditis or Graves' disease, appears hypoechogenic on ultrasound. The degree of hypoechogenicity correlates to some extent with plasma levels of thyroid autoantibodies. In Graves' disease, the chance of remission can be predicted based on the ultrasound appearance, i.e., marginal/normal echogenicity, pseudonodularity, marked hypoechogenicity. In addition, assessment of the thyroid volume is highly valuable in assessing the chance of remission in Graves' disease, in parallel with the thyroid echogenicity. The thyroid volume can be sonographically calculated from the ellipsoid formula, and with a reasonably precision unless the gland is grossly disconfigured due to thyroid nodularity. Thyroid planimetry is even more precise for volume estimation, but this method is rarely employed. Thyroid ultrasound can also be used to diagnose subacute thyroiditis, in which case the gland is tender, and ultrasound will show patchy avascular areas of marked hypoechogenicity in one or both thyroid lobes. Thyroid ultrasound, using the Doppler signal, may help differentiating between amiodarone-induced type 1 and type 2 thyrotoxicosis. the latter being an inflammatory condition.

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PCC2.1

Welcome

Paolo Giacobini[1] & Elisabet Stener-Victorin[2]
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Polycystic ovary syndrome (PCOS) is the most common reproductive and cardiometabolic disorder in women. It is a complex disorder involving the reproductive and endocrine systems, marked by a dysregulation in the hypothalamus-pituitary-gonadal (HPG) axis, affecting communication between the brain and reproductive organs. Additionally, the gut-brain axis contributes to the metabolic disturbances in PCOS, with altered gut microbiota interacting with neuroendocrine pathways to worsen both metabolic and reproductive symptoms. This altered brain-body communication also influences the central nervous system, impacting cognitive function and mood. The 2025 AE-PCOS Update Meeting will explore these interconnected topics to advance our understanding of PCOS.

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PCC2.10

Session 2: PCOS and the HPG axis: Alterations of the hypothalamo pituitary-gonadal axis in animal models of PCOS

Aleisha Moore[1]
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Polycystic ovary syndrome (PCOS) is a distressing condition and a prevalent cause of anovulatory infertility in individuals of reproductive age. Although PCOS is characterized by ovary dysfunction, growing evidence suggests that the brain plays a crucial role in the development and pathophysiology of the syndrome. In PCOS patients, there is an impairment in gonadal steroid hormone negative feedback to the hypothalamus, which contains the gonadotropin-releasing hormone (GnRH) neuronal network that governs fertility. This leads to an increase in GnRH and pituitary luteinizing hormone (LH) pulsatile release, which, in turn, acts on the ovary to induce ovarian dysfunction and hyperandrogenism. Androgen excess may then act back on the brain to further promote GnRH secretion, resulting in a vicious cycle that continually promotes androgen secretion and reproductive symptoms. The location and mechanistic changes that underlie impaired steroid hormone feedback remain unknown due to the challenges of studying the human hypothalamus at the cellular level. However, in recent years, animal models generated using exposure to excess androgens during critical developmental periods have significantly advanced our understanding of the brain's role in PCOS. In this talk, I will discuss recent results that identify key neural circuits involved in controlling GnRH release, as well as evidence showing that disruptions in these circuits play a crucial role in the pathogenesis of PCOS symptoms in animal models. In particular, this talk will emphasize new evidence regarding the role of cells in the arcuate nucleus of the hypothalamus that express the neuropeptide kisspeptin, which constitutes the GnRH pulse generator, in the syndrome's pathogenesis. Overall, this talk will highlight that identifying and understanding central defects will be vital for establishing effective treatments for PCOS.

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PCC2.11

Session 3: PCOS and the Brain: PCOS and the Brain

Aled Rees[1]
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Polycystic Ovary Syndrome (PCOS) is a multi-system disorder characterized by cutaneous, reproductive and metabolic sequelae with the potential to affect brain structure and function. In a large retrospective study of women with PCOS in the UK, we confirmed a significantly increased prevalence and incidence of depression and anxiety, in addition to bipolar disorder and eating disorder compared with matched controls. Linkage analysis found an increased risk of a recorded diagnosis of autism spectrum disorder and attention-deficit hyperactivity disorder in children born to mothers with PCOS, raising the possibility that increased exposure to androgens *in utero* might affect neonatal brain development. Cognitive function may also be affected: compared with age- and BMI-matched controls, subjects with PCOS displayed subtle decrements across a broad range of cognitive tests, despite similar education and premorbid intelligence. Advances in MRI technology allow for interrogation of the potential underlying mechanisms in unprecedented detail: in a diffusion MRI study, PCOS was associated with a widespread reduction in axial diffusivity and increased tissue volume fraction in the corpus callosum. Alterations in brain structure and function may also contribute to long-term health risks beyond mental health and cognition. Epidemiological studies have confirmed an increased risk of cardio- and cerebrovascular disease among people living with PCOS, with hypertension representing an important modifiable target. Using blood oxygen level-dependent functional MRI, we found evidence of enhanced sympathoexcitation in women with PCOS, accompanied by increased brain activation in the right orbitofrontal cortex. Studies of neurovascular coupling, cerebrovascular reactivity, dynamic cerebral autoregulation, cerebral blood flow and metabolic rate of oxygen consumption in the resting state were not different between subjects with PCOS and age/BMI-matched controls. However, an exaggerated rise in blood pressure was unmasked in PCOS subjects in response to an acute exercise stimulus.

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PCC2.12

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PCC2.13

Abstract Unavailable

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PCC2.14

Session 4: periphery-brain communication in pcos and metabolic co morbidities: autonomic brain-liver communication in metabolic diseases

Alexandre Caron[1]
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The brain influences liver metabolism through many neuroendocrine and autonomic mechanisms that have evolved to protect the organism against starvation and hypoglycemia by maintaining energy and glucose homeostasis. Unfortunately, these sophisticated homeostatic processes can be impaired in metabolic diseases such as obesity, type 2 diabetes and metabolic associated steatotic liver disease (MASLD). However, the precise mechanisms by which the brain regulates hepatic metabolism, how autonomic dysfunctions can alter brain-liver communication, and whether alterations in the autonomic outflow to the liver contribute to disease progression, remain to be defined. Based on recent tissue clearing studies showing that neural innervations within the liver are of sympathetic nature, we hypothesized that adrenergic receptors expressed by hepatocytes directly mediate the autonomic control of liver metabolism. Our data indicate that liver adrenoceptors play a protective role in the progression of metabolic diseases. We found sex-dependent mechanisms by which the sympathetic nervous system regulates energy and glucose homeostasis through the liver. We believe that a better understanding of the receptors and pathways involved in the sympathetic outflow of the liver will help.

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Nurses' Pre-Congress Course

PCC3.1

Abstract Unavailable

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PCC3.2

Diabetes from cardle to grave - Growing up with diabetes

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The incident of type 1 diabetes is increasing, especially among young children. There is no cure yet, treatment with insulin together with careful control of blood glucose is necessary. International guidelines recommend that youths with diabetes shall be offered the most advanced insulin delivery technology that is available, accessible and acceptable for them. At the onset of diabetes, most children are admitted to a paediatric in-patient-clinic for about a week. Insulin treatment and intensive training in self-management start there. After discharge from the ward, self-management takes place at home, with continuous support and education from the diabetes team at the clinic. Despite the development of technologically advanced products, self-management for diabetes is demanding. There are different challenges for different ages. Young children have a total dependence on parents and caregivers for self-management. Injections, infusion set and sensor insertions, and BG checks seen as pain inflicted by caregivers. Parents may feel increased stress, diminished bonding, and depressive feelings. Education for nursery and kindergarten staff is essential. As the child gets older and develop an independence a progressive stepwise transfer of responsibilities is actual. The goal is to be able to manage self-management independently before transfer to an adult clinic.

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PCC3.3

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Nurses' Sessions

N1.1

A nurse-led transition clinic: Good example and nurse roles in transitional care

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Background
Transition Clinics (TCs) are specialized, multidisciplinary healthcare settings that support young people with chronic conditions as they move from pediatric to adult care. These clinics are considered essential in ensuring continuity of care, fostering self-management skills, and preventing adverse outcomes such as medication non-adherence and loss to follow-up. This study aimed to identify best practices in nurse-led TCs and determine key nurse roles contributing to high-quality transitional care.
Methods
This study used a mixed-methods approach consisting of semi-structured interviews with nurse specialists in six transition clinics and surveys among young adults. . Additionally, an integrative review analyzed the roles and responsibilities of nurses and nurse practitioners, highlighting their impact in the transition process.
Results
Nurse-led TCs incorporated individualized transition plans (ITPs), transition coordinators (often nurses/nurse practitioners), and warm handovers to create a structured and seamless transfer of care. These elements contributed to high levels of satisfaction among young adults and increased their trust in healthcare providers. Nurses played a multifaceted role in the transition process, offering personalized guidance and self-management support. The review identified eight critical nurse roles in transitional care: service coordinator, innovator, researcher, advocate, coach, educator, clinician, and liaison to the community. Despite the effectiveness of nurse-led TCs, challenges persist. Resource limitations, gaps in interdisciplinary collaboration, and barriers to fully integrating transitional care into routine practice remain significant concerns. Addressing these challenges requires greater institutional support, encouraging nurses to take up advanced roles, youth participation, and system-wide collaboration. This would help to optimize long-term patient outcomes and ensure equitable access to transitional care.
Conclusion
Nurse-led TCs are vital in facilitating smooth transitions, not only by managing medical transitions but also by empowering young adults and supporting families. By fulfilling diverse roles, nurses enhance the effectiveness of transitional care programs. However, addressing financial constraints, engagement difficulties, and collaboration gaps with primary and mental healthcare services is essential for further improvement.
Keywords
Transitional care, nurse-led clinics, transition clinics, nurse roles, self-management, young adults, nurse practitioners
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Fertility in Patients with CAH

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Fertility in patients with classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) is lower compared to the general population, although with adequate glucocorticoid replacement treatment, comparable fecundity can be achieved. The causes of reduced fertility differ between men and women. In women with classic CAH elevated androgen and progesterone levels lead to menstrual irregularities, affecting endometrial development and ovulation. In addition, genital surgeries for virilization and urogenital anomalies can impact fertility and sexual function, resulting in fewer heterosexual relationships. Psychosexual issues also contribute to impaired fertility. Spontaneous pregnancies are less frequent, and the time to successful conception is often prolonged. Despite these challenges, with adequate glucocorticoid replacement therapy, women with classic CAH can conceive and fecundity is not impaired. In women with classic CAH achieving pregnancy is more complex than disease management during pregnancy. Successful pregnancy management necessitates a complex, individualized approach to treatment and support. In men with classic CAH, fertility is often affected by hypogonadotrophic hypogonadism and complications like testicular adrenal rest tissue (TART),

which can impair spermatogenesis. However, regular monitoring and optimized glucocorticoid therapy may restore spermatogenesis. Genetic counselling is crucial to understand transmission risks and the implications for prenatal care. To prevent virilization in affected female fetuses prenatal dexamethasone treatment can be used but raises ethical and safety concerns that require careful consideration.

Key learning points

- Patients with CAH due to 21-OHD have reduced fertility compared to the general population.
- With adequate replacement therapy, normal fecundity can be achieved in both female and male patients with CAH.
- Reduced fertility in women with classic CAH is caused by elevated androgen and progesterone levels, psychosexual factors and the consequences of genital surgeries for virilization.
- Women with classic CAH experience a prolonged time to conceive compared to healthy women.
- In men with classic CAH, fertility is impacted by hypogonadotropic hypogonadism and testicular adrenal rest tissue (TART), which impairs spermatogenesis.

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Guidelines

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How Do I Sessions

H1.1

How do I evaluate and manage arginine vasopressin deficiency and arginine vasopressin resistance?

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Arginine Vasopressin (AVP) deficiency belongs to the polyuria polydipsia syndrome, which is defined as polyuria of >40-50ml/kg BW per day and accompanying polydipsia. It is crucial to differentiate AVP deficiency from AVP resistance and primary polydipsia since treatment differs and a wrong treatment can have dangerous consequences. For decades, the "gold standard" for differential diagnosis has been the standard water deprivation test. However, this test has several limitations leading to an overall limited diagnostic accuracy. Direct measurement of Vasopressin upon osmotic stimulation was first shown to overcome these limitations, but failed to enter clinical practice mainly due to technical limitations of the AVP assay. New test methods based on stimulated measurement of copeptin, the surrogate marker of AVP, have shown promising results. The hypertonic saline stimulation test is currently the test with the highest diagnostic accuracy, but other test methods have either been tested (e.g. arginine) or are currently under investigation. **This talk will show how AVP deficiency can be diagnosed or excluded at the baseline exam and will highlight different stimulation tests in those patients in which the diagnosis at baseline can not be made.** Treatment of AVP deficiency is usually straight forward and consists of exogenous desmopressin orally or nasally, started at bedtime, and if symptoms persist during the day, a morning dose is added. The most common side effect is hyponatremia, and it is therefore important to inform patients about the risk of hyponatremia following desmopressin treatment and to instruct them about the Desmopressin escape method. Also, **data will be shown highlighting psychological comorbidities in patients with AVP deficiency, and the possibility of an oxytocin deficiency underlying these psychological comorbidities will be discussed**.

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H1.2

How do I diagnose and manage adolescence with PCOS?

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PCOS is common and heterogeneous with reproductive, metabolic, dermatological and psychological features. Presentation is often in adolescence, yet diagnosis delays are common internationally, with patient dissatisfaction with care, inadequate provided information and resources and evidence of long-term health impacts. Gaps in clinician and patient knowledge are demonstrated, as are inconsistencies in care. The Australian Centre for Research Excellence in PCOS, funded to drive research and translation, has partnered with leading international societies including ESE and ESPE among 40 organisations. Together we have updated the International Evidence-based Guideline for Assessment and Management in PCOS and included a focus on the adolescent life stage. The Guideline was developed and updated using world's best practice processes leveraging an international network across six continents and widespread engagement and international partnership to drive awareness, patient self-management, improved, evidence-based practices and better health outcomes in PCOS. Here we will cover updated evidence in adolescents, apply this through a number of case studies on diagnosis and management and explore priority areas for research and care moving forward.

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H1.3

How do I manage the adolescent with Congenital Adrenal Hyperplasia

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Congenital adrenal hyperplasia (CAH) remains a challenging condition to manage during adolescence due to the limitations of current treatments. A major issue is the inability to adequately suppress early morning androgen surges, requiring supraphysiological doses of glucocorticoids (GC) to suppress ACTH. This can lead to both over- and undertreatment throughout the day, particularly in childhood, where the available preparations are suboptimal. Adolescents with CAH are at risk of various complications. These include adrenal crises, salt-wasting crises, mainly due to noncompliance which can be life-threatening. Elevated androgens due to poor hormonal control may result in precocious puberty, pubertal disturbances, delayed menarche, and ultimately, a reduced final adult height. Additionally, gonadal dysfunction and testicular adrenal rest tumors (TART) are frequently described. Furthermore, mental health challenges can significantly impact quality of life. Despite advances in treatment, no curative therapy exists for CAH, and glucocorticoid therapy remains the mainstay of management. However, balancing effective androgen suppression while avoiding GC-related side effects remains difficult. The risk of adrenal crises persists, necessitating careful monitoring and education on stress-dose adjustments. Modified-release glucocorticoids offer a potential strategy to better mimic physiological cortisol rhythms and improve HPA axis suppression, but optimal treatment regimens in adolescence are still under investigation. Future advancements should focus on improving disease control while minimizing long-term complications and enhancing quality of life.

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Oral Communications

Oral Communications 1: Adrenal and Cardiovascular Endocrinology

OC1.1

JOINT2567

Biochemical profile, age at diagnosis and patient ancestry are associated with the risk for positive genetic testing for PPGL susceptibility genes

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Approximately 30% of patients with pheochromocytoma and paraganglioma (PPGLs) have a genetic predisposition due to a germline pathogenic variant (PV) in a susceptibility gene. We aimed to assess the prevalence of PPGL-related hereditary syndromes based on a multi-center national-level study, and to identify risk factors for hereditary PPGL based on clinical and biochemical data.
Methods
This is a retrospective study of patients with a personal history of PPGL. All patients underwent germline DNA sequencing (whole exome or panel sequencing). Demographic, clinical, biochemical, and genetic data were gathered.
Results
Of a total of 225 patients, 90 were evaluated for personal history of PPGL and 135 for family history. Overall, 76 patients (33.8%) carried a likely\PV in a PPGL-related gene, including 43 of the 135 patients with family history (31.8%); 30 with *SDHB* (three different PVs), eight with *SDHD* (two variants) and five with *VHL* (three variants). We found higher risk for positive genetic testing in patients with family history of PPGL among patients of Arab ancestry: 46 patients (60.5%) from 6 kindreds, carried *SDHB* PV ($n=38$), *VHL* PV ($n=7$) and *SDHC* ($n=1$), compared with 22.4% ($n=17$) among Jewish patients and 17.1% ($n=13$) among patients of Druze ancestry. Ninety patients with personal history of PPGL underwent genetic evaluation (median age at diagnosis 47 [7-73], 35.6% males), of them 29 (33.7%) had a family history of PPGL. Forty-one patients had pheochromocytoma, 45 had paraganglioma, and four had both. Thirty-four patients (37.8%) carried a PPGL susceptibility gene PV, most often in *SHDB* (14 patients, 41.1%), followed by *SDHD* ($n=9$, 25.7%), *VHL* ($n=6$, 17.6%), *NF1* ($n=2$, 5.9%), *SDHC*, *SDHAF2*, and *RET* (one patient each, 2.9%). Age at diagnosis was significantly younger in the PV-carriers vs. non-carriers (31.63 ± 2.71 vs. 50.48 ± 2.41, $P<0.00001$). All 17 carriers with elevated plasma/urine catecholamines had purely elevated normetanephrine (NMN) levels (52.2% vs 10.0% pure normetanephrine secretion in hereditary vs. sporadic PPGL, respectively, $P=0.002$). NMN-only secretion was associated with a younger age at diagnosis vs. other secretion profiles (36.1 ± 3.7 vs. 48.85 ± 3.1 years, $P=0.0006$). Twelve patients (13.3%) had aggressive tumor behavior (recurrence\metastases), with a significantly higher rate of PV compared with patients with non-aggressive disease ($n=8$ [66.7%] vs. $n=10$ [27.0%], respectively, $P=0.01$).
Discussion
Among patients with family history of PPGL, those from Arab ancestry had higher risk for positive testing for hereditary syndrome.

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OC1.2

JOINT1081

Evaluation of microRNAs as liquid biopsy markers n adrenocortical tumours

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Introduction
Adrenal tumours (ATs) encompass a wide differential diagnosis, necessitating a multi-step process for accurate identification. Liquid biopsy emerges as a promising non-invasive technique for distinguishing malignant from benign cases. Recent studies have highlighted the potential of microRNAs as circulating biomarkers; however, their clinical utility remains underexplored.
Aim
This study aims to validate the diagnostic performance of selected circulating microRNAs, (miR-483-5p, miR-210, miR-335), identified through microRNA profiling studies, as markers of malignancy in a cohort of patients with ATs.
Methods
We collected serum samples from 90 participants, including 75 patients with ATs and 15 controls. The ATs comprised 50 cases of adrenocortical adenomas (ACA) and 25 cases of adrenocortical carcinomas (ACC). In the ACC subgroup, 16 samples were obtained preoperatively or upon detection of recurrence (active ACC group), while the remaining from disease-free patients with long-term follow-up (disease-free ACC group). Quantitative real-time polymerase chain reaction was employed to analyze microRNA expression.
Results
Circulating levels of miR-483-5p and miR-210 were significantly elevated in patients with active ACC compared to both ACAs ($P<0.001$ and $P=0.004$, respectively) and controls ($P=0.002$ and 0.003, respectively). Notably, miR-483-5p serum levels were higher in the group of active compared to disease-free ACC patients ($P=0.01$). MiR-483-5p demonstrated the best diagnostic accuracy for distinguishing active ACC cases from ACAs (AUC=0.869, 95%CI: 0.761–0.978, $P<0.001$), achieving a sensitivity of 81.3% and a specificity of 88%, and from disease-free ACC patients (AUC=0.854, 95%CI: 0.672–1, 230 $P=0.004$), reaching sensitivity of 81.3% and specificity of 89%. In contrast, miR-335 levels were not sufficient to differentiate the groups. A sub-analysis within ACC cases revealed a trend toward higher marker levels in preoperative samples compared to recurrent cases, although the observed differences were not statistically significant.
Conclusion
Our study highlights the potential of circulating miR-483-5p and miR-210 as promising non-invasive biomarkers for distinguishing active ACC cases from ACA. The absence of miR-483-5p expression in disease-free ACC patients, in which tumor burden is low or absent, suggests that this biomarker may be useful not only for diagnostic purposes but also for disease monitoring. Future research should focus on analyzing serial serum samples from ACC patients to better understand miRNA dynamics throughout disease progression and in response to treatment.

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OC1.3

JOINT1209

Quantitative proteomics of pediatric adrenocortical tumors reveals a continuum of molecular alterations and identifies prognostically relevant subgroups

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Introduction
Pediatric adrenocortical tumors (pACTs), comprising highly malignant carcinomas (pACCs) and less aggressive adenomas (pACAs), pose significant diagnostic and therapeutic challenges due to their molecular heterogeneity and variable clinical outcomes. In this study, we performed an extensive quantitative proteomic analysis of pACTs and matched normal adrenal tissue to delineate molecular alterations, identify deregulated proteins and pathways, and define novel prognostically relevant subgroups.
Methods
Bulk proteomes were extracted from 85 pACTs and 43 matched normal adrenal samples, macrodissected from H&E-stained sections. Following protein extraction, lysis, and enzymatic digestion, the samples were analyzed on a Thermo Orbitrap Astral mass spectrometer coupled to an Evosep One LC system operating at 60 samples per day. The resulting data were $\log_2$ transformed and Z-score normalized prior to further analysis.

Results
A total of 10,714 proteins were quantitatively identified. Protein counts were robust, with tumor samples yielding a median of 8,246 proteins (range: 7,312–8,806) and normal samples a median of 7,497 proteins (range: 4,128–8,578). Unsupervised hierarchical clustering and principal component analysis (PCA) effectively separated normal from tumor samples, yet revealed a proteomic continuum between these states. Notably, traditional histological subtypes (ACA, ACC, and ACX) did not segregate into distinct clusters in PCA or clustering analyses. Differential expression analysis identified approximately 3,400 significantly regulated proteins, with roughly four times more downregulated (2,766) than upregulated (628) in pACTs. Key steroidogenic enzymes such as 3β-hydroxysteroid dehydrogenase were consistently downregulated, supporting a common origin in the adrenal cortex's zona reticularis. Among the top hits were IGF2, CCNE, and SGCG, with significant enrichment of proteins involved in the IGFR signaling and β-catenin pathways. Further dimensionality reduction using PCA and UMAP followed by k-means clustering delineated four distinct tumor clusters (comprising 17, 25, 13, and 30 samples, respectively) that differed in protein signature enrichment, gene ontology profiles, and prognostic outcomes. Moreover, samples of these clusters grouped together in a pseudotime analysis, suggesting a cancer development–associated transition between the clusters.
Conclusions
Our high-sensitivity mass spectrometry approach enables an in-depth proteomic characterization of pACTs, uncovering a continuum of molecular alterations from normal to tumor tissue and identifying novel molecular subgroups with distinct prognostic implications. These findings advance our understanding of pACT pathophysiology and pave the way for refined diagnostic stratification and targeted therapeutic interventions.

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OC1.4

JOINT1579

Pediatric adrenocortical tumors (pACTs) reveal typical patterns of impaired relative activities of steroid metabolizing enzymes

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Introduction
pACTs comprise adenomas (pACAs) and carcinomas (pACCs). They are functional and thus symptomatic with the latter having a poor prognosis. We investigated whether precursor/product ratios of steroid hormone metabolites were suitable to diagnose patients with adrenal tumors and to differentiate adenomas from carcinomas. Method: We investigated 46 patients (median 6.9; range 0.7-17 yrs; 36 females) with ACTs from the GPOH-MET Registry (German Society for Pediatric Oncology and Hematology for Malignant Endocrine Tumors) at the time of initial diagnosis. Patients were recruited between 2001 and 2024. $n=21$ were diagnosed with pACAs and $n=25$ with pACCs according to histopathological criteria. $n=145$ urines from healthy children served as controls. 36 steroid metabolites were quantified (µg/l) from spot urines by targeted GC-MS urinary steroid metabolome analysis. Relative enzyme activities were calculated according to typical precursor/product metabolite ratios. Data underwent computational analysis by Z-transformation of log transformed values followed by logistic regression and machine learning classifiers.
Results
Most expressed differences ($P<0.001$) between the group of ACTs and healthy controls concerned decreased activities of the following enzymes: 3β-hydroxysteroiddehydrogenase (3βHSD, e.g. ratio 5-pregnenetriol-17α/pregnanetriol, OR 5.01), 11β-hydroxylase (11OHase, e.g. ratio tetrahydro-11-deoxycortisol/cortisol metabolites, OR 5.35) and 21-hydroxylase (21OHase, e.g. ratio pregnandiolone-5β/tetrahydrocortisone, OR 3.54). Recursive partitioning and regression trees showed a sensitivity of 94% and a specificity of 87%. Differences between ACAs and ACCs were less expressed ($P<0.05$) and primarily showed reduced activities for 5α-reductase (5αR, e.g. pregnandiolone-5α/pregnandiolone-5β, OR 2.68) and 17-hydroxylase/17,20-lyase (17OHase, e.g. corticosterone-metabolites/cortisol-metabolites, OR 2.03). Recursive partitioning and regression trees revealed sensitivities of 84% for carcinomas and 86% for adenomas.
Conclusions
1) targeted GC-MS urinary steroid metabotyping from spot urine using metabolite precursor/product ratios is non-invasive and highly useful in delineating pACTs. 2) pACTs showed gross differences compared to controls. Most common was reduced activity of 3βHSD with dominance of 5-ene-steroids, a finding pointing to the zona reticularis as probable site of tumorigenesis. 3) pACCs and pACAs showed only subtle differences primarily impaired activities of 5αR and 17OHase. 4) pACTs behave differently from those in adults. Findings in adult ACT patients cannot be transferred to pediatric patients.

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OC1.5

JOINT2115

Clinical predictors of treatment response in advanced adrenocortical carcinoma: a multicentre ENSAT study

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Background
Pharmacological treatment for advanced adrenocortical carcinoma (ACC) consists of mitotane alone or combined with cytotoxic chemotherapy. However, reliable predictors of response to therapy are lacking. We aimed to explore the predictive role of clinical parameters in a large cohort of patients with advanced ACC treated with systemic therapy.
Methods
We investigated a total of 418 patients with advanced ACC (61.5% = women, median age = 52 years) from 11 European centres, treated with mitotane monotherapy (mitotane cohort, $n=161$), etoposide + cisplatin ± doxorubicin ± mitotane (EDP cohort, $n=178$) or two different 2nd-line chemotherapy schemes (gemcitabine + capecitabine ± mitotane or temozolomide + mitotane $n=79$). Clinical parameters were collected at start of therapy including age, cortisol excess, ECOG-performance status (ECOG-PS), tumor burden (4 grades defined depending on size, number and site of metastasis), neutrophil-to-lymphocyte-ratio (NLR). Patients underwent regular radiological surveillance according to European and local guidelines. Our endpoints were overall-survival (OS) and time-to-progression (TTP) from treatment initiation and best objective response to treatment according to RECIST 1.1 criteria. Descriptive, contingency table, Kaplan-Meier survival and Cox regression analyses were performed using STATA version 17.
Results
At multivariable analysis tumour burden, cortisol excess, ECOG-PS and NLR ≥ 5 significantly and independently predicted shorter OS in all cohorts (HR between

1.55 and 2.68). We therefore calculated a combined **BUCEN**score as a sum of the following points: tumour **BU**rden (1 = 0, 2 = 1, 3/4 = 2), **C**ortisol excess (present = 1), **E**COG-PS (0 = 0, 1 = 1, 2/3 = 2), and **N**LR (≥5 = 1). A high BUCEN (≥3) resulted a significant predictor of shorter OS and TTP in all groups (mitotane cohort: OS HR = 3.05, 95%CI = 2.06-4.51, TTP HR = 2.68, 95%CI = 1.81-3.98, EDP cohort: OS HR = 3.38, 95%CI = 2.22-5.14, TTP HR = 2.53, 95%CI = 1.68-3.84, 2nd-lines cohort: OS HR = 3.96, 95%CI = 1.68-9.29, TTP HR = 3.08, 95%CI = 1.31-7.24). BUCEN score ≥ 3 also predicted best objective response to mitotane ($P < 0.01$) and 2nd line therapies ($P = 0.04$), without reaching significance for EDP ($P = 0.07$).
Conclusions
Our new proposed BUCEN score resulted a promising predictor of response to pharmacological treatment in patients with advanced ACC. This score can be calculated starting from readily available clinical and biochemical parameters and could be used in routine practice to pre-select patients who could most benefit from systemic therapy.

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OC1.6

JOINT822

Single-cell, single-nucleus, and spatial transcriptomics reveal the cellular atlas and developmental mechanisms of aldosterone-producing micronodules and adenomas

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Background
Primary aldosteronism is frequently caused by aldosterone-producing adenomas (APAs). Aldosterone-producing micronodules (APMs) are distinct histopathological lesions consisting of subcapsular clusters of *zona glomerulosa* (zG) cells. APMs have been proposed as potential APA precursors, but molecular evidence supporting this hypothesis remains limited.
Objective
This study aimed to create a comprehensive cellular atlas of APAs and APMs and elucidate their developmental mechanisms through integrated single-cell, single-nucleus and spatial transcriptomics analyses.
Methods
We performed single nucleus (sn) RNA-seq on two APA specimens and integrated publicly available single cell (sc) RNA-seq data from two APMs. To map spatial gene expression, we conducted spatial transcriptomics analyses on 12 captured areas from formalin-fixed paraffin-embedded adrenal glands from five patients with primary aldosteronism. Functional *in vitro* studies were performed in human adrenocortical cells (HAC15).
Results
Integration of sn and scRNA-seq transcriptome data revealed distinct phenotypic profiles and variable frequencies of major cell types between APM and APA. APAs exhibited an immunosuppressive tumour microenvironment, potentially driven by enhanced VISFATIN pathway activity promoting M2 macrophage polarisation. Gene regulatory network analysis identified APA-specific transcription factors *LEF1* and *FOXO1*, while *JUN* and *FOS* expression in APMs suggested their role in early tumour responses. Trajectory analyses revealed two main developmental pathways: direct progression from zG to APA, and stepwise progression from zG through APM to APA. Within APAs, we identified two distinct cellular states with different differentiation potentials: a progenitor-like state (low differentiation potential) and a mature state (high differentiation potential). Compared to the progenitor state, the mature state was characterised by increased *PCP4* and *CYP11B2* expression and high copy number variation. Functional enrichment analysis revealed a dynamic regulatory environment during APA development, involving pathways of oxidative stress (including mechanisms leading to cell death by ferroptosis) and focal adhesion (influenced by cell density). We demonstrate that RSL3-induced ferroptosis sensitivity is modulated by cell density. TAZ knockdown in low-density HAC15 cells conferred resistance to ferroptosis, mimicking the effect observed in high cell densities.
Conclusion
Our findings reveal an immunosuppressed tumour microenvironment in APAs, characterised by increased M2 macrophages. We demonstrate dynamic changes in molecular profiles and cell cluster composition during APA initiation and progression. These insights enhance our understanding of APA pathobiology and may inform the development of novel diagnostic and therapeutic strategies for primary aldosteronism.

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Oral Communications 2: Diabetes and Insulin Part 1

OC2.1

JOINT3329

War-provoked glycemic shift: 4-years dynamics of HbA1c levels in Ukrainian population

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Background
War is one of the strongest stressors that affects the physical and psychological heath. In Ukraine, full-scale military operations have led to significant deterioration in access to medical care, chronic stress, a shortage of vital medicines, changes in diet and the lifestyle. These can provoke metabolic disorders predisposing to insulin resistance and diabetes mellitus development. One of the important indicators for diabetes diagnosis and control is the level of glycated hemoglobin (HbA1c). In this study we assessed the impact of war on distirbution of HbA1c values at populational level with respect to gender of people tested at pre-war and 3-year war period.
Methods
This population-based study involved 106,883 participants who underwent HbA1c testing from over Ukraine at the period from 2021 to 2024. This sample included 68,696 males and 38,187 females, of different age.
Results
According to the data analysis, the start of full-scale aggression in 2022 significantly affected HbA1c levels, which differed substantially from 2021, 2023, and 2024 ($P < 0{,}001$). The prewar level of HbA1c in the Ukrainian population comprised 5.82%. The beginning of the war in Ukraine was associated with a sharp increase of HbA1c in males from 6.01% (5.47-8.54%) in 2021 to 6.88% (5.54-10.26%) in 2022 when the full-scale invasion began. In 2023 and 2024, HbA1c levels returned to prewar values reaching 5.98% (5.44-8.14) and 6.02% (5.58-7.43), respectively. In women, the highest levels of HbA1c were also noted in 2022, when the full-scale invasion began (6.24; 5.43-9.14%), compared with the pre-war period in 2021 (5.77; 5.33-7.15%). However, the following decline of HbA1c in 2023 and 2024 was insignificant, so HbA1c levels in 2023 (5.89%; 5.40-7.50%) and 2024 (5.98%; 5.54-7.10%) kept higher than in prewar period. Thus, females demonstrated long-term glycemic shifts induced by war-related factors. This data reflects gender differences in scale and length of HbA1c level changes in response to war.
Conclusions
The war significantly affects the health of Ukrainians, provoking acute and chronic shifts in carbohydrate metabolism and glycemic profile indicators. The start of the war was associated with a rise in HbA1c levels. While men demonstrated a sharp increase with further normalization of HbA1c, females showed prolongation of changes in HbA1c.

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OC2.2

JOINT2606

Early detection of type 1 diabetes through population-based antibody screening: design and initial results from the adir program in Israel

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Introduction
Type 1 diabetes (T1D) demonstrates a distinctive early immunological signature, with approximately 80% of affected children developing multiple islet autoantibodies (IA) before age 5. These children face an 84% risk of progressing to symptomatic diabetes within 15 years. Population-based antibody screening presents a critical opportunity to identify preclinical T1D, enabling proactive intervention through family preparation for insulin therapy, prevention of diabetic ketoacidosis (DKA) at diagnosis, and timely initiation of disease-modifying treatments.

Research design and methods
The Antibody Detection Israeli Research (ADIR) program, launched in October 2021 with support from Breakthrough T1D, represents a comprehensive national screening initiative. The study targets 35,000 children aged 9 months to 5 years across Israel for IA screening, with longitudinal assessment planned for 5,000 participants through repeat screening. The program's infrastructure comprises 65 community-based screening sites, six specialized diabetes centers following the children detected with preclinical T1D, a dedicated central laboratory, and a coordinating center. ADIR distinguishes itself through two key innovations: its focus on early childhood screening and the implementation of Antibody Detection by Agglutination PCR (ADAP) technology for autoantibody detection performed in capillary blood.
Preliminary results
As of January 2025, the study has enrolled 17,000 children (median age: 19 months). Analysis of over 12,000 samples revealed 57 children (0.475%) with multiple IA. Following confirmatory testing per the study protocol, 15 children were diagnosed with preclinical T1D, while others are still evaluated. Additionally, 120 children were identified with single islet antibody positivity. A comprehensive analysis and progression patterns will be presented.
Conclusions and future directions
The ADIR program represents one of the largest population-based screening initiatives for preclinical T1D in young children. Our preliminary results demonstrate the successful implementation of a nationwide screening infrastructure and validate the feasibility of early autoantibody detection using the novel ADAP technology. Identifying children with preclinical T1D and over 120 with single islet antibody positivity underscores the program's potential for early intervention. These findings support the viability of large-scale screening programs for type 1 diabetes and establish a foundation for future preventive strategies. Long-term follow-up of this cohort will provide valuable insights into the natural history of T1D and create opportunities for early therapeutic intervention.

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OC2.3

JOINT3725

Novel insights in understanding the relation of glycemic excursions and concomitant sleep macro- and micro-architecture among adolescents with type 1 diabetes

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Background and objective
The bidirectional influence between glycemic variability and quality of sleep among patients with type 1 Diabetes (T1D) has not been fully elucidated yet. We aimed to characterize real-time interactions of sleep parameters, including electrical activity, with immediate glycemic excursions, among adolescents with T1D, compared to their healthy siblings.
Methods
Twenty-two patients with T1D, 50% males, median age 14.6 years (13.7,15.8), and 13 of their healthy siblings, 61.5% males, median age 14.8 years (13.2,16), were included in the study. They were divided to well-controlled (WC-T1D) and poorly controlled (PC-T1D), according to HbA1c cutoff 8.3%. All were monitored continuously and simultaneously with an actigraph, electroencephalogram (EEG) and continuous glucose monitoring system (CGMS) for interstitial glucose concentrations (IGC), for one night. EEG recordings were used to calculate EEG power at frequency bands from delta to high gamma, averaged over different brain regions. IGC was divided to near-normal glucose range of 61-180 mg/dl, and high glucose of >180 mg/dl.
Results
During awakening (WASO), the percentage of time spent in optimal range was significantly higher in the Healthy group compared with the T1D group, (100% vs. 45.4%, $P=0.001$), mainly the WC-T1D subgroup, in which longer time was spent at the higher glucose levels during WASO. Higher percentage of time spent in 61-180 mg/dl range, was associated with longer NREM3 $r=0.51$, $P=0.012$, but with a shorter TST $r=-0.49$, $P=0.03$, in the T1D group. A similar trend with negative correlation between percent of time spent in 61-180 mg/dl and TST was seen in the Healthy group, $r=-0.51$, $P=0.07$. Lower EEG power was demonstrated in T1D group compared with the Healthy group, mainly at frequency bands delta, theta and beta during NREM stage 1, and bands delta, beta and gamma during WASO. Significantly lower EEG power was detected during N1, REM and WASO when IGC was >180 mg/dl in the T1D group, compared with the Healthy group, at most frequency bands and brain regions. Those differences were not detected with near normal IGC. In contrast, higher HbA1c was associated with lower EEG power during all sleep stages and across most frequency bands and brain regions.
Conclusions
EEG power in various sleep stages is differently regulated by chronic glycemic control and by acute glucose excursions, explained physiologically according to reflective cortisol secretion and modulation of autonomous nervous system. Effective management goals among the pediatric population with T1D, should include both lower HbA1c and longer time spent with IGC <180 mg/dl.

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OC2.4

JOINT865

Rebound hyperglycemia in children with type 1 diabetes using automated insulin delivery

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Background and aims
To investigate how rebound hyperglycemia (RH) affects CGM-assessed time-in-range and how different automated insulin delivery systems (AID) manage RH.
Methods
This cross-sectional study included children and adolescents with type 1 diabetes (T1D) using either Tandem Control IQ (CIQ) or Medtronic Minimed 780G (780G) at Steno Diabetes Center Copenhagen, Denmark. RH was defined as ≥ 1 sensor glucose value (SG) >10.0 mmol/l within two hours of a preceding SG <3.9 mmol/l, with RH-severity measured by area under the curve (AUC).
Results
Among 190 children and adolescents, 94 used CIQ and 96 used 780G. The median age (range) for CIQ and 780G was 11.9 (1.8-18.0) versus 11.3 (1.2-17.4) years ($P=0.49$), diabetes duration was 7.0 (1-16) versus 4.0 (0-13) years ($P<0.001$), and HbA1c was 53 (37-102) versus 53 (37-147) mmol/mol ($P=0.29$) . RH-severity (AUC) was inversely related to time-in-range (TIR: 3.9-10.0 mmol/l) ($P<0.001$), regardless of the AID systems ($P=0.57$). The frequency of hypoglycemia, frequency of RH, and the percentage of hypoglycemia leading to RH were similar for 780G and CIQ ($P>0.05$). However, CIQ-users had a significant increased RH-duration of 30% (95%CI:16-46%) and RH-severity of 34% (95%CI: 18-53%) compared with 780G-users, despite having a shorter duration of hypoglycemia leading to RH of 23% (95%CI:14-32%).
Conclusions
Even though the frequency of RH was similar between AID systems, the severity and duration of RH were less and shorter for children and adolescents with T1D using 780G than CIQ. The inverse association between RH-severity and TIR suggests that addressing hypoglycemia management in AID-users could improve glycemic outcomes.

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OC2.5

JOINT55

In-hospital diabetes management by a diabetes team using insulin algorithms with continuous glucose monitoring or point-of-care testing in patients with type 2 Diabetes: the DIATEC RCT

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Objective
The DIATEC trial investigates the glycaemic and clinical effects of inpatient continuous glucose monitoring (CGM)-guided insulin titration by diabetes teams.
Research design and methods

This two-centre trial randomised 166 non-intensive care unit patients with type 2 diabetes. Diabetes management was performed by regular staff, guided by diabetes teams using insulin titration algorithms based on either point-of-care glucose testing or CGM. The primary outcome was the difference in time in range (TIR) (3.9–10.0 mmol/l) between the two arms. Outcomes were assessed during the entire hospitalisation.
Results
The CGM-arm achieved a higher TIR (median, IQR) of 77.6% (24.4) vs 62.7% (31.5) in the POC-arm ($P < .001$). Time above range (TAR) >10.0 mmol/l was lower in the CGM-arm of (median, IQR) 21.1% (24.8) vs 36.5% (30.3) in the POC-arm ($P = .001$). Time below range (TBR) <3.9 mmol/l was reduced by CGM, with a relative difference to POC of 0.57 (95% CI 0.34–0.97) ($P = .042$). Prolonged hypoglycaemic events decreased (IRR 0.13, 95% CI 0.04–0.46) ($P = .001$), and the coefficient of variation (mean, SD) was lower in the CGM-arm of 25.4% (6.3) vs 28.0% (8.2) in the POC-arm ($P = .024$). Total insulin doses (mean, SD) were reduced in the CGM-arm with 24.1 IU/day (13.9) vs 29.3 IU/day (13.9) in the POC-arm ($P = .049$). A composite of complications was lower in the CGM-arm (IRR 0.76, 95% CI 0.59–0.98) ($P = .032$).
Conclusions
In-hospital CGM increased TIR by 15%-points, mainly by reducing TAR. CGM also lowered TBR, glycaemic variability, prolonged hypoglycaemic events, insulin usage, and in-hospital complications.
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OC2.6

JOINT408
Delayed puberty and early-onset type 2 diabetes: a nationwide cohort study of 1.6 million adolescents
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Objective
The relationship between delayed puberty in males and the risk of type 2 diabetes (T2D) in adulthood is unclear. We investigated the association between delayed puberty during adolescence and the likelihood of developing T2D in early adulthood.
Research design and methods
A nationwide, population-based study of 964,108 Israeli adolescent males (mean age 17.3 years) who were examined before military recruitment during 1992–2015 and were followed until December 31, 2019. The diagnosis of delayed puberty was made by board-specified specialists based on physical examination and laboratory evaluation. Data were linked to the Israeli National Diabetes Registry. Cox proportional hazard models were applied.
Results
Delayed puberty was diagnosed in 0.45% (4307 of 964,108) of adolescent males. Over a cumulative follow-up of 15,242,068 person yeas, T2D was diagnosed in 111 individuals (2.58%) with delayed puberty and in 6,259 individuals (0.65%) without delayed puberty. The incidence rate of T2D per 105 person-year was 140.3 (95%CI, 114.2–166.4) in the delayed puberty group versus 41.3 (95%CI, 40.3–42.3) of adolescents without delayed puberty. The hazard ratio (HR) for T2D among individuals with delayed puberty was 2.52 (95%CI, 2.09–3.04, $P = 4.7$×10-22), remaining materially unchanged after adjustment for birth year, socioeconomic status, cognitive function, education level and country of birth HR 2.47 (95%CI, 2.04–2.99). After additional adjustment to baseline BMI, the HR was 1.37 (95%CI 1.13-1.66). The association was further strengthened when restricted to individuals diagnosed at or before 35 years of age 1.65 (95%CI 1.22-2.23) and persisted after controlling for baseline health status. In a sensitivity analysis limited to adolescents with overweight and obesity, using those without hypogonadism as the reference group, the adjusted HR was 1.31 (95% CI 1.05–1.21).
Conclusions
Delayed puberty in adolescent males is associated with a significantly increased risk of T2D in early adulthood, independent of baseline BMI and other confounders. These findings highlight delayed puberty as a potential marker of metabolic risk, warranting further investigation.
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Oral Communications 3: Metabolism and Aging

OC3.1

JOINT520
Fecal microbiota transplantation improves diabetic kidney disease by regulating gut tryptophan metabolism
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Objective
Diabetic kidney disease (DKD) is a major microvascular complication of diabetes, with complex pathogenesis and limited effectiveness of current prevention and treatment strategies. Identifying novel therapeutic approaches and their molecular targets is therefore of critical clinical significance. This study aims to investigate the therapeutic effects and underlying mechanisms of fecal microbiota transplantation (FMT) in the prevention and treatment of DKD.
Methods
This study was conducted across population, animal, and cellular levels. Metagenomics, serum metabolomics, and tryptophan-targeted metabolomics were employed to analyze changes in gut microbiota composition and serum metabolic flux in both human subjects and DKD mouse models. An 18-week FMT treatment was administered to db/db mice, during which dynamic changes in glucose and lipid metabolism, renal function, and inflammatory markers were evaluated. Renal tissues were collected for transcriptomic sequencing and pathological analysis. Molecular biological techniques, including western blotting, immunoprecipitation, luciferase reporter assays, and gene over-expression/knockdown, were used to further explore the molecular mechanisms underlying the effects of FMT in ameliorating DKD.
Results
FMT effectively improved glucose and lipid metabolism disorders, reduced urinary microalbumin levels, delayed renal function decline, and alleviated renal inflammatory infiltration in db/db mice. In addition, FMT normalized the altered gut microbiota composition and structure in db/db mice, particularly restoring microbial populations associated with gut tryptophan metabolism. This intervention significantly modulated the abnormal serum tryptophan metabolic flux observed in db/db mice. Elevated serum levels of indole-3-acetic acid (IAA) in the DKD state were closely associated with metabolic disorders and renal dysfunction. Mechanistically, IAA promoted NEMO SUMOylation, leading to activation of the NF-κB signaling pathway, which further exacerbated renal inflammatory damage. FMT reduced IAA production, suppressed the activation of the miR-145a-5p/SENP2 signaling axis, inhibited NEMO SUMOylation, and mitigated the excessive activation of the NF-κB inflammatory signaling pathway.
Conclusion
In DKD, increased NEMO SUMOylation activates the NF-κB signaling pathway, resulting in renal inflammatory injury. The gut-derived tryptophan metabolite IAA upregulates renal miR-145a-5p expression, which further enhances NEMO SUMOylation via the miR-145a-5p/SENP2 axis, aggravating inflammatory damage. FMT alleviates DKD and its associated inflammatory injuries by regulating gut tryptophan metabolism, reducing IAA production, and inhibiting the miR-145a-5p/SENP2/NEMO-SUMOylation axis.
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OC3.2

JOINT887
Epigenetic aging in turner and klinefelter syndrome: correlations with clinical aging markers
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The sex chromosome aneuploidies Turner syndrome (45,X; TS) and Klinefelter syndrome (47,XXY; KS) are associated with aging-related comorbidities, reduced life expectancy and genome-wide DNA methylation changes. The objective of this study was to investigate whether the aging-related comorbidity pattern and the reduction in lifespan was associated with epigenetic aging. We assessed epigenetic age and age acceleration using six different epigenetic clocks predicting chronological age, phenotypic age, aging pace and telomere length. DNA methylation was obtained from existing cohorts of TS (TS, $n=47$; female controls, $n=33$) and KS (KS, $n=65$; male controls, $n=63$). In addition, we evaluated correlations between epigenetic aging and clinical variables, aiming to identify clinical aging markers in TS and KS. Epigenetic age and age acceleration based on predictors of chronological age were increased in both TS and KS compared to respective controls ($P<0.015$). Epigenetic age and age acceleration based on predictors of phenotype were increased in TS ($P<0.019$), as well as aging pace ($P<0.001$). Telomere length was decreased in TS ($P<0.001$) and slightly increased in KS ($P=0.06$). Markers of body composition and muscle mass were correlated to age acceleration in TS, while these traits were correlated to chronological and epigenetic age in female controls. Similarly, markers of body composition were more consistently correlated to aging pace in KS than male controls, while an age-dependent increase in triglyceride levels and body fat percentage seemed to be diminished in KS. We demonstrated that biological aging was clearly increased in TS and, to some extent, in KS. This could explain some of the excess mortality observed in these syndromes. Additionally, unfavorable changes in body composition, which are common in both syndromes, particularly if left untreated, could result in accelerated aging – or be the result hereof.

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OC3.3

JOINT2852

Role of clock gene Bmal1 in mitochondrial function and lipid metabolism in skeletal muscle

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Bmal1 is the key transcription factor of the molecular circadian clock, whose cyclic expression influences energy metabolism and regulation of cell growth and maintenance. The current study aims to elucidate the role of Bmal1 muscle metabolism regulation, with a focus on mitochondrial activity and lipid accumulation. The murine C2C12 cells differentiated into myocytes (C2C12 WT), and C2C12 in which the Bmal1 gene was deleted through CRISPR/Cas9 genome editing technology (C2C12 KOBmal1) were used. Mitochondrial oxidative capacity and efficiency were evaluated using Seahorse assays and MitoTracker Red CMXRos staining, respectively, in both cells. Simultaneously, the expression levels of DRP-1 protein, a key marker of mitochondrial fission, as well as the subcellular localization of myogenin, a transcription factor involved in muscle differentiation, and of HSP70, a molecular chaperone regulating stress response, were investigated via immunofluorescence. In addition, Bodipy staining was performed in both cell models to monitor potential ectopic lipid accumulation, while gene and protein expression levels of the mTOR pathway, myogenin, C/EBPα and PGC1α, key regulators of muscle anabolism, lipogenesis and mitochondrial biogenesis, were assessed by RT-qPCR and western blot, respectively. Furthermore, irisin levels, a myokine involved in mitochondrial function and muscle health, were quantified in both cell models through ELISA assay. Compared to C2C12 WT , basal respiration was significantly lower ($P=0.03$) while maximal respiration and reserve respiratory capacity were significantly higher ($P=0.009$; $P=0.003$) in C2C12 KOBmal1cells. Morphologically, C2C12 KOBmal1 cells showed a reduction in mitochondrial branching (-18.22%) and a significant decrease in mitochondrial branch length ($P=0.01$) compared to C2C12 WT cells. These changes were associated with increased DRP1 protein levels (+17%) and a significant reduction in PGC1α gene ($P=0.01$) and protein ($P=0.03$) levels. These mitochondrial alterations in C2C12 KOBmal1 were accompanied by significantly increased lipid accumulation ($P=0.03$) and C/EBPα protein expression ($P=0.03$), indicating a shift toward lipid storage. A marked downregulation of mTOR (-42.86%), p70S6K (-61.43%), and 4E-BP1 (-38.82%) genes was observed in C2C12 KOBmal1 cells compared to C2C12 WT , alongside reduced levels of myogenin (-27.70%). Immunofluorescence revealed perinuclear distribution of myogenin protein in C2C12 KOBmal1 , unlike its nuclear expression in C2C12 WT concomitantly with increased HSP70 nuclear expression, potentially linking reduced myogenic signalling to cellular stress. Lastly, C2C12 KOBmal1 showed significantly decreased irisin levels ($P=0.03$), reinforcing the impairment in metabolic balance. Concluding, Bmal1 deletion in myocytes disrupts mitochondrial morphology and function, promoting lipid accumulation and suppressing mTOR-driven anabolism through nuclear HSP70 accumulation.

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OC3.4

JOINT447

Nuclear resident AMPK ?2 enhances adipose tissue browning through Neuregulin 4

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AMP-activated protein kinase (AMPK) is a heterotrimeric serine/threonine kinase playing a key role in metabolic regulation. The γ subunit of AMPK is the regulatory subunit responsible for binding and sensing the adenine nucleotides and the most understudied subunit. We found the expression of AMPK γ2 subunit, encoded by *Prkag2* gene, is abundantly expressed in the mature adipocytes and its expression was significantly downregulated in obesity while boosted by cold exposure. Adipocyte-selective deletion of *Prkag2* exacerbates diet-induced obesity and compromises adipose tissue browning in mice. Notably AMPK γ2 contains a unique nuclear localization signal (NLS). Mutation of the NLS mitigates the nuclear localization of AMPK γ2 along with its biological function in potentiating adipose browning. WT but not mutant AMPK γ2 stimulates the transcription of Neuregulin 4 (*Nrg4*). Additionally, CUT&Tag analysis reveals a direct binding of AMPK γ2 on *Nrg4* gene locus, suggesting AMPK γ2 acts as a transcriptional co-activator of *Nrg4*. Supplementation of NRG4 reverses the compromised adipose browning in Prkag2 AKO mice. In human, NRG4, and other adipokines are tightly correlated with adipose AMPK γ2 expression. Our findings unravel the previously unrecognized function of AMPK γ2 as a transcriptional co-regulator independent of AMPK kinase activity in adipocytes.

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OC3.5

JOINT1641

Modeling adipose tissue dysfunction in polycystic ovary syndrome in vitro using 2D and 3D cell culture systems

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Background
Polycystic ovary syndrome (PCOS), characterized by hyperandrogenism, is the leading cause of female infertility and is associated with insulin resistance and type 2 diabetes. Impaired adipose tissue function is a key determinant of the metabolic phenotype in PCOS, with dysfunction evident in altered lipid metabolism, energy homeostasis, and adipokine production. Our group has identified enlarged fat cells as drivers of insulin resistance and linked aberrant genetic and epigenetic expression in adipose tissue to PCOS-related metabolic disturbances. However, the molecular mechanisms remain poorly understood and are not addressed by current drug development. Treatment for insulin-resistant PCOS primarily focuses on symptom management through lifestyle changes, diet, exercise, and antidiabetic drugs, including metformin and GLP1 receptor agonists. Yet, their direct effects on adipocytes in PCOS remain unclear. To address this, we are generating a single-nuclei transcriptome atlas of subcutaneous adipose tissue from women with and without PCOS to identify

disease- and cell type-specific signatures and treatment responses (see abstract Li *et al*). In parallel, we are developing and characterizing 2D and 3D *in vitro* adipose tissue cultures to investigate adipogenic differentiation, adipose dysfunction, and drug responses, focusing on metformin and GLP1-RA (semaglutide).
Methods
We collect subcutaneous white adipose tissue from hyperandrogenic, insulin-resistant women with PCOS and age and BMI-matched controls. Fresh biopsies are used to isolate adipose stem cells (ASCs) to assess adipogenic capacity, tissue recapitulation, and responses to metformin and semaglutide. We perform bulk RNA sequencing at day 0 (ASC), day 6 (preadipocytes), and day 12 (mature adipocytes). Moreover, we analyse lipid accumulation ad lipid droplet size, basal and stimulated lipolysis, and bioenergetics using Seahorse XFe96. Additionally, 3D adipocyte spheroids are generated and characterized.
Results & Future Perspectives:
Preliminary data indicate that 2D-differentiated PCOS adipocytes retain larger lipid droplets, mimicking tissue biopsies. PCOS adipocytes exhibit lower basal oxygen consumption and higher basal lipolysis, both partially reversed by metformin and semaglutide. Bulk RNA sequencing reveals persistent PCOS-specific differential gene expression related to mitochondrial function throughout differentiation. Preliminary 3D spheroid data suggest similar lipid droplet enlargement. Ongoing work includes profiling the secretome and extracellular vesicles and comparing transcriptomic data from *in vitro* and freshly isolated mature adipocytes for model validation and with single nuclei RNA-seq data. Future efforts aim to develop advanced *in vitro* PCOS models, such as microfluidic co-culture systems integrating adipose and reproductive tissues, including endometrial epithelial organoids and stromal cells, to study tissue interactions in PCOS.

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OC3.6

JOINT1825

Sedentary behavior, physical activity, and risk of mortality in adults with obesity

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Background
Obese individuals tend to lead sedentary lifestyles and avoid physical activity (PA). It remains unclear whether increasing PA can offset the health risks associated with sedentary behavior (SB), as well as the intensity of PA required to achieve such an effect.
Objectives
This study aimed to evaluate the joint and stratified associations of SB and PA with all-cause, cancer, and cardiovascular disease (CVD) mortality, and to estimate the theoretical effects of replacing SB with sleep or PA.
Methods
A total of 90,971 adults with obesity from the UK Biobank were included in the analysis. Information on sedentary time (sum of television watching, computer using and driving behavior) and PA (measured by International Physical Activity Questionnaire) were collected by self-reported at baseline. Participants were followed up for mortality events according to the ICD-10 code using linkage to national health records until 2021. Cox proportional hazards regression models were used to calculate multivariable-adjusted hazard ratios (HRs) for each SB-PA combination group and within SB strata. The isotemporal substitution model was applied to investigate the impact of replacing SB with sleep, walking, moderate physical activity (MPA), and vigorous physical activity (VPA), adjusting for potential confounders.
Results
During a median follow-up of 12.7 years, 8,357 deaths occurred, including 1,784 from CVD and 2,673 from cancer. Among groups with no PA, reducing sedentary time was not significantly associated with all-cause or cancer mortality. Compared with the reference group (no PA and SB >8 h/day), the group with VPA and 4–8 h/day of SB exhibited the lowest all-cause mortality risk (HR 0.70, 95% CI 0.65–0.75). The group with VPA and <4 h/day of SB showed the lowest cancer mortality risk (HR 0.68, 95% CI 0.60–0.78), while the group with VPA and >8 h/day of SB had the lowest CVD mortality risk (HR 0.66, 95% CI 0.57–0.78). Across SB subgroups, increased PA was significantly associated with reduced all-cause and cause-specific mortality, demonstrating an almost dose-response relationship. Replacing SB with walking or VPA showed stronger associations, with mortality risk declining as the replacement duration increased. For example, replacing 3 h of SB with an equivalent amount of VPA reduced all-cause mortality (HR 0.80, 95% CI 0.77–0.84).
Conclusions
In adults with obesity, reducing sedentary time and increasing PA of any Intensity are significantly associated with lower risks of all-cause and cause-specific mortality. Increasing PA or replacing SB with PA attenuates the association between SB and mortality.

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Oral Communications 4: Pituitary, Neuroendocrinology and Puberty Part 1

OC4.1

JOINT206

Differential temporal onset of kisspeptin action following intranasal and intravenous administration supports a novel human olfactory-reproductive pathway

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Background
The most characterised pathway for kisspeptin's activation of the reproductive axis involves the stimulation of kisspeptin receptors on GnRH neurones *within the hypothalamus*. However, recent rodent evidence reveals an *extra-hypothalamic* population of GnRH neurons in the olfactory bulb that also express kisspeptin receptors. Intranasal kisspeptin administration could directly activate these olfactory bulb-GnRH neurones, triggering reproductive hormone release and unveiling a novel olfactory-reproductive pathway. Herein, we compare the reproductive hormone responses to intranasal and intravenous kisspeptin administration in humans for the first time, providing mechanistic insights and highlighting a non-invasive clinical route of kisspeptin administration.
Methods
Healthy male participants received 12.8 nmol/kg of kisspeptin-54 via either intranasal delivery ($n=12$) or intravenous bolus injection ($n=5$). Reproductive hormone levels were measured at 15 minute intervals over 6 hours following administration. The mean maximum increase in reproductive hormones from baseline and the median time to peak response between the two groups were analysed using an unpaired t-test and Mann-Whitney test, respectively.
Results
Both intranasal and intravenous kisspeptin-54 elicited significant gonadotrophin and testosterone responses. Although the peak LH response was lower with intranasal, compared to intravenous, administration (mean $\pm$ SEM [IU/l]: 4.5 ± 0.6 above baseline for intranasal vs. 11.3 ± 1.4 for intravenous, $P<0.0001$), intranasal kisspeptin-54 induced a notably earlier LH peak, with a median time of 38 minutes, compared to 300 minutes for intravenous administration ($P=0.0002$) . Similar patterns were observed for FSH, with a peak (mean $\pm$ SEM [IU/l]) of 0.7 ± 0.2 above baseline at 38 minutes (IQR: 30–79) following intranasal administration, compared to 2.3 ± 0.22 above baseline at 345 minutes (IQR: 345–360) following intravenous kisspeptin-54 ($P=0.0003$ for magnitude, $P=0.0002$ for timing). The peak testosterone responses did not differ significantly following intranasal and intravenous kisspeptin-54 ($P=0.1864$), but the median peak was attained earlier following intranasal administration (165 minutes; IQR: 109–240), compared to intravenous administration (345 minutes; IQR: 240–360, $P=0.0116$). Neither intranasal nor intravenous kisspeptin-54 administration were associated with any adverse effects.
Discussion
The remarkably faster onset of reproductive hormone responses following intranasal compared to intravenous kisspeptin-54 suggests that this route leverages a direct olfactory-reproductive pathway mediated by kisspeptin receptors on olfactory GnRH neurones. These findings have significant clinical implications for the therapeutic use of kisspeptin for common reproductive and psychosexual disorders, whilst also providing evidence for a newly identified kisspeptin mediated olfactory-reproductive pathway in humans.

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OC4.2

JOINT3779

B2R overexpression in resistant prolactinomas promotes B2R-D2R dimerization, with B2R precluding D2R signalling generating resistance to D2R agonists

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Among the pituitary tumours PROLACTINOMAS, are the most frequently observed in the clinic. The dopamine receptor 2 (D2R) agonists represent a highly effective first-line therapy. However, between 15 and 20% of patients do not respond to the treatment or become resistant. These RESISTANT prolactinomas represent a major challenge for clinical management as there are no alternative treatments. During the last few years, our focus has been on why D2R doesn't work. Then we start studying whether D2R dimerization disrupts its signalling in lactotrophs promoting resistance to D2R agonists. The bradykinin receptor type 2 (B2R) is overexpressed in prolactinomas. We postulated that the increased B2R expression in prolactinomas could facilitate D2R-B2R dimerization disturbing D2R signalling, promoting resistance to D2R agonists. We first characterized the bradykinin receptors in the pituitary, and we found that B2R is the most expressed, mainly in lactotrophs cells. Then, the formation of B2R-D2R complexes in cultured cells transiently expressing both receptors was validated using the NanoBiT technology. Interestingly, while the stimulation of D2R did not alter B2R-induced intracellular calcium mobilization, B2R stimulation abolished D2R signalling (modulation of cAMP levels). The existence of B2R-D2R complexes in human pituitary adenomas biopsies was evaluated. B2R-D2R complexes were detected, using the ALPHALisa approach, in human prolactinomas and nonfunctioning pituitary adenomas (NFPA), but not in mixed (prolactin + growth hormone) secreting adenomas. These results suggest that overexpression of B2R in resistant prolactinomas may promote the formation of B2R-D2R complexes, with B2R disrupting D2R signalling, generating resistance to D2R agonists.

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OC4.3

JOINT3502

Exploration of pituitary stem cells heterogeneity and their contribution in gonadotroph tumors

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Pituitary tumors (PiTs) are heterogeneous intracranial neoplasms with limited personalized treatment options. Despite significant advances in understanding their genetics, epigenetics, and the cellular composition of their microenvironment, the underlying processes driving their tumorigenesis and heterogeneity remain poorly understood. The use of single-cell omics and tumour-derived cultures has confirmed the existence of various stem cell (SC) populations in all PiT-subtypes, raising questions about their role in tumorigenesis. Interestingly, while physio-pathological insults activate mouse pituitary SC (PSC) differentiation into endocrine pituitary lineages, their functional contribution has never been addressed in the context of murine tumours or human pituitary adenomas. Here, we questioned the heterogeneity and function of intratumoural PSCs using animal models, single cell-/spatial-omics, and patient-derived primary cultures. Through these approaches, we first confirmed that tumour growth, whether resulting from the orthotopic injection of tumour-cells or the consequences of aging, drives a remodelling of the SC-rich marginal zone (MZ). This was supported by the identification of MZ-budding structures containing SOX2+ cells and their expression of tumour-associated SCs (TA-SCs) markers. Following this observation, we confirmed the presence and the heterogeneity of SCs between 44 gonadotroph tumours (0.02%-4.78% SOX2+ cells). Bioinformatic analysis of single-nuclei sequencing (SnPatho-Seq) performed on three tumours with the highest SC numbers confirmed the presence of two SC populations with unique features and a series of differentiating stem-state identities. These findings were further confirmed by spatial-transcriptomic analysis (Visium/Xenium) and immunohistological validations, pointing to the existence of two major SOX2-expressing SC populations, respectively defined as Stem Cells and TA-SCs. Trajectory and pseudotime analyses confirmed that TA-SCs were differentiating into cell-states primed to the three major pituitary lineages: PIT1, TPIT and SF1, a result further validated by histological analysis. Finally, we addressed the mechanistic cues that control the TA-SC state. Regulon analysis identified STAT1/3 as a transcriptional pathway strongly activated in TA-SCs, a result supported by the identification of intratumoural SOX2-SCs showing a phospho-STAT3 activation. To assess the functional impact of JAK-STAT pathway modulation in vitro, we tested the effect of pharmacological inhibitors on SC-enriched cultures derived from patients. These inhibitors significantly decreased stemness markers while increasing the expression of endocrine differentiation markers. Altogether, these findings provide evidences that TA-SCs may contribute to pituitary tumorigenesis. Moreover, our results support that JAK-STAT inhibition impact SC maintenance and differentiation, suggesting this pathway as a potential therapeutic target to modulate TA-SC behaviour in PITs.Fundings: FRIEMM, Ligue-Cancer (CD26/CD69), HCL (PJC), ANR-23-CE45-0017, ANR-17-CONV-0002, ANR-18-CE45-0023, ANR-22-PESN-0002, CD24-00240, PRE2020-05930.

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OC4.4

JOINT711

SDHB loss in anterior pituitary embryonic progenitors and postnatal SOX2+ stem cells is insufficient to drive pituitary tumorigenesis and results in pituitary hypoplasia in mice

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Succinate dehydrogenase (SDH) is an enzyme complex at the centre of aerobic respiration with a dual role in the Krebs cycle and electron transport chain. Mutations in any of the four SDH subunits (SDHA, SDHB, SDHC and SDHD) have been implicated in driving tumorigenesis of neuroendocrine tumours including phaeochromocytoma and paraganglioma, underscoring the link between metabolic dysregulation and tumorigenesis. Pituitary neuroendocrine tumours (PitNETs) associated with germline or somatic *SDHx* mutations, particularly in the *SDHB* subunit, can display clinically aggressive behaviour. The molecular pathogenesis, clinical behaviour and treatment outcomes of *SDHx*-mutated PitNETs remain poorly characterised. The role of *SDHx* mutations in driving tumour development, whether alone or in concert with other factors, and the cell-of-origin of these tumours are also unknown. Understanding these pathways is essential for developing targeted therapies for these tumours. Using *in vivo* mouse models, we assessed the consequence of mutating *Sdhb* during anterior pituitary (AP) embryonic development and in postnatal stages. We utilised two *Cre* drivers to delete Sdhb across Rathke's pouch in the embryo ($Hesx1^{Cre/+}$; $Sdhb^{fl/fl}$), as well as in the postnatal SOX2+ stem cell compartment ($Sox2^{CreERT2/+}$; $Sdhb^{fl/fl}$) using a tamoxifen-inducible model. We confirm a reduction in *Sdhb* expression and activation of pseudohypoxic signalling in the AP, with upregulation of *Hif1a* and its transcriptional targets, a pattern seen in other *SDHx*-mutated tumours. Through metabolic flux analyses, we observe metabolic reprogramming in pituitary stem cells, consistent with the Warburg effect (a metabolic switch that is a hallmark of cancer), in response to SDHB loss. Despite these changes, homozygous loss of *Sdhb* in our mouse models is not sufficient to lead to pituitary tumour formation. However, strikingly, loss of SDHB leads to pituitary hypoplasia, characterised by a reduction in AP volume,

with normal anterior pituitary lineage commitment and differentiation. Together, these findings support a potential two-hit tumorigenesis model. They also emphasise the potential role of altered cellular metabolism in hypopituitarism, which could inform regenerative medicine approaches in the future. These have important implications for the screening, diagnosis, and treatment of *SDHx*-mutated pituitary disorders.

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OC4.5

JOINT2764

Glucocorticoid negative feedback in regulating hypothalamic-pituitary-adrenal axis: the epigenetic role of miR-27

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In a physiological state, activation of hypothalamic-pituitary-adrenal (HPA) axis induces the release of ACTH by pituitary and, in turn, of cortisol from adrenal glands according to a circadian rhythm. HPA axis undergoes negative feedback regulation due to the elevated circulating cortisol that induces negative feedback on the hypothalamus and pituitary. In corticotroph cells, the control is provided by the coordinated action of the co-chaperones FKBP4 and FKBP5, which regulate the cytoplasmic and nuclear localization of glucocorticoid receptor (GR) and, consequently, the action of glucocorticoids (GCs). Cortisol excess in Cushing's syndrome (CS) is associated with a complete loss of clock gene rhythmicity and reduced clock gene BMAL1 acrophase; therefore, the current study aimed at investigating the BMAL1 potential impacton GCs negative feedback on pituitary corticotroph cells. A wild-type murine corticotroph cell line, AtT20^{WT}, and AtT20 BMAL1 knockout (AtT20^{KO}), by CRISPR-Cas9, were used. GR, BMAL1, FKBP5, FKBP4 and POMC protein expression were evaluated by western blot (WB) in both cell models treated with or without dexamethasone 10^{-7}M (DEX) for 6 h and 24 h. Bioinformatic analysis predicted miRNAs targeting BMAL1, and concomitantly, the expression of these potential miRNAs was analyzed by RT-qPCR in both cell models treated with or without DEX and in 17 CS patients and 17 healthy subjects. AtT20^{KO} exhibited FKBP4 (91.2%, $P=0.04$ and FKBP5 (346%, $P=0.002$) higher expression compared to AtT20^{WT}. Interestingly, in AtT20^{WT}, DEX induced GR lower expression (52.2%, $P=0.01$) at 6 h, and FKBP5 higher expression (134%, $P=0.03$) and POMC lower expression (65.5%, $P=0.01$) at 24 h compared to untreated cells, while in AtT20^{KO} DEX effect on FKBP5 and POMC was lost and only lower expression of GR was observed at 6 h (40.7%, $P=0.005$) and 24 h (29.4%, $P=0.03$). Bioinformatic analysis revealed that miR-27a-3p and miR-27b-3p might target BMAL1. miR-27a-3p and miR-27b-3p circulating levels resulted upregulated in CS patients compared to healthy subjects ($P<0.0001$ respectively). AtT20^{KO} expressed miR-27b-3p lower levels ($P=0.03$) compared to AtT20^{WT}. Notably, 24 h DEX increased miR-27b-3p ($P=0.02$) in AtT20^{WT} but not in AtT20^{KO}. Even POMC could be a target of miR-27. Accordingly, AtT20^{WT} treated with 24 h DEX almost completely reduced POMC protein expression, but this effect was reverted when miR-27a-3p and miR-27b-3p inhibitors were added to DEX. In conclusion, these results added a small piece to the physiological knowledge by unveiling a new mechanism of negative feedback regulation of HPA at the pituitary level where BMAL1 expression allows DEX to increase miR-27b-3p levels, which in turn reduces POMC expression.

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OC4.6

JOINT1294

Multi-omics analysis of USP8 mutated and wild type corticotroph pituitary tumors enhances understanding of tumorigenesis, proliferation, immune response and hormone excess in Cushing's disease

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Cushing's disease (CD) is a rare disease caused by adrenocorticotropic hormone (ACTH) secreting pituitary tumors. Recurrent mutations in *USP8* have been identified as drivers of tumorigenesis in about 40% of cases. However, their direct impact at molecular level remains largely unknown. Therefore, our aim was to unveil the effect of USP8 mutations at chromosomal, genomic, transcriptomic and proteomic levels in patients' material. We gathered 26 cryo- and 90 formalin-fixed paraffin-embedded (FFPE) tumors from patients with CD and normal pituitaries (3 cryo, 10 FFPE). Mutational status was determined using Sanger sequencing. Chromosomal and genomic changes were studied using whole exome sequencing (WES) and shallow whole genome sequencing (sWGS). Transcriptomic changes were investigated using NanoString® nCounter® RNA analysis and single-nucleus RNA sequencing (snRNA-seq.). Protein expression was evaluated using immunohistochemistry. WES and sWGS identified low copy number variation (CNV) levels for *USP8* mutated tumors whereas *USP8* WT tumors showed variable CNV with higher CNV levels associated with higher recurrence rates. Immunity targeted nCounter® analysis revealed higher expression of inflammation and immune response transcripts in *USP8* wild type (WT) tumors. Consistently, snRNA-seq. confirmed enhanced percentage of T-cells in WT tumors and showed complement activation and higher protein secretion in corticotropes of *USP8* mutated tumors. Furthermore, *USP8* mutated tumors contained higher percentage of corticotropes in G2M and S cell cycle phases compared to WT tumors and normal anterior pituitaries. Interestingly, protein expression analysis revealed weaker staining of Prostaglandin E receptor PTGER4 and growth arrest regulator GADD45B in *USP8* mutated tumors, further indicating differences in cell proliferation. Higher staining of ubiquitin-like modifier SUMO1 and secreted protein Osteopontin were found in both tumor groups compared to normal anterior pituitaries, indicating converging roles in tumor progression. Surprisingly, no significant differences of galanin (GAL) and ACTH staining could be found between the tumor groups, however there was a positive correlation between GAL and ACTH solely in *USP8* mutated tumors ($r=0.411$, $P=0.03$). In addition, stronger staining of corticotroph marker TBX19 was found in *USP8* mutated tumors. As both GAL and TBX19 are known regulators of ACTH expression, these findings indicate distinct mechanisms of ACTH regulation in CD tumors based on mutational status, despite similar tumor ACTH levels. To conclude, our study presents extensive insights into Cushing's disease, highlighting higher genomic stability and cell proliferation in *USP8* mutated tumors, higher immune reaction in *USP8* WT tumors and differences in ACTH excess regulation based on mutational status.

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Oral Communications 5: Reproductive and Developmental Endocrinology Part 1

OC5.1

JOINT1200

Autoimmune diseases in 30,340 Danish women with polycystic ovary syndrome (PCOS) before and after PCOS diagnosis and in 151,520 controls. A national cohort study

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Objective
Autoimmunity could be part of the pathogenesis of polycystic ovary syndrome (PCOS), but data regarding risk of autoimmune diseases in population based cohorts are limited.

Aim
To investigate incidence rates of autoimmune diseases in Danish women with PCOS before and after PCOS diagnosis compared to controls.
Design
National register-based study in Danish women with PCOS (PCOS Denmark, $n=30,340$) and age-matched controls ($n=151,520$). Type 1 diabetes, thyroid disease or other autoimmune diseases were study outcomes (defined by ICD10 diagnosis and/or medical treatment for type 1 diabetes or thyroid disease). Baseline was the date for PCOS diagnosis.
Results
The median age at PCOS diagnosis was 28 years (interquartile range (IQR) 23; 35). Before baseline (mean risk time 11.4 years), the incidence rate of type 1 diabetes (IRR = 2.18 (1.33; 3.55), thyroid disease (IRR = 1.81 (1.68; 1.96) and other autoimmune disease (IRR = 1.12 (1.03; 1.22) was significantly higher in women with PCOS compared to controls (all $P<0.001$). In PCOS, the prevalence of T1D before baseline was 0.09%, thyroid disorder 3.25% and other autoimmune disease 2.6%. The mean risk time after the index date was 9.8 years. After baseline, the incidence rate of type 1 diabetes (IRR = 3.41 (3.02; 3.86), thyroid disease (IRR = 1.49 (1.41; 1.59) and other autoimmune disease (IRR = 1.13 (1.04; 1.22) was significantly higher in women with PCOS compared to controls (all $P \leq 0.003$).
Conclusion
The incidence rate of autoimmune disease was higher in women with PCOS compared to controls before and after PCOS diagnosis.

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OC5.2

JOINT3817

PCOS-like hyperactivity in the reproductive axis following arcuate nucleus-specific progesterone receptor knockdown

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Mammalian reproduction and fertility rely on gonadal steroid hormone feedback within the hypothalamic-pituitary-gonadal (HPG) axis. In polycystic ovary syndrome (PCOS), diminished sensitivity to progesterone negative feedback contributes to impaired reproductive function, leading to increased pulsatile release of gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH). Although the precise mechanisms underlying progesterone negative feedback in the HPG axis remain unclear, both clinical and preclinical evidence suggest that progesterone signalling through progesterone receptors (PR) in the arcuate nucleus of the hypothalamus (ARC), and potentially GABAergic neurons, plays a key role. To pinpoint the critical site of progesterone negative feedback, we investigated whether selectively disrupting progesterone sensitivity in the ARC of adult females or in all GABA neurons from birth is sufficient to induce HPG axis hyperactivity. To disrupt PR in the ARC, bilateral injections of AAV-Cre or AAV-control were stereotaxically injected into the ARC of adult transgenic $PR^{fl/fl}$ mouse. To knock out (KO) PR in GABAergic neurons, $PR^{fl/fl}$ mice were crossed with vesicular GABA transporter (VGAT)-Cre mice to generate GABA-specific PRKOs. Immunohistochemistry was used to assess viral targeting and site/ cell-specific loss of PR. Vaginal cytology was monitored for 14 days before and 4 weeks after Cre-mediated PR knockdown and for 3 weeks in adult GABA-specific PRKOs. Lutienizing hormone (LH) pulsatility was assessed in serial blood samples by ELISA and analysed with Pulsar software. PR expression in the ARC of AAV-Cre injected animals was significantly reduced in comparison to controls ($P>0.001$) and PR expression was completely absent from VGAT+ neurons in GABA-specific PRKOs. PR knockdown specific to the ARC was found to significantly decrease estrous cycle frequency ($P>0.001$), increase cycle length ($P>0.01$), and reduce time spent in proestrus ($P>0.01$). ARC-specific PR knockdown also increased LH pulse frequency in comparison to controls ($P<0.05$). In contrast, although GABA-specific PRKOs demonstrated delayed first estrous ($P<0.05$) and decreased estrous cycle frequency ($P>0.001$), there were no significant differences in LH pulse parameters from controls. Using these different transgenic approaches, we have demonstrated that although GABA-specific PRKO does not impact LH pulse frequency, knockdown of PR exclusively in the ARC in adulthood is sufficient to drive LH hypersecretion and mimic other reproductive impairments common to PCOS. Together, this work supports neurons in the ARC as the critical site for progesterone negative feedback regulation of the reproductive axis.

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OC5.3

JOINT3135

Building 3D ovaroids to understand mechanisms of human ovary formation and its pathologies

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Background
Sex-determination (SD) is defined as differentiation of the bipotential anlage into either testes or ovaries. The gene networks and mechanisms involved in the cell fate decision that direct the precursor somatic cells to commit to either Sertoli (testis) or granulosa cells (ovary) in the human are poorly understood, in part, due to a lack of evolutionary conservation and the absence of a suitable *in-vitro* model.
Material and methods
Using only defined culture media, we have developed robust protocols to sequentially differentiate human XX iPSCs to granulosa-like cells (iGLCs) and primordial germ cell-like cells (PGCLCs).
Results
During differentiation lineage appropriate markers are expressed, with terminally differentiated cells expressing those for primary follicle (e.g. *FOXL2*, *RSPO1*) even in prolonged culture (>2 months), suggesting that they are *bona fide* ovarian somatic cell precursors. We also derived primordial germ cell-like cells (PGCLCs) from iPSCs, defined by expression of *SOX17*, *BLIMP1*, *TFAP2C* and *NANOS3*. To generate 3D ovarian organoids (ovaroids) we have co-cultured *in-vitro* derived PGCLCs with iGLCs to evaluate their ability to reconstitute follicular structures and development associated with primordial germ cell differentiation towards oogonia. Using genome editing, we are using this system to introduce variants we previously defined as causing *SRY*-negative 46,XX testicular or ovotesticular Disorders/Differences in Sex Development (e.g. NR5A1, NR2F2).
Conclusion
Ovaroids provide an infinite and powerful supply of material to define the mechanisms involved in directing and maintaining cellular identity in human gonadal cells. This system will lead to a better understanding of factors and mechanisms involved in human ovary formation and a wide range of ovarian pathologies, including infertility.

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OC5.5

JOINT2381

The effect of intranasal insulin on post prandial thermogenesis in obese women with and without polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is a lifelong condition associated with reproductive and metabolic consequences. Obesity worsens PCOS and women with PCOS are more likely to be obese and find weight loss difficult. Women with PCOS have a reduced adaptive thermogenesis response to food meaning they don't burn off as many calories after eating. Previous studies conducted in a clinically realistic large animal model highlighted that this is due to a centrally-regulated defect in subcutaneous adipose tissue function. These studies have also suggested intranasal insulin (INI) as a novel therapeutic strategy with the hypothesis that it could help obese women with PCOS to regulate their metabolism and lose weight. This research was conducted as part of a single site basic experimental study looking at the effect of INI on postprandial energy expenditure (PPEE) in obese women with and without PCOS. Obese women with PCOS ($n=12$), and obese controls without PCOS ($n=12$) were fed a standard meal on two occasions with either intranasal saline placebo or 40iu INI in a random and blinded manner. A subset of PCOS patients ($n=6$) also underwent a third linked visit with 80iu INI to determine if there was a dose-response. The effect of INI on PPEE was assessed by indirect calorimetry. Area under the curve (AUC) of PPEE was used for statistical analysis. With 40iu INI participants with PCOS had significantly

greater postprandial energy (AUC 1580±166) expenditure than with saline placebo (AUC 1079±227), measured as a change in PPEE over time per kg of body fat ($P<0.05$). Within the subset group 80iu INI (AUC 1972±94) also caused a significant increase in PPEE vs saline placebo ($P<0.01$). There was a dose-response with 80iu INI increasing PPEE more than 40iu INI ($P<0.05$). In obese control women without PCOS 40iu INI (AUC 1314±154) had no effect in PPEE when compared to control (AUC 1393±173). There were no adverse effects on blood glucose concentrations. These results suggest proof of concept and provide additional safety data for INI in the improvement of PPEE in obese women with PCOS. There is still an unmet clinical need for accessible and cost-effective weight management treatment for patients with PCOS and this strategy warrants further investigation with proof of efficacy studies.

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OC5.6

JOINT650

Gonadotropin rise following intranasal kisspeptin administration is heightened in women with hypothalamic amenorrhoea compared to healthy women

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Background

Kisspeptin administration by *intravenous* or *subcutaneous* routes activates hypothalamic GnRH neurons to stimulate downstream reproductive hormone release and is under rapid development for treating common reproductive disorders, including hypothalamic amenorrhoea (HA). However, these invasive routes limit patient acceptability and clinical use. Intranasal offers a novel non-invasive delivery route, which would be clinically preferable to patients and clinicians. Herein, we compare the reproductive endocrine responses following *intranasal* kisspeptin administration in healthy women to women with HA.

Methods

Randomised, double-blinded, placebo-controlled, crossover study in 12 healthy (ovulatory) women during the follicular phase (mean age±SEM 22.1±0.9 yrs, BMI 22.1±0.8 kg/m^2) and 10 women with HA (age 25.8±2.7 yrs, BMI 19.9±1.3 kg/m^2). After intranasal administration of kisspeptin-54 (12.8 nmol/kg) or 0.9% saline (placebo), reproductive hormones were measured every 15 minutes for 4 hours. Groups were compared by unpaired t-tests.

Results

Intranasal kisspeptin-54 administration rapidly and robustly stimulated gonadotropin release in both study groups, without any side effects or adverse events encountered. However, LH and FSH release were significantly augmented in women with HA, compared to healthy women: mean area under the curve (AUC) for the change in LH across 4 hours 96.0±45.8 h·IU/litre (healthy women) vs. 600.6±146.7 h·IU/litre (women with HA) ($P=0.002$). Consistently, mean AUC for the change in FSH was -36.1±23.4 h·IU/litre (healthy women) vs. 474.9±237.3 h·IU/litre (women with HA) ($P=0.02$). The mean maximal increase in LH following kisspeptin-54 was over three-fold greater in women with HA at 4.4±0.2 IU/l vs. 1.4±0.3 IU/l in healthy women ($P<0.001$). Similarly, the mean maximal increase in FSH was over ten-fold greater in women with HA at 3.1±0.3 IU/l vs. 0.3±0.1 IU/l in healthy women ($P=0.03$).

Summary

Intranasal kisspeptin robustly stimulates reproductive hormone release in healthy women, with an even greater stimulation in women with HA. Therefore, intranasal kisspeptin offers not only a novel, effective, safe, and non-invasive route of administration for the management of reproductive disorders but also a potential simple diagnostic test to interrogate hypothalamic function and identify women with HA.

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Oral Communications 7: Bone and Mineral Metabolism

OC7.1

JOINT2255

Bone mineral density and biochemical parameters after one year of treatment with denosumab or zoledronate in postmenopausal women with osteoporosis and primary hyperparathyroidism: a pilot study

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Background

Optimal medical treatment of postmenopausal women with osteoporosis and primary hyperparathyroidism (PHPT) who decline surgery has not been determined. We compared the therapeutic effects of denosumab or zoledronate in this population.

Methods

Postmenopausal women with osteoporosis and PHPT were randomized 1:1 to treatment with either denosumab 60 mg sc every six months (DMAB group) or zoledronate 5 mg iv once a year (ZOL group) (ClinicalTrials.gov Identifier NCT04085419). Bone mineral density (BMD) at four standard sites and trabecular bone score (TBS) were measured by DXA at baseline and after twelve months (12M). Serum calcium (S-Ca), intact parathyroid hormone (iPTH), and bone turnover markers (C-terminal telopeptide (CTX), N-terminal propeptide of type I procollagen (PINP), and bone-specific alkaline phosphatase (BAP)) were determined at baseline, 3M, 6M, and 12M.

Results

Forty females (aged 73.0 (7.8 SD) years; 22.6 (10.0) years from menopause; BMI 27.77 (5.1) kg/m^2) were included. After one year of treatment, LS BMD was significantly and similarly higher in both groups (LS BMD 12M ΔDMAB +0.038 g/cm^2; $P<0.001$ and ΔZOL +0.040 g/cm^2; $P=0.003$). TH BMD was significantly higher only in the DMAB group (TH BMD 12M ΔDMAB +0.036 g/cm^2; $P=0.006$), while FN and 1/3R BMD did not change. All patients together had significantly higher TBS (ΔTBS 12M +0.066; $P=0.016$). There was a statistically significant decrease of 3M S-Ca in both groups (S-Ca 3M ΔDMAB -0.07 mmol/l; $P=0.045$, ΔZOL -0.08 mmol/l; $P<0.01$). The iPTH level increased significantly in both groups at 3M, remained high at 6M, and slowly decreased thereafter, with no statistically significant difference between the groups (iPTH 3M ΔDMAB +61.91 (126.93); $P=0.042$ vs. ΔZOL +30.24 (56.84) ng/l; $P=0.003$). CTX, PINP, and BAP decreased significantly in both groups at 3M (CTX 3M ΔDMAB -0.952 (0.639) vs ΔZOL -0.556 (0.439) µg/l; $P=0.03$; PINP 3M ΔDMAB -75.45 (33.9) vs ΔZOL -54.06 (32.06) µg/l; $P=0.003$; BAP 3M ΔDMAB -19.72 (8.12) vs ΔZOL -13.68 (9.55) µg/l; $P=0.685$), and remained low and unchanged thereafter. CTX and PINP at 3M were significantly lower in DMAB group.

Conclusion

One year of denosumab or zoledronate had similar effects on BMD and TBS in postmenopausal women with osteoporosis and PHPT. The effects on S-Ca, iPTH at 3M were also comparable between treatments. Denosumab had a more potent short-term effect on decreasing bone turnover than zoledronate.

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OC7.2

JOINT1472

Diagnostic performance of parathyroid 4d-ct in men1 syndrome-associated primary hyperparathyroidism

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Background

In multiple endocrine neoplasia type 1 (MEN1) related primary hyperparathyroidism (PHPT), recognition of asynchronous parathyroid involvement has led to

consideration for targeted surgical approaches that require accurate preoperative localization modalities. However, data on parathyroid 4-dimensional computed tomography (4D-CT) in this context remains sparse.
Objectives
To assess 4D-CT diagnostic performance in MEN1 PHPT and report outcomes of parathyroidectomy where surgical extent was tailored as per the CT findings.
Study setting
Retrospective study in an endocrine referral center where 4D-CT is routinely used as first-line imaging for parathyroid localization.
Methods
CT scans of MEN1 PHPT patients from Jan 2008–Dec 2022 (20% clinical, 80% genetic diagnosis) were independently reviewed by two radiologists (15 & 11 years of experience) aware of MEN1 but blinded to original radiology reports, clinical/surgical details, histopathology, and outcomes. The per-patient analysis comprised the entire cohort. The per lesion analysis was limited to operated patients and used pathology/surgical outcome as the gold standard.
Results
Among 60 MEN1 PHPT patients, 43% were symptomatic and 93% had hypercalcemia at the time of CT (median calcium 11.7 mg/dl, PTH 248 pg/ml). The per-patient analysis included 61 4D-CT scans (53 previously unoperated, 8 for persistent/recurrent PHPT). The original report and radiologists identified abnormal glands in 96.7-100% of patients (mean 2.25 lesions per patient in unoperated, 1.71 in persistent/recurrent). In the per lesion analysis ($n=33$), 4D-CT had 85-89.5% sensitivity and 90-94% specificity, outperforming ultrasonography and Sestamibi scan ($P<0.001$ for both). There was good inter-observer agreement on CT for lesion quadrant localization in the overall cohort and operated subgroup (Cohen's kappa 0.64-0.91). In 24/33 patients, only CT-identified abnormal glands were resected, while glands not seen on CT were left unexplored (imaging-guided group). The remaining 9 had bilateral neck exploration (BNE) with subtotal/total parathyroidectomy and autotransplantation, regardless of CT findings. Both imaging-guided and BNE groups had similar baseline characteristics and number of lesions identified per patient on 4D-CT. The imaging-guided group had more adenomas and fewer hyperplasia (35% vs. 64%; $P<0.001$) and normal glands (2% vs. 17%; $P=0.01$) on pathology than BNE. Despite resecting fewer glands per patient ($P<0.001$), the imaging-guided group had comparable remission (91.7% vs 100%) and recurrence rates (9.5% vs 0%; $P=1.00$) to the BNE group over similar follow-up duration, with lower permanent hypoparathyroidism (4 vs. 44%; $P=0.01$).
Conclusion
4D-CT demonstrated good diagnostic performance and facilitated favorable operative outcomes in MEN1 PHPT, supporting its role in planning surgical extent.

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OC7.3

JOINT1912

The prevalence of neurodevelopmental disorders in a large UK cohort of children with achondroplasia

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Objective
This project aims to better understand the rates of developmental delay and neurodevelopmental disorders in patients with achondroplasia. Achondroplasia is the most common genetic cause of short stature world-wide and is associated with a range of skeletal abnormalities and resultant chronic sequalae. Due to anthropomorphic differences, the developmental profile in achondroplasia is unique, particularly in the area of gross motor skills, with skills such as independent sitting and walking often being achieved later than other children. Achondroplasia it is not thought to be associated with neurodevelopmental abnormalities. It is noteworthy however that other conditions caused by variants in same gene (*FGFR3*) are associated with higher rates of neurodevelopmental abnormalities. There is also increasing anecdotal evidence of higher rates of neurodevelopmental disorders in achondroplasia patients. This relationship is however poorly explored and warrants further assessment.
Methods
Retrospective developmental milestones and neurodevelopmental data was collected from all individuals with a diagnosis of achondroplasia seen in the specialist achondroplasia clinic at the Evelina London Children's Hospital. Data regarding additional procedures and diagnosis was also collected. Developmental data was compared to the gold standard achondroplasia development charts (*Ireland et al*), using the 90th percentile cut-off for delays. Neurodevelopmental disorder rate, in particular Autism, ADHD and Special Education Needs in this cohort was compared to population prevalence.
Results
In this study, data from 240 children with achondroplasia was included. In total 52 children (21.6%) had a delay in one or more developmental domains with respect to achondroplasia milestones. Looking at specific milestones (Independent walking and first word), the proportion greater than the 90th centile cut-off for delay was not statistically different to that seen in the Australian cohort assessed by Ireland *et al*. When assessing neurodevelopmental disorders, statistically higher rates of autism (Bonferroni corrected $P=0.0032$) were seen in this cohort when compared to population prevalence. When assessing the rates of special education needs, the cohort as a whole did not have higher rates of special education needs compared to population prevalence. When specifically assessing those with a developmental delay there was a higher rate of long term special education needs when compared to population prevalence (Bonferroni corrected $P=0.031$).
Conclusions
This large cohort provides valuable insights into the extent of developmental delay and neurodiversity in achondroplasia patients. It offers further evidence of increased neurodevelopmental disorders, particularly autism, and highlights a potential link between early developmental delays and long-term special education needs in Achondroplasia patients.

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OC7.4

JOINT1216

Long-term height gain and maintenance of treatment effect in children with achondroplasia receiving vosoritide

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Achondroplasia (ACH) is a common form of disproportionate short stature caused by impaired endochondral bone growth. Vosoritide, a recombinant C-type natriuretic peptide, stimulates endochondral bone growth and is approved in 42 countries for children with ACH until the closure of epiphyses. Here, we demonstrate the effect of long-term vosoritide treatment on sustained annualized growth velocity (AGV) and estimate height gain compared to untreated children with ACH if vosoritide treatment was continuous from age 6 months until final adult height (FAH). Pooled mean AGV (cm/year) by integer age and sex while on treatment is reported from the phase 3 study 111-301 (NCT03197766) and its ongoing long-term extension (LTE) 111-302 (NCT03424018) and the phase 2 study 111-206 (NCT03583697) and its ongoing LTE 111-208 (NCT03989947). Study 111-301 evaluated 15 μg/ kg/day vosoritide in children with ACH aged ≥ 5 to <18 years at screening until FAH, and 111-206 evaluated 30 and 15 μg/ kg/day vosoritide in children with ACH from 4 months to <5 years until near-FAH. Untreated data from CLARITY served as an external ACH control population. Interval AGV for 6 ± 1 and 12 ± 3 months were derived from paired height assessments from age 4 months to 3 years and age 3 years to FAH, respectively. The midpoint of the 2 height assessments determined the associated age to summarize AGV. Total height gain was derived by subtracting the difference in AGV between the treated and untreated population per age. Confidence intervals (CIs) were estimated by bootstrap methods. By the data cutoff (February 25, 2024), mean treatment follow-up in 192 total participants was 4.7 (range, 1.8-7.1) years for those from 111-302 ($n=119$) and 3.8 (range, 1.1-5.7) years for those from 111-208 ($n=73$). Both studies provided mean AGV (95% CI) estimates at ages 5-9 years; CIs overlapped with no trend whether treatment started before or after age 5 years. Given these analyses, expected estimated height gain for children with ACH if continuously treated from 6 months to FAH was 21.7 cm (95% CI, 18.7-24.6) in females and 26.4 cm (95% CI, 22.9-29.8) in males compared to untreated children. In these results from the longest follow-up of a phase 3 study of children with ACH, vosoritide treatment sustained increases in AGV. For the first time, we predict total height gain for children with ACH if they

were to be treated continuously with vosoritide from age 6 months to FAH compared to untreated children.

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OC7.5

JOINT1778

Effects of navepegritide on bone morphometry in children with achondroplasia: 52-week results from the approach clinical trial

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Background

In children with achondroplasia (ACH), morphometric changes in the spine and lower extremities are associated with a range of orthopaedic and neurological complications. Increased rates of thoracolumbar kyphosis, lumbar lordosis, stenosis of the spinal canal, and genu varum may lead to pain, altered mobility, and the need for orthopaedic surgery. Navepegritide is an investigational prodrug of C-type natriuretic peptide (CNP), administered by subcutaneous injection once weekly and designed to provide a low Cmax through sustained release of active CNP. Continuous exposure to the released CNP stimulates natriuretic peptide receptor B (NPR-B) to counteract the constitutively active fibroblast growth factor receptor 3 (FGFR3) in ACH. We report radiographic findings from ApproaCH, a pivotal randomized, double-blind, placebo-controlled trial evaluating navepegritide in children with ACH.

Methods

Participants ($n=84$, aged 2-11 years) were stratified by age and sex and randomized 2:1 to receive navepegritide (100 µg/ kg/week) or placebo. The primary endpoint was annualized growth velocity (AGV) at week 52. Bone morphometry parameters were exploratory endpoints assessed by blinded central readers using spine and lower extremity radiographs, with data expressed as changes from baseline at week 52.

Results

Navepegritide demonstrated superiority over placebo in AGV at Week 52, with a least square (LS) mean AGV of 5.89 cm/year in children treated with navepegritide vs. 4.41 cm/year with placebo (LS mean treatment difference 1.49 cm/year [$P<0.0001$]). Safety and tolerability were comparable between treatment groups. Spinal canal dimensions were numerically improved with navepegritide compared to placebo across L1-L5, with a significant increase from baseline observed for interpedicular distance at L1 (LS mean difference of 0.618 mm, $P=0.0222$). No statistically significant changes were observed in thoracolumbar kyphosis or lumbar lordosis. Compared to placebo, navepegritide significantly reduced tibia femoral angle (LS mean difference of -1.814 degrees, $P=0.0094$) and mechanical axis deviation in the lower limbs (LS mean difference of -2.781 mm, $P=0.0063$). These changes corresponded to a normalization in fibular overgrowth, considered the key cause of leg bowing, as reflected in the reduced fibula-to-tibia ratio (LS mean difference of -0.016, $P=0.0001$).

Conclusion

In the ApproaCH trial, weekly administration of navepegritide demonstrated superiority over placebo in AGV and improved aspects of bone morphometry in children with ACH. These findings highlight that the design of navepegritide, which provides continuous exposure to active CNP, may deliver benefits that go beyond promoting linear growth – actively targeting and addressing critical aspects of skeletal dysplasia in ACH, which are key contributors to health-related complications.

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OC7.6

JOINT1839

Hippocampal malrotation and transverse temporal sulcus abnoramlities: sensitive and specific neuroradiological markers of hypochondroplasia

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Introduction

Hypochondroplasia (HCH), caused by pathogenic variants in *FGFR3*, presents significant diagnostic challenges due to its phenotypic variability and subtle radiological findings. MRI findings, particularly hippocampal malrotation and abnormalities of the transverse temporal sulcus, have been identified as being more prevalent in conditions secondary to pathogenic variations in *FGFR3*, such as HCH. Hippocampal malrotation has a reported prevalence of 15-20% in the general population, and is more frequently observed in the left hemisphere (20%) than in the right (9%). We hypothesized that hippocampal malrotation and transverse temporal sulcus abnormalities are more common in HCH compared to the general population, and therefore could be helpful in the diagnostic workup of children with short stature.

Methods

A cohort of 29 children with genetically confirmed HCH was included in this study, involving Great Ormond Street Hospital and Evelina London Children's Hospital. Their high-resolution brain MRIs were anonymised and randomized with a cohort of 29 age-matched controls with short stature and suspected growth hormone deficiency. Two neuroradiologists (of 15 and 5 years' experience) were asked to separately assess the MRIs for hippocampal malrotation and transverse temporal sulcus abnormalities for each hemisphere. Significant differences from the age-matched cohort were calculated, and sensitivity and specificity in identifying HCH were evaluated. Inter-rater reliability was assessed using Cohen's kappa.

Results

The findings for each hemisphere in the HCH and age-matched control cohort are presented in the table. Overall, transverse temporal sulcus abnormalities showed the highest sensitivity and specificity in identifying children with HCH. Chi-squared test showed a significant association between hippocampal malrotation, transverse temporal sulcus abnormalities and HCH. Excellent inter-rater reliability was observed in evaluating hippocampal malrotation (Cohen's kappa: 0.83 right, 0.76 left) and transverse temporal sulcus abnormalities (Cohen's kappa: 0.93 right, 0.96 left).

	HCH % (*n*)	Age Matched Cohort % (*n*)	Sensitivity	Specificity	χ^2 (*P* value)
Hippocampal malrotation (Right)	86% (25/29)	10% (3/29)	89%	86%	33.42 (<0.05)
Hippocampal malrotation (Left)	90% (26/29)	14% (4/29)	86%	89%	33.42 (<0.05)
Transverse temporal sulcus abnormalities (Right)	97% (28/29)	3% (1/29)	96%	96%	50.27 (<0.05)
Transverse temporal sulcus abnormalities (Left)	97% (28/29)	7% (2/29)	93%	96%	46.68 (<0.05)

Conclusions

Our novel findings suggest that transverse temporal sulcus abnormalities and hippocampal malrotation are highly sensitive and specific biomarkers and may be important in the diagnosis HCH, especially in cases where skeletal findings are ambiguous. Future studies should explore whether these findings could also be useful for prenatal diagnosis through foetal imaging.

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OC7.7

JOINT1537

Sustained normalization of mineral homeostasis in autosomal dominant hypocalcemia type 1: results from a phase 2 study over 42 months of encaleret (cltx-305) treatment

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Autosomal dominant hypocalcemia type 1 (ADH1), due to activating calcium-sensing receptor gene (*CASR*) variants, manifests as low PTH, hypocalcemia, hypercalciuria, hyperphosphatemia and hypomagnesemia. Calcium and active vitamin D treatment worsens hypercalciuria, which may induce renal complications. Calcilytics are negative allosteric modulators of the calcium-sensing receptor that decrease its sensitivity to extracellular calcium and normalize biochemical abnormalities in ADH1 mice. This Phase 2b open-label study (NCT04581629) of the oral investigational calcilytic encaleret included 2 5d inpatient periods followed by a 24W outpatient period and a long-term extension (LTE). Conventional therapy was stopped prior to encaleret initiation. After about 18 months in the LTE, participants continued encaleret in the Phase 3 LTE (NCT05680818). Thirteen adults with ADH1 received encaleret individually titrated to normalize albumin-corrected calcium (cCa). Encaleret was well-tolerated. There were 2 unrelated serious adverse events during the LTE: chest pain and post-surgical pain. There were no treatment discontinuations/withdrawals prior to the LTE. Mean ± SD values taken pre-dose at P3W24 and LTEM36 compared to baseline (BL) are presented. PTH was low at BL (6.3 ± 7.8 pg/ml [nl 10-65]) and normal at P3W24 (35.3 ± 10.2) and LTEM36 (23.7 ± 16.8 [$P < 0.01$]). Similarly, hypocalcemia at BL (cCa = 7.1 ± 0.4 mg/dl [nl 8.4-10.2]) had normalized at P3W24 (9.0 ± 0.5) and LTEM36 (9.0 ± 0.3 [$P < 0.01$]). BL hypercalciuria (395 ± 216 mg/d [nl <250-300]) normalized to 202 ± 83 at P3W24 and LTEM36 (162 ± 103 [$P < 0.01$]). BL blood phosphate (4.5 ± 1.1 mg/dl [nl 2.3-4.7]) decreased at P3W24 (3.7 ± 0.5) and LTEM36 (3.7 ± 0.7 [$P < 0.05$]). Blood magnesium rose (BL 1.7 ± 0.2 mg/dl [nl 1.6-2.6]); P3W24 2.0 ± 0.2; LTEM36 2.0 ± 0.2 [$P < 0.01$]). Bone turnover markers, adjusted for age, sex, and menopausal status by dividing by the ULN for each participant [nl 0-1], were low at BL and increased at P3W24 and LTEM36 [$P < 0.05$; $P < 0.01$]). Compared with screening, DXA Z-scores had decreased at LTEM24 but then stabilized at LTEM36 ($n = 10$-11). In patients with ADH1, encaleret corrected biochemical abnormalities and increased bone turnover, with stabilization of bone density by 42 months of continuous treatment. These consistent and sustained results are clinically meaningful and support ongoing efficacy and safety evaluation of encaleret as the first potential treatment for ADH1.

	Baseline	P3W24	LTEM12	LTEM24	LTEM36
CTx (value/ULN)	0.4 ± 0.3	1.15 ± 1.0*	1.45 ± 1.23*	0.73 ± 0.48*	0.71 ± 0.53*
P1NP (value/ULN)	0.3 ± 0.1	1.22 ± 1.05*	1.04 ± 0.57*	1.1 ± 0.68*	1.37 ± 0.98*
AP spine Z-score	2.6 ± 1.5	2.3 ± 1.7	2.5 ± 1.7	2.2 ± 1.6*	2.2 ± 1.6*
Total Hip Z-score	2.2 ± 1.4	2.0 ± 1.4*	2.0 ± 1.3*	1.8 ± 1.1*	1.7 ± 1.1*
1/3 Radius Z-score	0.2 ± 0.9	0.3 ± 0.9	0.5 ± 0.5	-0.2 ± 0.4*	-0.1 ± 0.5*

*$P < 0.05$ compared with Baseline

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OC7.8

JOINT1420

Differential regulation of phosphate transport in epididymis and prostate: implications for sperm motility in mice and men

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Seminal phosphate concentrations are several folds higher than serum levels in healthy men, which implies an active phosphate transport within the male reproductive system. However, phosphate regulation in the male reproductive organs remains poorly understood. This study investigated the expression profiles of the sodium-phosphate co-transporters (NPT2a, NPT2c, NPT2b, PIT1, and PIT2) and phosphate regulation in the epididymis and prostate using rodent models and human tissues. In rodents, high dietary phosphate intake increased epididymal phosphate transporter expression without affecting epididymal phosphate levels. In contrast, prostatic phosphate concentrations increased with serum phosphate, independent of transporter expression. Human tissues exhibited distinct transporter expression profiles compared to rodents, warranting further investigation. A retrospective analysis of 301 healthy men further demonstrated that high seminal phosphate levels correlated with improved sperm quality and elevated testosterone levels. In conclusion, this study revealed distinct expression profiles of phosphate transporters in the male reproductive organs, with species-specific differences between mice and humans. These findings highlight the distinct phosphate regulation in the epididymis and prostate, underscoring the critical role of phosphate in male reproductive health, particularly its association with sperm quality and testosterone levels. Together, these results provide novel insights into phosphate metabolism in male reproductive function and suggest presence of potential therapeutic targets for addressing male infertility.

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OC7.9

JOINT1232

Long-term efficacy and safety of palopegteriparatide treatment in adults with chronic hypoparathyroidism: 4-year results from the phase 2 path forward trial

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Background
Hypoparathyroidism is an endocrine disease caused by insufficient levels of parathyroid hormone (PTH). Conventional therapy for hypoparathyroidism (active vitamin D, elemental calcium) aims to alleviate hypocalcemia but does not address insufficient PTH. Palopegteriparatide is a prodrug of PTH (1-34), administered once daily, designed to provide active PTH within the physiological range for 24 hours/day in adults with chronic hypoparathyroidism. It is approved by the EC, MHRA, and FDA. This analysis investigated the long-term efficacy and safety of palopegteriparatide in adults with chronic hypoparathyroidism through week 214 of the PaTH Forward trial.
Methods
PaTH Forward is a phase 2 trial with a 4-week randomized, double-blind, placebo-controlled period, followed by an ongoing open-label extension period. Renal function was assessed by estimated glomerular filtration rate (eGFR). Bone turnover markers C-terminal telopeptide of type 1 collagen (CTx) and procollagen type 1 N-terminal propeptide (P1NP), and bone mineral density (BMD) measured by DXA, were assessed at baseline and regular intervals through week 214. Safety assessments included 24-hour urine calcium and treatment-emergent adverse events (TEAEs).
Results
At week 214, 95% (56/59) of participants remained in the trial; of those, 93% were independent from conventional therapy (no active vitamin D and ≤600 mg/day elemental calcium) and 98% had normal albumin-adjusted serum calcium levels (2.07-2.64 mmol/l) with a mean (SD) of 2.24 (0.10) mmol/l. Mean CTx and P1NP increased from the low end of normal at baseline, peaked by week 26, and declined thereafter and remained stable above baseline levels through week 214. The elevated baseline mean BMD Z-scores trended towards age- and sex-matched norms at the lumbar spine, femoral neck, and total hip and largely stabilized after 26 weeks of treatment, remaining above zero through week 214. Changes in Z-scores were larger in participants with longer duration of hypoparathyroidism but were similar across the population when considering sex and age/menopausal status. Mean (SD) eGFR at week 214 was 86.0 (21.7) ml/min/1.73 m^2, reflecting a mean (SD) increase of 7.6 (13.7) ml/min/1.73 m^2 from baseline. Mean (SD) 24-hour urine calcium levels normalized with

palopegteriparatide treatment, remaining below the upper limit of normal (≤6.2 mmol/day) through week 214 (4.4 [2.1] mmol/day). TEAEs were mostly mild or moderate; no new safety signals were identified.
Conclusion
These results demonstrate sustained efficacy and safety of palopegteriparatide in adults with chronic hypoparathyroidism through week 214 of the PaTH Forward trial, highlighting continued benefits in skeletal dynamics and renal function.

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Oral Communications 8: Diabetes and Insulin Part 2

OC8.1

JOINT1533

Economic disparities and gender differences in pediatric diabetes Care: the SWEET international Registry

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Introduction and objective
Treatment strategies for pediatric Type 1 Diabetes (T1D) show substantial variation across countries. However, the role of national economic wealth interacting with gender differences on the outcome of care remains poorly defined. This study aims to assess these disparities using data from the worldwide SWEET registry.
Methods
We analyzed data from 54,285 pediatric patients with T1D (<25 years of age, diagnosed for >3 months) treated in 2022-2023. Participants (median age: 14.5 years; 52% male) were categorized into four groups based on their countries' GDP: low, lower-middle, upper-middle, and high income. Z-scores for height and BMI were calculated using the WHO reference standards. We performed linear and logistic regression analyses, adjusted for age, diabetes duration, and sex, to compare the outcomes across GDP groups. Gender-specific analyses were also conducted.
Results
Males consistently had higher height SDS across all income groups ($P<0.0001$). In contrast, females had higher BMI SDS, with the largest gender differences observed in the low-income groups ($P<0.0001$). HbA1c levels were highest in the low GDP group (8.7%) and lowest in the lower- and upper middle groups (7.5%). Overall, females had higher HbA1c levels ($P<0.0001$), with notable gender disparities in lower GDP quartiles (+0.07 to +0.15%), but no significant differences in the highest quartile. DKA episodes were most frequent in the high GDP group, and these were significantly more common in females ($P<0.001$). Females in the lower GDP quartiles had higher rates of severe hypoglycemia compared to males (0.10 vs. 0.07; $P<0.001$), with no gender differences in the highest GDP quartile. Insulin doses were found to be significantly higher in females ($P<0.001$). The use of diabetes technologies increased with GDP: insulin pump use ranged from 17% in low-GDP countries to 70% in high-GDP countries, CGM use from 36% to 91%, and AID systems from 11% to 38% (all $P<0.0001$). Females showed slightly higher adoption rates for both CGM and AID systems compared to males.
Conclusion
Females with T1D presented with shorter stature, higher BMI, and elevated HbA1c compared to males, particularly in lower-income settings. While they showed higher adoption rates of diabetes technologies, these advances did not fully close the gender gap, highlighting the need for targeted interventions addressing both gender and socioeconomic factors to ensure equitable outcomes in pediatric diabetes care.

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OC8.2

JOINT1832

Lipid profile in children living with Type 1 Diabetes: A novel approach using Z-scores for standardized comparison

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Background
Type 1 diabetes (T1D) is characterized by disrupted carbohydrate and lipid metabolism, predisposing individuals to cardiovascular disease and early death. Understanding lipid variations during childhood is crucial for assessing cardiovascular risk in T1D. A recent study from our team shows that lipid concentrations in healthy children vary across ages 5–17. Building on this, the current study aimed to assess the HDL, LDL, triglycerides, and remnant cholesterol profile in Danish children with T1D compared to healthy children, using age-adjusted z-scores.
Methods
Participants with type 1 diabetes (T1D) were recruited for the Copenhagen T1D 2016 cross-sectional cohort. Of the 256 participants diagnosed with T1D for at least one year, those younger than five or older than 17 years ($n=32$) were excluded to enable comparison with previously collected z-score data from a healthy control group, leaving 224 for analysis.
Results
The T1D cohort had significantly higher z-scores for total cholesterol in girls (median = 0.374, median control = 0.051; $P<0.001$) and LDL in girls (median = 0.287, median control = 0.019, $P=0.029$) as well as triglycerides in girls (median = 0.428, median control = 0.009, $P<0.001$) and boys (median = 0.356, median control = -0.018, $P=0.002$) and remnant cholesterol in girls (median = 0.651, median control = 0.049, $P<0.001$) and boys (median = 0.452, median control = 0.080, $P<0.$ 001). After adjusting for BMI z-score, the effect of BMI on all cholesterol z-scores was similar in both cohorts. Patients with T1D with an average weight (BMI z-score = 0), had significantly elevated total cholesterol z-scores compared to the control cohort in girls (Δz-score = 0.382, $P=0.002$), triglyceride in girls (Δz-score = 0.330, $P=0.006$) and boys (Δz-score = 0.314, $P=0.002$) and remnant cholesterol in girls (Δz-score = 0.489, $P<0.001$) and boys (Δz-score = 0.583, $P<0.001$). Non-compliance with the International Society for Pediatric and Adolescent Diabetes (ISPAD) LDL guidelines, whit an upper limit of 2.6 mmol/l, was 36% in the T1D cohort, compared to 31% in the control cohort.
Conclusions
This study highlights significant cholesterol differences in children with T1D through the novel application of age-adjusted z-scores, which provide a more precise comparison of lipid profiles between children with T1D and their healthy peers.

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OC8.3

JOINT320 The Proof of Concept INCEPTR trial 12 month outcomes – Intracutaneous islet transplant in humans into pre-vascularised Novosorb® neodermis

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Introduction
Allogeneic islet-cell-transplantation (ICT) is an established treatment for hypoglycaemic unawareness for selected people living with Type-1 diabetes (T1D) available in Europe, the UK and Australia. As ICT is currently practiced, allogeneic human islets are transplanted into the liver via the portal vein. However, up to 75% of the transplanted islet mass is lost within the first 48 hours post-transplant, due to the Instant Blood Mediated Inflammatory Reaction.

Pt	Pre-Islet transplant Novosorb® integration period	Total IEQ transplant	3/12 c-pep	3/12 HbA1c reduction	3/12 insulin reduction	6/12 HbA1c reduction	6/12 insulin reduction	12/12 HbA1c reduction	12/12 Insulin reduction
1	25 days	485,584	pos	1.1%	21%	1.8%	22%	1.8%	28%
2	33 days	204,633	neg	1.1%	10%	0.6%	7%	0.8%	21%
3	76 days	276,026	pos	0.3%	44%	0.3%	44%	1.3%	62%

Furthermore, the hepatic transplant site is unable to be easily biopsied, transplanted islets are unable to be monitored or retrieved, limiting the ability to detect and treat islet graft rejection. In order to develop an alternative to intrahepatic ICT we pre-implanted a Biodegradable Temporizing Matrix (Novosorb®) into the inner-bicep of three trial participants prior to ICT as part of our **IN**tra-**C**utaneous **E**ctopic **P**ancreas **TR**ial – INCEPTR. Pre-implantation of Novosorb® created a fully functional dense vascular bed capable of supporting transplanted islets within the intracutaneous-transplant site (Diabetes 2023 PMID: 36929171). Unlike the hepatic site, intracutaneous islet grafts can be monitored *in vivo*, enable topical immunosuppression and removed in toto, thus creating an attractive site for gene modified, xenogeneic- and stem-cell-derived ICT.

Method

INCEPTR is a prospective first-in-human study of allogeneic ICT into a prevascularised intracutaneous transplant site : Australian and New Zealand Clinical Trials Registry (ACTRN12621001573842). The INCEPTR trial primary outcome was detectable c-peptide at 3 months post-transplant. Secondary outcomes included average daily exogenous insulin usage and HbA1c measured at baseline, 3, 6 and 12 months post-transplant.

Results

Three immunosuppressed kidney transplant patients with longstanding T1D (c-peptide negative) underwent Novosorb® implantation under local anaesthesia as outpatients prior to intracutaneous cadaveric human islet transplantation.

Conclusions

In this study two of three participants had positive c-peptide at 3 months with all patients showing improvement in glycaemic control over 12 months. One of the patients with positive c-peptide at 3 months has ongoing long-term detectable graft function out to 2.5 years post engraftment. The prevascularised Novosorb® neo-dermis is safe and supported human islet cell survival in an intracutaneous transplant site outside of the liver.

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OC8.4

JOINT858 Crosstalk between neuronal mitochondrial dynamics and microglial activation during the hypoglycemic neuronal damage progression with cognitive deficit

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Severe hypoglycemia (HPG) is a critical adverse effect of insulin therapy in diabetes, potentially leading to brain damage and cognitive impairment. This risk is one of the major hurdles for enough glucose control and can be a fear to patients and healthcare providers. Our study investigates the crosstalk between mitochondrial dynamics and neuroinflammation to understand hypoglycemic neuronal damage mechanisms and identify potential therapeutic interventions. Male C57BL/6 mice were fasted for 24 hours and HPG (below 20 mg/dl) was induced by intraperitoneal (i.p.) injection of insulin. HPG was induced for 5 hours and terminated by glucose solution i.p. injection. Mice were then sacrificed on day 1, 4, and 7. Unbiased screening in cortex and hippocampus area revealed the retrosplenial cortex (RSC) as vulnerable to HPG among other cortex regions, evidenced by elevated oxidative stress with 4-hydroxynonenal immunohistochemistry on day 7. Progressive increases in oxidative stress and apoptosis, analyzed by terminal deoxynucleotidyl transferase dUTP nick end labelling staining, were observed in the RSC. While mitochondrial fragmentation, examined through transmission electron microscopy, immunoblotting, and immunohistochemistry, and inflammatory activation with IL-1β expression level were already significantly increased at day 1 whereas TNF-α and IL-6 expression levels were unchanged. Treatment with mitochondrial fission inhibitor [mdivi-1] or IL-1 receptor antagonist (IL-1ra) effectively mitigated hypoglycemic neuronal damage. Notably, elevated mitochondrial fission was only significantly increased in neurons, not microglia and astrocytes, as analyzed by co-localization of phosphorylated dynamin-related protein, a marker of activated mitochondrial fission, with markers specific to neurons, microglia, and astrocytes. In vitro experiments with cell-type-specific regulation using transwell co-culture system revealed that preventing mitochondrial fragmentation with mdivi-1 in neuronal cells [SH-SY5Y], and inhibiting IL-1 signaling with IL-1ra in either microglial cells [BV-2] or SH-SY5Y significantly prevented hypoglycemic damage. Morris water maze assessments confirmed the protective effects of these interventions against spatial memory impairment induced by HPG. These results suggest that direct regulation of neuronal mitochondrial fission, combined with indirect modulation through the crosstalk between neuroinflammation with IL-1 signaling, could prevent hypoglycemic neuronal damage and spatial memory impairment.

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OC8.5

JOINT1881 Redefining islet adaptations in human pregnancy: insights from immunohistochemistry and proteomics

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Introduction

Pregnancy requires pancreatic islet adaptations to maintain glucose homeostasis. Human studies show that β-cell mass increases in pregnancy, murine studies suggest that prolactin receptor (PRLR) and serotonin 2B (5-HT2B) receptor signalling are key to these adaptations. However, little is known about the islet proteome and α cells in human pregnancy. This study investigates pregnancy-associated islet changes using rare human pancreatic tissues from pregnant women, focusing on proteomic alterations, whole islet, α- and β-cell metrics, and the expression of the PRLR, 5-HT2B receptor, and glucagon-like peptide-1 (GLP-1).

Methods

Formalin-fixed paraffin-embedded pancreatic tissue from pregnant human donors ($n=7$, third trimester) and non-pregnant controls ($n=7$) best-matched by age, race, and BMI were obtained from the Network for Pancreatic Organ Donors with Diabetes. Islets were isolated using laser-capture microdissection, and proteomic profiling performed using liquid chromatography-mass spectrometry (LC-MS/MS). Islets were labelled by immunofluorescence, and images acquired using spinning disc confocal microscopy. Unbiased, automated computational image analysis of whole pancreatic tissue sections was used to quantify whole islet, α- and β-cell areas, and the abundance of PRLR, 5-HT2B receptor, and GLP-1. For each metric, values were normalised to total tissue area prior to comparisons to account for the size differences between tissue sections.

Results

LC-MS/MS identified 7,546 proteins in human islets, generating the largest dataset of islet proteins from pregnant women to date. Four proteins—cathepsin Z, β1,4-galactosyltransferase 4, cyclin-dependent kinase 5, and laminin subunit alpha 4—were significantly more abundant in third-trimester islets. In pregnancy, whole islet area increased 1.9-fold (3.0% vs. 1.6%, $P=0.0145$), α-cell area 4.3-fold (0.44% vs. 0.1%, $P=0.0206$), and β-cell area 1.9-fold (1.26% vs. 0.65%, $P=0.0241$), driven by increased cell numbers. In pregnant islets, PRLR expression was upregulated in α cells (302.3 vs. 267.7 AU/mm^2, $P=0.0398$) but not β cells ($P=0.0610$). The 5-HT2B receptor was absent in β cells, confirmed by colocalisation analysis and positive ductal staining as an internal control for antibody functionality. Additionally, GLP-1 abundance in α cells increased 2.9-fold (0.69% vs. 0.24%, $P=0.0184$).

Conclusion

Human islet adaptations in pregnancy differ from those in mice. While α- and β-cell areas expand, the absence of β-cell 5-HT2B receptor expression and minimal proteomic changes suggest alternative regulatory mechanisms. The increased α-cell area and GLP-1 expression highlight the potential role of α-cell-derived paracrine signals in supporting β-cell function. These findings underscore the need for human-based studies to further elucidate mechanisms driving islet plasticity in pregnancy and their relevance to gestational diabetes.

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OC8.6

JOINT459

68Ga-Exendin-4-guided surgery in children with congenital hyperinsulinism (CHI)

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Congenital hyperinsulinism (CHI) is a critical condition predominantly manifesting in neonates through severe hypoglycemic episodes. This can lead to severe brain damage and retardation of cognitive development if not detected and treated in time. Importantly, CHI is differentiated into focal and diffuse forms based on the distribution of affected pancreatic beta cells. Focal CHI typically arises from a paternally inherited heterozygous mutation in the ATP-sensitive potassium channel (*ABCC8, KCNJ11*) and can be identified by ^{18}F-DOPA or ^{68}Ga-Exendin-4 PET scan. However, intra-operative localization of focal CHI remained challenging until recently. This proof-of-concept study expands on previous work investigating the suitability of ^{68}Ga-Exendin-4, a GLP-1 receptor-binding tracer, as a diagnostic tool and as a tracer for radio-guided surgery to improve preciseness of intraoperative detection and resection of focal CHI lesions[1]. We describe a cohort of 27 patients with CHI. Preoperative imaging included ^{18}F-DOPA CT and ^{68}Ga-Exendin-4 PET MRI scans. During surgery, approx. 45 MBq of ^{68}Ga-Exendin-4 were administered intravenously. Beginning one minute after tracer application a handheld, cable-free positron probe was used at intervals of one minute to five minutes to intraoperatively locate the lesion by detecting positron emissions from the radiotracer. In 26 out of 27 cases, it was possible using ^{68}Ga-Exendin-4 to identify the CHI focus localization correctly. Additionally, the radio-guided surgery approach successfully facilitated the identification and resection of focal CHI lesions in 23 of 27 cases. Except for a significant increase in heart rate 1 min (mean = 125 ± 18/min vs. 139 ± 20/min, $P < 0.001$) and 30 min (mean = 141 ± 19/min, $P < 0.001$) after the administration of ^{68}Ga-Exendin-4, no adverse effects were observed. We compared the data with 12 patients with CHI, which were operated on without radio-guidance. The radio-guided approach reduced time of surgery (mean = 343 ± 83 min vs. 280 ± 107 min), though the difference was not statistically significant ($P = 0.072$), while also minimizing surgical complications (58.3% vs. 20%, $P < 0,05$). In conclusion this study confirms the efficacy of ^{68}Ga-Exendin-4 as both a diagnostic and intraoperative tool for focal CHI. Radio-guided surgery using ^{68}Ga-Exendin-4 improves lesion localization and reduces operative time, offering a promising advancement in the management of focal CHI.

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Oral Communications 9: Endocrine Related Cancer

OC9.1

JOINT2138

Cellular tumor microenvironment cross-talk in pediatric adrenocortical tumors: insights from single-nucleus RNA sequencing

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Pediatric adrenocortical tumors (pACTs) are rare adrenal cortex neoplasms, often presenting with Cushing's syndrome, virilization, or both. These tumors range from benign pediatric adrenocortical adenomas (pACAs) to aggressive pediatric adrenocortical carcinomas (pACCs). Our prior research identified four DNA methylation-based risk groups correlating with survival outcomes, yet their tumor microenvironment characteristics remain poorly understood. We performed single-nucleus RNA sequencing on 29 pACT samples to characterize immune infiltration and cell-cell communication across these risk groups. Cellular identities were determined using clustering and marker gene expression analysis. Low Risk 1 tumors exhibited significantly greater lymphoid (8.72%) and macrophage (19.75%) infiltration than High Risk tumors (lymphoid: 0.41%; macrophage: 3.6%), suggesting a more active immune environment in lower-risk tumors. Ligand-receptor analysis revealed distinct cell signaling patterns. High Risk tumors demonstrated increased fibroblast-to-endothelial signaling, particularly through collagen-related pathways (COL1A1, COL1A2, COL3A1-ITGA10_ITGB1), indicative of extracellular matrix remodeling and a pro-tumorigenic microenvironment. The MMRN2-CLEC14A interaction emerged as a dominant signal in High Risk tumors, suggesting increased endothelial activation and angiogenesis potential. In contrast, Low Risk 1 tumors showed homeostatic endothelial-fibroblast interactions, with COL1A2-CD93 and COL1A1-CD93 signaling likely contributing to extracellular matrix stabilization and tissue integrity. Notably, immune infiltration and cellular signaling patterns correlated more strongly with DNA methylation-based risk groups than with clinical manifestations such as Cushing's syndrome or virilization, emphasizing the limitations of clinical features in predicting tumor biology. These findings reveal distinct tumor microenvironment landscapes across pACT risk groups, with High Risk tumors exhibiting a pro-tumorigenic, angiogenic profile, while Low Risk tumors maintain a structured, immune-active microenvironment. The identification of key signaling pathways, such as MMRN2-CLEC14A, suggests potential targets for future therapeutic interventions. Our study underscores the importance of molecular profiling in risk stratification and treatment planning for pediatric adrenocortical tumors.

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OC9.2

JOINT894

Characterization of metastatic dissemination in Znrf3/Trp53 double knock-out mouse model

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Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with very poor prognosis due to the lack of successful therapies for patients with metastatic or recurrent tumors. However, the urgent need for the development of new therapies clashes with the lack of preclinical models that accurately represent ACC. Using Cre-loxP technology to mimic inactivation of *ZNRF3* and *TP53*, the most commonly found alterations in ACC patients from the most aggressive subgroup, we developed a new clinically relevant mouse model allowing for the study of the molecular basis of metastatic ACC. Using a combination of Kaplan Meier analysis, bulk RNA sequencing and immunohistochemistry, we demonstrate that adrenal cortex specific ablation of *Trp53* and *Znrf3* results in development of metastatic and lethal ACC over a 6-month time course. This is associated with other characteristics observed in most aggressive ACC patients, as the molecular signature of C1A subgroup, immune poor, steroidogenic high, and proliferation high signatures or the overexpression of the EZH2 methyltransferase and a constitutive activation on WNT pathway. Single nucleus RNA sequencing of primary tumors showed that acquisition of aggressive features is associated with amplification of a population of proliferative cells characterized by expression of *Dab2*, *Wnt4*, *Lef1*, *Mki67*, *Rad51* and *Ezh2*. These molecular features are also found in lung metastases, as assessed by both immunohistochemistry and spatial transcriptomic analysis, suggesting that these originate from dissemination of this set of cells. In addition, metastatic dissemination is associated with upregulation of senescence-related signatures. Immunolabeling for P16 and SA-β-galactosidase revealed the presence of senescent macrophages in the most aggressive primary tumors and their corresponding metastases. Single cell transcriptomic analysis of the immune compartment showed that senescent macrophages also express immune-checkpoint and pro-tumoral signatures, suggesting a role for senescent cells in promoting metastatic progression by inhibiting the anti-tumor response. Interestingly, multi-omics analyses of TCGA data have correlated senescence with poor prognosis and survival, highlighting this process as a new ACC therapeutic target. We are therefore currently evaluating the therapeutic potential of senolytics in our ACC mouse model. Altogether, these data shed light on the underpinnings of metastatic dissemination and establish these mice as a good *in vivo* model to investigate novel therapeutic options.

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OC9.3

JOINT1268

Genetic and functional heterogeneity in aldosterone producing adenomas

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Primary aldosteronism (PA), the most common secondary form of hypertension, results from excessive and autonomous aldosterone production by the adrenal cortex. Gain-of-function mutations in genes encoding ion channels or transporters underlie both inherited and acquired forms of PA. These mutations typically promote cell depolarization and increase intracellular Ca^{2+} levels, driving the overexpression and activity of the aldosterone synthase. Cellular heterogeneity is thought to be an intrinsic feature of PA, modulating its presentation and severity. However, understanding this complexity at the single-cell level has been challenging due to the limitations of traditional methods and lack of functional read-outs. To overcome this, we have combined single-cell long-read RNA sequencing (scRNA-seq), PatchSeq and high-throughput automated patch-clamp (HT-APC) techniques. This approach was applied to freshly dissociated cells from adrenal tissues resected from patients with aldosterone-producing adenomas (APA) or adrenal hyperplasia at the University Hospital Zurich. Preliminary analysis of 2,177 adrenocortical cells from seven patient samples (from normal, tumor and hyperplasia tissues) revealed over 100 likely pathogenic variants, as per ClinVar. These include known PA-driver mutations in KCNJ5, CLCN2, CACNA1D, and CACNA1H, along with novel mutations in potential steroidogenesis-related genes such as WNK1, VDR, PEX1, and KCNJ1. Interestingly, some genetic variants co-occur with known PA-driver mutations, offering insights into the one- or two-hit models of APA development. For future functional analysis, we have developed an automated pipeline that integrates high-content imaging with HT-APC electrophysiological data to identify recorded cells using steroidogenesis markers. The use of PatchSeq enables correlation of cellular functional data with mutation status and transcriptomic profiles, contextualizing the datasets derived from scRNA-seq and HT-APC. Additionally, transcriptomic analysis is anticipated to uncover novel cell markers associated with increased steroidogenesis. This innovative approach provides a detailed understanding of PA's molecular and functional heterogeneity at the single-cell level. The tools developed in this study could be broadly applied to other tissues where alterations in electrophysiological properties drive disease progression.

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OC9.4

JOINT1033

Clinical and mechanistic implication of aspartyl-tRNA synthetase (DARS1) in the transition from MASLD to hepatocellular carcinoma

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Background and aims

With the increasing incidence of metabolic dysfunction-associated steatotic liver disease (MASLD) and its association with hepatocellular carcinoma (HCC) development, novel potential clinical strategies are required. We have demonstrated that aminoacyl-tRNA synthetases (ARSs), which catalyze the transfer of amino acids to tRNAs, are altered in MASLD/HCC. Here, we explore the potential of aspartyl-tRNA synthetase (DARS1) as diagnostic biomarker and therapeutic target, as its molecular implication in MASLD/HCC.

Method

Tissular DARS1 levels were analyzed in *in silico* cohorts (mRNA/protein) of MASLD and HCC and in cytosolic/nuclear protein fractions of HCC patients ($n=42$). DARS1 levels were measured in plasma samples of two cohorts (Cohort1: 21 controls, 15 MASLD, 14 cirrhosis, 32 HCC; Cohort2: 8 controls, 8 HCC). Functional assays were performed in liver-derived cell lines (HepG2, Hep3B, SNU-387) after DARS1 modulation (silencing, overexpression, pharmacological inhibition). DARS1-overexpressing Hep3B cells were used for *in vivo* xenograft and orthotopic tumor formation. DARS1 immunoprecipitation and quantitative proteomics were performed in cytosolic/nuclear Hep3B fractions.

Results

DARS1 abundance was reduced in MASLD but increased in HCC tissues (mRNA/protein) and plasma [Area Under Curve (AUC) of plasma levels: HCC vs. controls: 0.8376; HCC vs. MASLD: 0.9016; HCC vs. cirrhosis: 0.8095]. DARS1 levels were higher in aggressive tumors (i.e. invasive, dedifferentiated), in patients with adrenal/lung metastasis, and in patients with metabolic disease. Consistently, *DARS1* silencing/pharmacological inhibition reduced, while *DARS1* overexpression increased, functional parameters of aggressiveness *in vitro*. In fact, xenograft and orthotopic tumors formed by *DARS1*-overexpressing cells had increased establishment capacity *in vivo*. Mechanistically, DARS1 protein levels were higher in nuclear, but not cytosolic, samples of HCC. An immunoprecipitation assay revealed 132 nuclear DARS1 interactors, three of the latter being members of the Spt-Ada-Gcn5 acetyltransferase (SAGA) complex, which regulates MYC acetylation and stability. This non-canonical interaction was confirmed by *in silico* docking of DARS1/SAGA crystal structures. Additionally, *DARS1* modulation regulated MYC protein levels and phosphorylation, and the expression of MYC targets was reduced in RNA-seq data of *DARS1*-silenced liver cells. Consistently, *DARS1* silencing reduced drug-induced senescence (Gemcitabine, Etoposide, Cisplatin), suggesting a link between DARS1-SAGA interaction and MYC-regulated senescence.

Conclusion

DARS1 is reduced in MASLD and overexpressed in HCC tissues and plasma samples, especially in metabolic disease patients. DARS1 could be implicated in the development of MASLD and its progression to HCC, wherein it could serve as biomarker or therapeutic target.Fundings: ISCIII (PI20/01301, PI23/00652; co-funded by the European Union), MINECO (FPU20/03957), JdA (PEMP-0036-2020, BIO-0139), FSEEN and CIBERobn/ehd.

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OC9.5

JOINT395

Acromegaly and cancer - a nationwide study in Sweden 1991-2018

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Introduction
Growth hormone (GH) excess and elevated levels of insulin-like growth factor-1 (IGF-1) in acromegaly are associated with cell proliferation and cancer promotion. We aimed to investigate the incidence of cancer and the cancer-related mortality in patients with acromegaly.
Methods
A register-based cohort study was performed in patients with acromegaly diagnosed 1991-2018, and identified in the Swedish Pituitary Register and in the National Patient Register. For each patient we included ten controls from the genereal population matched by sex, age and municipality of residence. Cancer diagnoses were obtained from the National Cancer Register. A Cox proportional hazard regression model adjusted for age, sex and comorbidity was used to estimate adjusted Hazard Ratio (aHR) and 95% CIs.
Results
We included 1035 patients with acromegaly (median age at diagnosis 52 years (Q1-Q3: 40-62.5), 49.5% female) and 10 261 control subjects. Median follow up time was 10.8 years (Q1-Q3: 5.2-17.5). Eighty percent underwent surgery and 13.5% radiation therapy. In the National Prescribed Drug Register from 2005 pharmacological treatment with Somatostatin analogs was reported in 41%, and GH receptor antagonist in 10% of the patients diagnosed from 2005. At 10 years follow-up 83% had biochemical control. Cancer was more common in the patients with acromegaly (aHR 1.33 (95% CI: 1.14-1.56), $P < 0.001$). The highest aHR was found in the subgroups of colorectal cancer (aHR 1.73 (95% CI: 1.16-2.58), $P = 0.007$) and lung cancer (aHR 1.92 (95% CI: 1.18-3.11), $P = 0.008$). The aHR for these two cancer diagnoses was higher already from five years before acromegaly diagnosis until study end, which was also seen for breast cancer in women. Pituitary surgery, radiation therapy, hypopituitarism or biochemical control were not associated with cancer when they were included as covariates in a Cox regression model. The overall mortality rate was increased in the patients (aHR 1.19 (95% CI: 1.03-1.37), $P = 0.019$), which was associated with cardiovascular disease (aHR 1.76 (95% CI: 1.22-2.53), $P = 0.002$), but not with cancer, diabetes, hypertension or cerebrovascular disease. Biochemical control was associated with lower mortality (aHR 0.67 (95% CI: 0.49-0.91), $P = 0.011$) compared to patients not biochemically controlled.
Conclusions
This matched nationwide study indicates an increased risk of cancer in patients with acromegaly even years before the diagnosis was established, with colorectal and lung cancer showing the highest increase in hazard ratios. Our findings underscore the importance for clinicians to be vigilant for early signs of cancer in patients with acromegaly.

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Oral Communications 10: Pituitary, Neuroendocrinology and Puberty Part 2

OC10.1

JOINT1675

Single-nucleus multiome profiling of the arcuate-median eminence complex in male marmosets provides molecular insights into the postnatal dynamics of the hypothalamic-pituitary-gonadal axis

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Introduction
Minipuberty, a transient activation of the Hypothalamic-Pituitary-Gonadal (HPG) axis in early infancy, plays a crucial role in early gonadal maturation and serves as a diagnostic window for future reproductive function. Despite its critical importance, particularly in males, the molecular mechanisms and dynamics underlying minipuberty remain poorly understood. Rodent models offer limited insights, as they lack an activity phase comparable to human minipuberty. To address this gap, we aimed to investigate cell-specific expression and chromatin accessibility dynamics in the hypothalamus, specifically the arcuate nucleus/median eminence (ARC/ME) region, using male marmosets (*Callithrix jacchus*) as a translational model during this critical developmental phase.
Objectives and methods
We profiled a total of 9 animals from 3 developmental stages: newborn (0–1 day), 3-week-old (during minipuberty), and 12-week-old (post-minipuberty). In addition to brain tissues, serum was collected and androgen levels were measured via liquid chromatography-tandem mass spectrometry (LC-MS/MS) to further validate the selection of these developmental stages.
Results
Single-nucleus RNA sequencing (snRNA-seq) of the hypothalamus generated a comprehensive dataset of over 70,000 nuclei, allowing for the identification of distinct neuronal and non-neuronal populations. Analysis revealed stage-specific transcriptomic shifts across major cell types during early postnatal development, highlighting dynamic changes in hypothalamic function. We successfully profiled key HPG axis-regulating neurons, including KISS1-expressing populations, which play a central role in GnRH signaling. Additionally, hormonal measurements confirmed significant differences in androgen levels between developmental stages, supporting the physiological relevance of the selected time points.
Conclusions
These findings provide high-resolution insights into hypothalamic neuroendocrine regulation, emphasizing its role in growth and reproductive hormone dynamics during postnatal maturation. The observed stage-specific transcriptomic shifts and hormonal differences contribute to a deeper understanding of HPG axis activation and suppression, offering a framework for studying minipuberty and its implications for reproductive development.

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OC10.2

JOINT1276

PSA as a marker of androgen activity during pubertal transition in healthy boys

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Context
Prostate specific antigen (PSA) is an androgen-responsive biomarker regulated by testosterone (T) and dihydrotestosterone (DHT), with its expression tightly linked to androgen receptor activation. While PSA is primarily used in clinical practice for prostate cancer screening and monitoring, its physiological role as an androgen regulated protein suggests it may serve as a marker for androgen bioactivity in male pubertal development.
Objective
To evaluate PSA as an androgen-responsive biomarker in healthy boys during pubertal transition and to establish age-specific reference intervals for serum PSA concentrations.
Methods
This longitudinal study included 104 boys (corresponding to 890 serum samples) from The Copenhagen Puberty Study II conducted from 2006 to 2011. Serum PSA was measured using a commercially available assay with a limit of quantification (LOQ) of 0.014 µg/l. Age-specific RIs were developed using the generalized additive model for location, scale, and shape (GAMLSS). Total T was measured using a radioimmuno assay with a limit of detection (LOD) of 0.23 nmol/l. Free T was calculated using the Vermeulen equation. Pubertal onset was defined as a genital staging of G2.
Results
PSA concentrations were undetectable in prepubertal boys (G1) and at pubertal onset (G2). A significant increase in median PSA concentrations was observed from G2 to G3 (0.042 [0.009 - 0.104] µg/l, $P < 0.001$). This upward trend continued into later stages (G4: 0.215 [0.116 - 0.357] µg/l, $P = 0.005$; G5: 0.294 [0.204 - 0.447] µg/l, $P = 0.003$). The increase between G3 and G5 was significant ($P = 0.003$), whereas no significant difference was found between G3 and G4 ($P = 0.005$).
Conclusion
Serum PSA concentrations increase progressively with pubertal development, mirroring the rise in bioactive androgens. While PSA remains undetectable in early puberty, its significant rise from G3 onward suggests a threshold effect, where androgen levels must reach a critical point before inducing measurable PSA production. These findings confirm PSA as an androgen-responsive

biomarker, with its increase reflecting androgen receptor activation by testosterone and DHT. Our study provides clinically relevant reference intervals for PSA in the assessment of boys during pubertal transition.

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OC10.3

JOINT1497

Nuclear factor I/B interaction with PROP1 and its role in pituitary cell differentiation

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The transcription factor PROP1 is necessary to trigger the onset of pituitary development by promoting the differentiation of stem cells into hormone-producing cell lineages by an epithelial-to-mesenchymal transition-like (EMT-like) process. Biallelic loss of function mutations in PROP1 cause deficiencies in growth hormone, thyroid stimulating hormone, and prolactin. PROP1 target genes have been identified, but little is known about interacting protein partners. We genetically engineered mouse pituitary GHTF1 cells to express biotin-tagged PROP1 and performed Rapid Immunoprecipitation and Mass spectrometry Experiments (RIME) to identify PROP1 interacting proteins. From 43 candidate proteins detected, we selected Nuclear Factor I/B (NFIB) for further studies based on the role of this gene family (NFIA, NFIB, NFIC, and NFIX) in development of other tissues. This family plays a role in developing the central nervous system, lungs, hair follicles, and skeletal muscle tissue. Notably, NFIB is involved in promoting EMT in various types of cancer. Using immunostaining, we observed that the pattern of NFIB and NFIA expression during mouse pituitary development was similar to SOX2 from e12.5 to e16.5. NFIB and NFIA also colocalized early on (e12.5) with PROP1. NFIB and NFIA have overlapping function in some organ systems and biallelic loss of function causes embryonic lethality. Thus, we generated a pituitary-specific knockout mice of *Nfib* and *Nfia*:*Hesx1Cre*/+; $Nfia_{Flox/Flox}$; $Nfib_{Flox/Flox}$. At postnatal day 1 these mice have an increase in the number of alpha-GSU and TSH-positive cells (with normal corticotrophs and somatotrophs). The stem cell population expressing SOX2 was not different between mutant and controls. We found increased double-positive GH and TSH-producing cells, suggesting that NFIB and/or NFIA are required to maintain proper cell lineage differentiation during pituitary organogenesis. Together, our findings expose NFIA/NFIB as important factors for pituitary lineage confinement. Further research is needed to understand the molecular mechanisms underlying these processes.

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OC10.4

JOINT710

Unravelling the core regulatory network controlling stem cell fate in the anterior pituitary

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The anterior pituitary is a primary endocrine organ responsible for orchestrating major physiological processes including growth, metabolism, reproduction and our response to stress through hormone secretion. This dynamic gland contains a tissue-specific population of stem cells marked by the expression of the transcription factor (TF) SOX2, which are required for homeostasis throughout life. Although pituitary stem cells (PSCs) are highly proliferative during early postnatal life, their regeneration capacity declines with age, remaining largely quiescent during adult homeostatic conditions as a long-lived population. Knowing the genetic mechanisms of stem cell regulation is necessary to enable their exploitation in regenerative approaches for pituitary disorders. Previous research has demonstrated a central role for YAP/TAZ signalling in PSCs to promote self-renewal and proliferation while repressing differentiation *in vivo*, thereby positioning YAP as a key component of PSC regulation, acting through TEAD TFs. We carried out single nuclei (sn) multiome sequencing of anterior pituitaries from an inducible YAP overexpression model, where overexpression of non-degradable mutant YAP protein instigates self-renewal of PSCs. snMultiome studies enable gene expression profiling and chromatin accessibility simultaneously from individual cells. Transcription factor fingerprinting analyses revealed Nuclear Factor I (NFI) A, NFIB, NFIC and NFIX TFs as highly relevant to PSC regulation. The NFI family of TFs are important for cell fate of stem cell populations in other tissues, yet their role or possible involvement in pituitary disease has not been previously investigated. Here, we characterise NFI expression in the murine and human pituitary gland and demonstrate *in silico*, *in vitro* and *in vivo* data supporting that NFIs, together with YAP/TEADs and SOX2 are a core regulatory network driving stem cell self-renewal in the anterior pituitary.

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OC10.5

JOINT2959

Characterization of hormone-secreting hiPSC-derived pituitary organoids

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Background
The pituitary gland is the hub of our endocrine system as it is responsible for the production of hormones that drive and regulate important physiological processes including body growth, lactation and stress. Organoids are complex 3D structures that mimic the biological functions of the target organ and allow the study of physiopathological mechanisms. The development of *in vitro* models using human induced pluripotent stem cells (hiPSC)-derived pituitary organoids has helped gain knowledge on pituitary biology and disorders[1,2]. However, up to date the generation of hormone-secreting organoids remains challenging because of the paucity of cells that differentiate into hormone-secreting cells.
Objective
In this study, we aimed to generate pituitary organoids with an improved ratio of hormone-secreting cells.
Methods
AG08h and KOLF2.1J hiPS cell lines were both derived from healthy donors, and 10742L from a patient with Leber hereditary optic neuropathy. All three hiPS cell lines underwent to genomic characterization prior to their differentiation towards pituitary organoids. hiPSCs were differentiated into pituitary organoids as previously described 3. Cells were maintained in culture up to 108 days and the expression of pluripotency markers and pituitary differentiation markers as well as those of *ACTH*, *GH* and *PRL* was measured via real time- quantitative PCR (RT-qPCR). Protein levels of ACTH, GH and PRL were measured by immunofluorescence (IF) and ELISA.
Results
We observed the presence of an epithelial layer as early as day 10 in all hiPS cell lines. In line with this, as of day 30 mRNA levels of *EpCAM* increased. Whereas the expression of pluripotency markers (*SOX2* and *NANOG*) strongly decreased along with differentiation, mRNA levels of *POU1F1*, *PITX1* as early pituitary differentiation markers increased. In addition, we found increased levels of *HESX1* between day 30–48 suggesting proliferation of pituitary progenitors, followed by increased *TBX19* and *PROP1* between day 48-60 pointing at further differentiation towards both corticotroph and somato-lactotroph cell lineages. Consistently, from day 60 onwards, we found an increase of *ACTH*, *GH* and *PRL* mRNA levels.
Conclusion
Here, we induced pituitary differentiation using three different hiPS cell lines. Of note, all three hiPS cell lines showed variable basal levels of ACTH secretion in culture media, and 10724L showed also secretion of prolactin, thus representing an interesting model to study both pituitary development and diseases.

References
1. doi:10.3389/fendo.2023.1233714.
2. doi:10.7554/eLife.90875
3. doi:10.1016/j.stemcr.2023.05.002.

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OC10.6

JOINT2750

Hydroxytyrosol mitigates high-fat diet-induced precocious puberty in rats through gut microbiome remodeling

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Background
Precocious puberty (PP) may lead to multiple adverse outcomes. Growing epidemiological evidence implicates that a high-fat diet (HFD) is closely related to precocious puberty (PP). Emerging evidence suggests that PP is a gut–brain axis disorder involving microbial-endocrine crosstalk. Hydroxytyrosol (HT) demonstrates multiple bioactive properties, yet its impact on PP remains unexplored. We aimed to investigate the effects of HT on PP and gut microbiota (GM) in animals.
Objective
This study aimed to explore the therapeutic potential of HT in HFD-induced PP through modulation of the gut microbiota (GM)-hypothalamic-pituitary-gonadal (HPG) axis.
Study design and methods
A PP model was established in feeding female Sprague-Dawley rats through HFD administrated from postnatal day 21, and with HT by gastric until virginal opening. Four experimental groups were evaluated: normal diet control (NC) group, HFD group, NC + HT group, and HFD + HT group. Puberty onset was monitored via vaginal opening timing. Blood, fecal, and hypothalamic samples were harvested to evaluate potential mechanistic pathways. Furthermore, fecal microbiota transplantation (FMT) was conducted to confirm the causality between HT and PP risk.
Results
Administration of HT in female offspring rats delayed vaginal opening and extended the first estrous cycle, accompanied by reduced serum estrogen, serum luteinizing hormone (LH) and follicle stimulating hormone (FSH). The 25 mg kg^{-1} HT treatment significantly downregulated hypothalamic expression of gonadotropin-releasing hormone (GnRH) and kisspeptin proteins. These benefits were achieved through the modulation of the gut microbiome, which functionally suppressed the HPG axis and prevented PP progression. Notably, FMT experiments indicated that the causal correlation between HT intake and PP is mediated by the gut microbiome alterations.
Conclusion
Our findings establish HT as a novel microbiota-modulating agent that attenuates HFD-induced PP through gut microbiome-mediated regulation of neuroendocrine pathways. This suggests potential clinical applications of dietary polyphenols in PP prevention strategies.

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Oral Communications 11: Thyroid Part 1

OC11.1

JOINT872

Retrospective, multicentre evaluation of the clinical features and associated diagnostic challenges of central congenital hypothyroidism in the UK

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Introduction
Central congenital hypothyroidism (CeCHT) is a rare disorder occurring due to defective TSH-mediated stimulation of the thyroid, usually as part of multiple pituitary hormone deficiency (MPHD). CeCHT is not targeted by the UK TSH-based neonatal screening programme, in contrast to countries operating primary T4 ± TSH-based screening methodologies. Arguments in favour of CeCHT screening include the potential to prevent illness and associated neurodevelopmental sequelae through earlier management of otherwise undiagnosed pituitary hormone deficiencies. However, routes to detection and clinical consequences of CeCHT have not been evaluated in the UK, precluding predictions of whether neonatal screening could be beneficial.
Method
We assessed biochemical and clinical characteristics in 118 CeCHT cases diagnosed between 1996 and 2022 at 4 tertiary UK centres and considered diagnostic challenges in the context of the clinical picture, baseline biochemistry and the potential impact of screening. Pseudonymized, electronic case records were reviewed retrospectively, recording markers of neurodevelopmental outcome and comparing percentages or median values in patients with early ('ED', < 15 days, i.e. within a typical newborn screening window) versus late diagnosis ('LD') for whom definitive data was available.
Results
26% cases were preterm, and 96% exhibited MPHD. Early treatment was commenced in only 19% ('ED'). Neonatal symptoms included hypoglycaemia, (95% ED, 66% LD) consistent with more frequent ACTH deficiency in ED cases (96% ED, 64% LD) and prolonged neonatal jaundice (61% ED, 62% LD). Hypothyroidism was usually moderate (FT4 SDS -2.4 and -2.6 in 'ED' and 'LD' groups). FT4 was initially checked at 54 days in LD cases, but fell within the laboratory reference range in 29%, and was first defined as abnormal on testing a median of 474 days later. In 24% cases, levothyroxine commencement was delayed (median 169 days, max. 7 yrs) after the first abnormal biochemistry. Significant neurodevelopmental concerns were noted in 37% patients (36% ED, 38% LD) of whom 75% had concomitant ACTH deficiency and in whom midline defects were common (56% vs 18% cases without significant concerns).
Conclusions
This is the largest evaluation of clinical features and pathways to diagnosis in a UK CeCHT cohort. Our findings demonstrate a vulnerable group of children, in whom frequent, MPHD-associated neurodevelopmental concerns mandate optimal management of thyroid status. However, despite neonatal symptoms, challenges in interpreting thyroid biochemistry and delays in testing frequently impede prompt diagnosis. There is a clear need both for systematic identification of CeCH in early life and for improved biochemical diagnostic tools.

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OC11.2

JOINT1125

Functional non-coding variants in a TTTG microsatellite on chromosome 15q26.1 are a common genetic etiology of congenital hypothyroidism, and present with a mild phenotype

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Introduction
Variants affecting a microsatellite on the non-coding region of chromosome 15q26.1 are associated with familial non-autoimmune thyroid abnormalities that are characterized by mild congenital hypothyroidism (CH) with elevated thyroglobulin (Tg) levels. Individuals harboring these variants may develop multinodular goiter (MNG) in the absence of treatment. Although these variants have been recognized as genetic etiologies of CH, nongoitrous, 3 (CHNG3), the associated severity of CH remains unclear.
Methods
A cohort of 63 participants diagnosed with CH at Tohoku University underwent screening for genetic variants on 15q26.1. We subsequently analyzed the clinical phenotypes of the variant-carrying participants.
Results
We identified five 15q26.1 variant carriers from four families among the cohort. Family histories of thyroid abnormalities were documented in three particpants of these two families. The variant carriers exhibited mild CH phenotypes, with two discontinuing levothyroxine treatment and the others requiring relatively low doses (1.33–1.89 μg/ kg/day) at their final visit. Notably, the patients' elevated neonatal TSH levels decreased spontaneously within weeks. This suggests that congenital

thyroid hormone synthesis capacities are compensated for during early infancy in a subgroup of patients with CHNG3. All the variant carriers presented with ectopic and normal-sized thyroid glands. During levothyroxine treatment, serum thyroglobulin and thyroid-stimulating hormone (TSH) levels were within the reference ranges at the majority of the evaluation points. Three of the five participants continued treatment into adulthood, whereas the other two discontinued treatment and maintained their serum TSH levels within the reference range. All five participants demonstrated normal intellectual development and stature. Notably, in our sister participants who discontinued their treatments at puberty after 5 and 13 years of levothyroxine treatment, respectively, one of them with a short treatment period exhibited significantly higher Tg levels following treatment. This observation may be attributed to the fact that levothyroxine replacement can prevent thyroid gland enlargement resulting elevation in serum Tg levels, suggesting that levothyroxine treatment may prevent thyroid enlargement and lead to MNG requiring surgical intervention.

Conclusion

These findings provide further evidence supporting the role of 15q26.1 variants as a common genetic etiology of CH, with clinical phenotypes including transient CH. Early genetic evaluation may facilitate the identification of 15q26.1 variant carriers among patients who are diagnosed with CH.

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OC11.3

JOINT817

Subclinical hyperthyroidism, cardiovascular disease and all-cause mortality: insights from a large DUTCH primary care cohort study

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Background

Subclinical hyperthyroidism (SHT) has previously been associated with adverse cardiovascular outcomes, yet the magnitude and consistency of risk and its demographic variation remain unclear due to limited sample sizes of subgroups in previous cohorts.

Objectives

To evaluate the association between SHT and the risk of atherosclerotic complications, atrial fibrillation (AF), heart failure (HF), and all-cause mortality in a large primary care population.

Methods

This retrospective cohort study analyzed data from the PHARMO Dutch GP database. SHT was Based on thyroid hormone levels available in the dataset. Outcomes were compared between SHT patients ($n=11,163$) and a euthyroid reference group ($n=46,058$) using multivariable Cox regression models.

Results

SHT was not significantly associated with atherosclerotic complications. However, the risk of AF was markedly increased (multivariate HR 1.4; 95% CI, 1.2–1.6), particularly in patients with TSH <0.1 mU/l and younger patients (aged 30–49 years). HF risk was modestly elevated (multivariate HR 1.2; 95% CI, 1.0–1.4), with a stronger effect in younger patients (aged 30–49 years) and in women. All-cause mortality risk was also higher in the SHT group (multivariate HR 1.5; 95% CI, 1.4–1.6), especially in men and with younger age.

Conclusion

SHT is associated with increased risks of AF, HF, and all-cause mortality, with some notable demographic differences. Younger patients exhibited a higher relative risk, particularly for AF and all-cause mortality, challenging the traditional focus on older populations. These findings highlight the need for careful monitoring and individualized risk assessment in patients with SHT.

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OC11.4

JOINT1486

Use of thyroid hormones in euthyroid patients: results of an international survey among thyroid experts

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Introduction

Evidence consistently points against the use of thyroid hormones (TH) in euthyroid patients. It is unclear to what extent this therapeutic approach is adhered with.

Objectives

Questionnaires documenting the frequency of thyroid specialists' TH use in euthyroid individuals.

Methods

Data collected 2019-2022 by THESIS (Treatment of Hypothyroidism in Europe by Specialists; An International Survey), a large-scale survey of European, Australian and Latin American thyroid experts focused on the use of TH for hypothyroidism and non-hypothyroid indications. Eight questions explored respondent characteristics, and 23 the use of TH. Here we report on the use of TH in euthyroid female infertility with high level of thyroid antibodies, simple goiter growing over time, obesity resistant to lifestyle interventions, depression resistant to anti-depressant medications, severe hypercholesterolemia as complementary treatment, and unexplained fatigue.

Results

Of 18,543 endocrinologists invited, 5,863 valid responses were obtained (938 from 6 countries in Western Europe, 1,679 from 9 countries in Eastern Europe, 2,053 from 6 countries in Southern Europe, 713 from 5 countries in Northern Europe, 312 from 2 countries in Western Asia, 87 from Australia, 81 from Latin America). Between 35-55% stated that TH are never indicated for euthyroid patients. TH were more frequently suggested in female infertility (34-48%), and in growing goiter (10-41%); in other scenarios less frequently [obesity (0-7%), depression (4-17%), hypercholesterolemia (3-8%), unexplained fatigue (3-9%)]. TH were more frequently suggested in female infertility by female endocrinologists younger than 60 years managing a high number of thyroid patients, whereas in growing goiter by non-endocrinologists older than 60 years practicing in areas with present or former insufficient iodine intake (uni-multivariate analysis).

Conclusion

This large scale international survey shows that thyroid experts would use TH in different clinical scenarios in euthyroid individuals, particularly in female infertility and goiter. This finding is concerning and needs to be addressed.

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OC11.5

JOINT196

Efficacy and safety of veligrotug (VRDN-001), a full antagonist monoclonal antibody to IGF-1 receptor, in active thyroid eye disease (TED): THRIVE phase 3 topline results

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Purpose

Veligrotug (VRDN-001), a full antagonist humanized monoclonal antibody to the IGF-1 receptor (IGF-1R), is an investigational treatment for thyroid eye disease

(TED). Clinical and preclinical evidence indicate a central role for IGF-1R antagonism in reducing the inflammation and proptosis that occur in TED. Topline efficacy and safety results at 15 weeks were assessed from an ongoing phase 3 randomized double-masked placebo-controlled trial of veligrotug vs placebo in patients with active TED (THRIVE, NCT05176639).
Methods
Adults with moderate-to-severe active TED (onset $\leq$15 months, proptosis $\geq$3 mm, and clinical activity score [CAS] $\geq$3) were randomized to receive 5 IV infusions 3 weeks apart of either 10 mg/kg veligrotug or placebo. Outcomes included proptosis responder rate (PRR), defined as $\geq$2-mm reduction vs baseline by Hertel exophthalmometry, PRR by MRI/CT, complete resolution of diplopia, and mean changes from baseline in proptosis and CAS. Treatment-emergent adverse events (AEs) were assessed through 15 weeks, with follow-up ongoing through 52 weeks.
Results
A total of 113 patients were randomized to veligrotug ($n=75$) or placebo ($n=38$) and included in the intent-to-treat population. At baseline, mean proptosis was 23.2 mm in each group; CAS was 4.5 vs 4.8 and diplopia was present in 67% vs 68% of patients for veligrotug vs placebo. At 15 weeks, PRR by Hertel was 70% vs 5% ($P<0.0001$) for veligrotug vs placebo, with a mean proptosis reduction of 2.9 mm vs 0.5 mm ($P<0.0001$). PRR by MRI/CT was 69% vs 9% ($P<0.0001$) for veligrotug vs placebo, with a mean proptosis reduction of 2.9 mm vs 0.6 mm ($P<0.0001$). Mean CAS decreased by 3.4 vs 1.7 ($P<0.0001$) for veligrotug vs placebo. In patients with diplopia, complete resolution of diplopia occurred in 54% (27/50) vs 12% (3/26) ($P<0.0001$) for veligrotug vs placebo. AEs occurred for 66 (88%) veligrotug vs 24 (63%) placebo patients, and most were mild; 4 patients (veligrotug) had serious AEs (all unrelated to treatment). Hearing impairment AEs were reported for 12 (16%) veligrotug vs 4 (11%) placebo patients.
Conclusions
Topline results from the THRIVE phase 3 trial show 5 IV infusions of 10 mg/kg veligrotug were well tolerated and led to significant and clinically meaningful improvements in proptosis, CAS, and diplopia at 15 weeks. Additional follow-up through 52 weeks is ongoing.

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OC11.6

JOINT654

Evaluation of pediatric thyroid nodules with K-TIRADS, ACR-TIRADS, and clinical risk factors

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Background
A pediatric-specific biopsy cutoff for the Thyroid Imaging Reporting and Data System (TIRADS) is lacking.
Purpose
We investigated the utility of repeat biopsy by analyzing the initial and follow-up TIRADS and biopsy results. We analyzed a pediatric-specific biopsy cutoff considering clinical risk factors using the 2021 Korean (K) and American College of Radiology (ACR) TIRADS.
Methods
Pediatric patients who underwent thyroid nodule biopsy at Seoul National University Hospital between January 2010 and December 2021 were analyzed retrospectively. The diagnostic performance of TIRADS considering risk factors such as Hashimoto's thyroiditis, previous radiotherapy, a family history of thyroid cancer, or hereditary tumor syndromes was estimated.
Results
A total of 200 patients (median age, 16 years; 17 children $<$10 years and 183 adolescents 10–19 years; 153 females; 92 with risk factors) with 223 nodules (142 malignant nodules [64% of total; 86% of 166 resected nodules]) were analyzed. Repeat biopsies due to large size, interval growth, or TIRADS 4–5 category revealed that 6/21 (29%) nodules categorized as benign on initial biopsy were postoperative malignant. Compared to the current guideline, applying a modified pediatric-specific biopsy cutoff for both K-TIRADS and ACR-TIRADS (0.5 cm/1.5 cm for TIRADS 4 with/without risk factors and 0.5 cm for all TIRADS 5) improved sensitivity (85% vs. 78% for K-TIRADS, 84% vs. 60% for ACR-TIRADS, both $P<.005$), missed malignancy rate (33% vs. 39%, 30% vs. 46%, both $P<.05$), and accuracy (74% vs. 71%, 77% vs. 67%, $P=.30$ and.002).
Conclusion
For pediatric patients, especially adolescents, with either TIRADS 4 nodules with risk factors or TIRADS 5 nodules, the cutoff size for biopsy needs to be lowered to 0.5 cm. Repeat biopsy is required if clinical and ultrasound findings are discordant, even if the initial biopsy indicates a benign.

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Oral Communications 13: Adrenal and Cardiovascular Endocrinology Part 2

OC13.1

JOINT2385

Hydrocortisone treatment only partially restores systemic dysregulations caused by cortisol deficiency in a 21-hydroxylase deficient zebrafish model

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Background
It is known that conditions causing cortisol deficiency, such as congenital adrenal hyperplasia, lead to systemic dysregulations that are associated to the development of co-morbidities. We wanted to test to what degree dysregulations caused by cortisol deficiency are corrected by a physiological dose of hydrocortisone (HC) treatment in a 21-hydroxylase deficient zebrafish model (*cyp21a2-/-*).
Methods
We used wild-type (WT) and *cyp21a2-/-* zebrafish larvae, comparing between four groups: WT untreated, *cyp21a2-/-* untreated, WT treated and *cyp21a2-/-* treated on day 4 post-fertilisation with hydrocortisone 10μM solution for 24 hours. Following RNA sequencing, transcriptomic analysis including differential gene expression (DGE), and Gene Set Enrichment Analysis (GSEA) was performed.
Results
DGE and principal component analysis showed that 50% of the variance related to hydrocortisone treatment, and 16% to genotype. HC treatment in WT led to 3153 differentially expressed genes (DEG). GSEA showed that in WT larvae, HC caused the suppression of multiple biological processes pertaining to innate and adaptive immunity. ATP synthesis, provision of energy precursors, lipid and protein metabolism were among the most upregulated processes. In untreated *cyp21a2-/-* mutants there were 1096 DEG compared to WT, while in treated mutants only 334 DEG compared to treated WT. In untreated *cyp21a2-/-*, the majority of downregulated biological processes pertained to ribosomal biosynthesis and mitochondrion organisation, and the most upregulated ones to the mitotic cell cycle. In treated mutants, the dysregulation of ribosomal biosynthesis was no longer present, however, there was downregulation of the cell cycle processes which had been upregulated in untreated mutants. Treated *cyp21a2-/-* mutants shared 185 significantly supressed biological processes with treated WT, of which the majority related to the immune response. There were 195 processes upregulated following HC treatment in both mutants and WT, including ATP synthesis, fatty acid beta-oxidation and several other metabolic processes. However, 89 processes were upregulated by HC only in *cyp21a2-/-*, of which only 9 had been downregulated in untreated mutants, the remaining 79 representing additional dysregulations and including metabolic processes such as lipid synthesis, localisation and transport.
Conclusion
HC treatment administered in zebrafish larvae restored only some of the biological dysregulations caused by cortisol deficiency. However, it also overcorrected processes and resulted in additional dysregulations. Interestingly, HC treatment caused the upregulation of several lipid metabolic processes only in the cortisol deficient zebrafish. Translated to human cortisol deficiency, these findings highlight the challenge of adequate glucocorticoid replacement and the need for further research aimed at optimising treatment.

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OC13.2

JOINT2046

Towards durable genomic editing for the treatment of congenital adrenal hyperplasia

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Despite life-saving corticosteroid treatment, individuals with congenital adrenal hyperplasia (CAH) have increased morbidity and mortality. Gene therapy has the potential to restore physiological corticosteroid production, however, optimisation of the technology is required. Recombinant adeno-associated virus (rAAV) is the most common vector used in *in vivo* gene delivery. rAAV-based gene addition strategies have been explored in CAH, however due to adrenocortical cellular renewal, resultant phenotypic changes were temporary. Here, we introduced targeted editing events in the 21-hydroxylase locus (*Cyp21a1*) in the murine adrenal gland *in* vivo through rAAV-delivered genomic editing, with phenotypic effect to 15 weeks. Homology-independent targeted integration was utilised. A single-guide RNA (sgRNA) was designed targeting the first intron and a matching donor cassette was designed capturing the endogenous Cyp21a1 promoter. Both vectors were pseudo-serotyped with AAV-Rh10. Adult 21-hydroxylase deficient mice (C57BL/10SnSlc-H-2^{aw18}) were treated intravenously with the *Staphylococcus aureus* Cas9 (SaCas9)/sgRNA (2.5×10e12vg/mouse) and/or donor (1×10e12vg/mouse) vectors and harvested 4 (short-term) or 15 (long-term, dual vector only) weeks later. Sanger sequencing demonstrated editing events at the desired locus within the *Cyp21a1* gene in the dual vector-treated mice. Correctly oriented donor inserts were detected in 7% of total *Cyp21a1* alleles and 39% of total *Cyp21a1* transcripts in the short-term mice. Treated mice had improved corticosterone production, with 6.7-fold (males) and 9-fold (females) increases. There was no phenotypic benefit in the control groups that received a single vector. Four female mice were harvested at 15 weeks after treatment to determine durability of effect, as the adrenocortical turnover period has been estimated at 3 months. Correctly oriented donor inserts accounted for 5% of the total alleles and 25% of the total expressed transcripts in the adrenal. These mice had persistence of improvement in corticosterone, with no statistical difference between the serum corticosterone level in the group harvested at 4 weeks compared with the group harvested at 15 weeks. Renin expression was lower in the long-term group compared with the short-term group. There was no statistically significant difference in serum aldosterone, serum progesterone, aldosterone synthase expression or adrenal size between these treated groups. We demonstrated that rAAV delivery of genomic editing reagents to the adrenal gland resulted in targeted editing events that conferred durable phenotypic benefit. Targeted editing events in the *Cyp21a1* gene is possible despite challenges faced with the homologous pseudogene. This strategy could be adapted for use in the human locus once rAAV tropism for the human adrenocortical progenitor cells is determined.

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OC13.3

JOINT561

Home measurement of 24-hour corticosteroid dynamics in primary aldosteronism

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Background

Primary aldosteronism (PA) is common, affecting 5-20% of the hypertensive population and is associated with an increased cardiovascular risk and incidence of metabolic disease when compared with primary hypertension. To date, establishing a correct diagnosis is hampered by laborious and time-consuming protocols unable to capture the pulsatile variability of aldosterone across the day. In this study we applied a dynamic hormone profiling technique to study the dynamics of aldosterone and other corticosteroids in patients with established PA to lay the foundation for new diagnostic procedures and criteria.

Methods

Sixty PA patients were recruited, 26 unilateral, 24 bilateral, and 10 with undetermined PA subtype. Ambulatory 24-hour profiles of corticosteroids including aldosterone and the hybrid steroids 18-hydroxycortisol and 18-oxocortisol were quantified in subcutaneous tissue microdialysate by liquid chromatography tandem mass spectrometry and compared with 215 healthy participants. Specific dynamic features were extracted and used to develop a machine learning model to distinguish PA profiles from healthy normal variation.

Results

PA profiles under unstimulated conditions were characterised by a pulsatile secretion and diurnal rhythmicity of aldosterone, cortisol, intermediary steroids and hybrid steroids. Nocturnal and early morning hypersecretion of aldosterone, 18-hydroxycortisol and 18-oxocortisol was prominent in unilateral PA. 18-oxocortisol was seen almost exclusively in unilateral PA, both with and without somatic *KCNJ5*-mutations. 24-hour cortisol concentrations did not differ between PA and healthy participants. Applying dynamic hormone profiling with a machine learning classifier algorithm resulted in a diagnostic sensitivity of 88% and specificity of 80% in predicting PA. Normalisation of aldosterone hypersecretion was observed after adrenalectomy for unilateral PA.

Conclusions

24-hour tissue corticosteroid profiling in the home setting is achievable and reveals new insights into the pathophysiology of PA, characterised by nocturnal hypersecretion of aldosterone and hybrid steroids. The technique holds promise for faster and more accurate PA diagnosis with identification of unilateral cases.

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OC13.4

JOINT663

Cardiovascular risk factors in transgender adolescents before and during puberty suppression and sex steroid therapy

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Background

Transgender adolescents may be treated with gonadotropin-releasing hormone analog (GnRHa) and sex steroids. Hormone therapy (HT) may affect cardiovascular risk factors such as overweight, obesity and dyslipidemia.

Objective

To evaluate weight, body mass index (BMI), and lipid profiles at start and during HT in a Danish national cohort of transgender adolescents who started HT before 18 years of age.

Patients and methods

The cohort consisted of 164 trans boys and 55 trans girls. GnRHa was initiated before ($n=102$ trans boys and $n=43$ trans girls) or simultaneously with testosterone ($n=62$) or estradiol ($n=12$). Weight, BMI and lipid profiles were assessed at routine visits. Changes in the estimate (95% confidence intervals) were analyzed for weight standard deviation score (SDS), BMI SDS, and lipid profiles, using mixed model analyses.

Results

Before HT, overweight (BMI $\geq$1SDS) and obesity (BMI $\geq$2SDS) were found in 29.9% and 22.0% of the trans boys and in 5.7% and 5.7% of the trans girls,

respectively. Lipids profiles outside normal range were found in both trans boys and girls; total cholesterol ≥5.0 mmol/l (12.5% and 6.1%), low-density lipoprotein (LDL) ≥3.0 mmol/l (20.4% and 8.2%), high-density lipoprotein (HDL) ≤1.0 mmol/l (10.3% and 18.4%), and triglycerides ≥2.0 mmol/l (4.1% and 6.3%), respectively. During GnRHa monotherapy, weight SDS declined after one year of treatment ($n=56$, -0.2(-0.3–-0.0), $P=0.017$) in trans boys and after one ($n=28$, -0.3(-0.5–-0.1), $P=0.010$) and two years ($n=9$, -0.4(-0.7–-0.1, $P=0.013$) in trans girls. No consistent trends were observed in BMI SDS or the lipid profiles. During sex steroid therapy, weight SDS declined in trans boys only; after two ($n=70$, -0.4(-0.6–-0.2), $P<0.001$) and three years of treatment ($n=13$, -0.7(-1.2–-0.2), $P=0.006$). No consistent trends were observed in BMI SDS. During the first three years of sex steroid therapy, HDL decreased ($n=104$, -0.1(-0.2–-0.1), $P<0.001$, $n=62$, -0.2(-0.2–-0.1), $P<0.001$, $n=25$, -0.2(-0.3–-0.1), $P<0.001$), and triglycerides increased ($n=104$, 0.2(0.1–0.4), $P=0.003$, $n=62$, 0.3(0.2–0.5), $P<0.001$, $n=26$, 0.4(0.2–0.6), $P=0.002$) in trans boys, while HDL increased in trans girls; ($n=28$, 0.3(0.1–0.4), $P<0.001$, $n=19$, 0.3(0.2–0.5), $P<0.001$, $n=7$, 0.4(0.0–0.7), $P=0.038$).

Conclusion

The prevalence of overweight, obesity and dyslipidemia before HT was high compared with normal range. BMI SDS did not deteriorate during HT, but dyslipidemia worsened slightly during testosterone treatment. The results suggest that some transgender adolescents may benefit from lifestyle interventions and treatment of dyslipidemia to reduce the long-term cardiovascular risk.

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OC13.5

JOINT1853

The incidence of adrenal crisis in addison's disease is low a survey of the national norwegian registry

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Background

Adrenal crisis is a life-threatening emergency in patients with adrenal insufficiency. Despite preventive measures, previous studies indicate a rising incidence, yet detailed and validated investigations are lacking.

Methods

We included 743 patients with autoimmune primary adrenal insufficiency (Addison's disease) identified through the Norwegian National Addison Registry. All medical records were reviewed for admissions between January 1, 2000, and December 31, 2023. Overt adrenal crisis was defined as an acute deterioration of health status associated with hypotension (systolic blood pressure<100 mmHg), hyponatremia (<130 mmol/l), hyperkalemia (>5 mmol/l) or hypoglycemia (<3.5 mmol/l). Incipient adrenal crisis was defined as marked and typical symptoms in the absence of objective features.

Results

After a median follow-up of 15 years, 64% of the patients had one or more crisis-related admissions. The incidence of overt adrenal crisis was 4.4 per 100 person years, while the incidence of incipient adrenal crisis was 7.0 per 100 person years. Over time, admission rates with incipient crisis increased, while admission rates with overt adrenal crisis remained stable. At admission, s-sodium<130 mmol/l and s-potassium>5 mmol/l was found in 17% and 13% of the cases, respectively. Four percent had serum glucose below 3.5 mmol/l and 1.8% below 2 mmol/l. Infection was the most common precipitating cause (52%). In 29% of cases, patients had administered oral stress dosing before admission, and 24% had injected hydrocortisone. These treatments were associated with a reduced odds of having crisis on arrival to hospital (oral, OR 0.44; 95% CI, 0,33-0,58, $P=<0.001$ and injection OR 0.64; 95% CI, 0.49-0.85, $P=0.002$). Crisis-related admissions were highest among the youngest patients and those with type 1 diabetes. Out of 1254 admissions, 13 patients (1%) died during the hospital stay. Adrenal crisis was deemed as a contributing case of death in four cases (0.3%).

Conclusions

The incidence of overt adrenal crisis is low, and in-hospital crisis-related mortality nearly absent. Wider use of oral stress dosing and pre-emergency hydrocortisone injections is needed to further reduce the risk of overt adrenal crises.

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OC13.6

JOINT365

A double-blind study of modified-release hydrocortisones, chronocort versus plenadren, in adrenal insufficiency (CHAMPAIN)

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Background

Patients with adrenal insufficiency (AI) have impaired quality of life (QoL), low energy and increased mortality. Immediate-release hydrocortisone is first-line replacement therapy, however, fails to restore the physiologic diurnal cortisol rhythm. There are two modified-release hydrocortisone formulations: 1) Plenadren®, taken in a single morning dose, and 2) Chronocort® delayed release, taken twice daily in a toothbrush regimen (last thing at night, first thing in the morning). Chronocort but not Plenadren mimics the physiologic rise in early morning cortisol. We compared Plenadren to Chronocort to test the hypothesis that waking with physiological cortisol levels will reduce fatigue and improve QoL.

Methods

double-blind, double-dummy, two-way cross-over, randomised, study comparing Chronocort vs Plenadren, one month on each treatment at 25mg/24 hours. Inclusion criteria were primary AI with morning pre-dose cortisol <50 nmol/l (1.8 μg/dl). The primary endpoint was the difference in 07:00 h cortisol after 4 weeks of treatment. The key secondary outcome was the Multidimensional Assessment of Fatigue (MAF) score after 4 weeks. Other secondary outcomes included the disease specific questionnaire AddiQol, the fatigue questionnaire PROMIS 7b, and QoL as measured by SF36 and EQ-5D-5L.

Results

Of 49 evaluable participants, 45 achieved a physiological morning cortisol (>140 nmol/l, 5ug/dl) with Chronocort compared with 2 on Plenadren (median serum cortisol 417.0 (15) vs 6.04 (0.2) nmol/l (μg/dl), $P<0.0001$). The MAF score was not significantly different between the two treatments; however, a sensitivity analysis showed that in the first treatment period Chronocort reduced MAF Score ($P=0.008$) suggesting a carry-over effect from period 1 to 2. The majority of the other QoL measures in the secondary efficacy analysis showed significant benefit for Chronocort including: The disease specific questionnaire AddiQol ($P=0.03$), the fatigue questionnaire PROMIS 7b ($P=0.02$), SF36 physical functioning ($P=0.03$) and EQ-5D-5L ($P=0.02$). The sensitivity analysis for all these measures showed greater benefit for Chronocort and patients showed a preference for the Chronocort treatment period. The safety profiles were similar, as expected for patients with AI, with no new safety signals identified.

Conclusions

In adrenal insufficiency Chronocort provides physiological waking cortisol levels and is associated with reduced fatigue and improved QoL as compared to Plenadren.

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Oral Communications 14: Growth Axis and Syndromes

OC14.1

JOINT378

SEENEZ trial: Near adult height after withdrawing growth hormone treatment in mid-puberty in adolescents with transient idiopathic isolated growth hormone deficiency

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Background
The majority of children diagnosed with idiopathic isolated growth hormone deficiency (IIGHD) shows normal growth hormone (GH) secretion when retested at near adult height (NAH; height velocity <2cm/y). The question is whether continuing recombinant human GH (rhGH) treatment affects NAH if normal GH secretion is observed in mid-puberty.
Aim
To investigate if withdrawing rhGH treatment from mid-puberty onwards had no negative effect on attained NAH in adolescents who no longer fulfilled a diagnosis of GH deficiency.
Methods
Adolescents diagnosed with IIGHD in childhood (GH peak at diagnosis 1.7-10 µg/l) who started rhGH treatment between 2005-2018 and tested GH sufficient (GH peak >6.7 µg/l) at mid-puberty were included in this prospective multi-center SEENEZ-trial. Mid-puberty was defined as Tanner stage G3/4, testicular volume >12 ml, bone age 13-16 years in males and Tanner stage B3/4, bone age 11-14 years in females. Study participants had the choice to discontinue or continue rhGH treatment until NAH. Primary outcome was NAH-SDS minus target height (TH) SDS. Secondary outcomes were NAH-SDS and total pubertal growth. Additionally, attained versus predicted height gain from mid-puberty to NAH was calculated using a prediction model, developed from retrospective data of an IIGHD cohort who were GH sufficient upon retesting at NAH.
Results
A total of 127 patients (95 male, 75%) participated. Forty-four patients (35%) continued rhGH treatment until NAH (GHcont), and 83 patients (65%) stopped GH treatment (GHstop). Baseline height SDS and age at mid-puberty did not differ significantly between groups. Mean (SD) NAH-SDS minus TH-SDS was -0.16 (0.60) in the GHcont and -0.19 (0.62) in the GHstop group ($P=.78$). Mean NAH-SDS was -0.91 (0.76) (GHcont) vs -0.79 (0.76) (GHstop) ($P=.42$). Mean (SD) total pubertal growth in males was 27.4 cm (7.1) (GHcont) vs 25.9 cm (6.2) (GHstop) ($P=.30$) and in females 20.5 cm (5.7) (GHcont) vs 21.2 cm (7.6) (GHstop) ($P=.82$). The predicted vs attained height gain based on the prediction model did not differ between groups.
Conclusions
In IIGHD adolescents who tested GH-sufficient in mid-puberty, NAH is comparable between those who continued rhGH treatment until NAH and those who stopped rhGH treatment at mid-puberty. In transient IIGHD adolescents, rhGH treatment can be stopped at mid-puberty. Implementing these results in guidelines reduces the duration of rhGH treatment by 2-3 years in most children with IIGHD, leading to a substantial decrease in patient burden, need for medical care and healthcare costs.

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OC14.2

JOINT1336

Chemogenic activation of growth hormone-releasing hormone neurons stimulates the luteinizing hormone secretion

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Neurons expressing growth hormone-releasing hormone (GHRH) are found in the arcuate nucleus of the hypothalamus (ARH), and they play a key role in stimulating GH secretion. Conversely, neurons expressing gonadotropin-releasing hormone (GnRH) and kisspeptins are stimulators of the luteinizing hormone (LH) secretion. Previous studies have shown that a subpopulation of GHRH neurons co-expresses kisspeptins in adult female mice but not in adult males or prepubertal animals. Thus, whether GHRH neurons can influence other endocrine axes beyond the somatotropic axis is unclear. The objective of this study was to evaluate whether the chemogenetic activation of GHRH neurons is able to modulate LH secretion in addition to GH. Initially, mice that constitutively express the cholinergic muscarinic receptor type 3 (hM3Dq) in GHRH neurons were produced. These animals were generated by crossing GHRH-Cre mice with a Cre-dependent hM3Dq-expressing strain. For acute stimulation of GHRH neurons, mice received an intraperitoneal injection of clozapine N-oxide (CNO) or vehicle solution (as control). Serial blood samples were collected before and after injection for subsequent hormonal dosage by ultra-sensitive enzyme-linked immunosorbent assay. Our findings indicate that the activation of GHRH neurons led to a robust GH secretion. Remarkably, a statistically significant increase in LH secretion was also observed in both male and female mice, either in adult (2-3 months) or prepubertal (~21 days of life) animals. Subsequently, GHRH-Cre and Kiss1-Cre adult mice received a bilateral injection in the ARH of an adeno-associated virus, inducing the expression of hM3Dq in Cre-positive cells. The chemogenic activation of either GHRH- or Kiss1-expressing cells also increased GH and LH circulating levels. Our findings indicate a crosstalk between the somatotropic and reproductive axis via ARH neuroendocrine neurons.

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OC14.3

JOINT1382

Insulin promotes the expression of aromatase in growth plate chondrocytes by activating the PI3K/AKT signaling pathway and enhancing the activity of the CYP19A1 specific promoter

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Objectives
The mechanisms behind the increased height velocity and accelerated epiphyseal growth plate maturation since early childhood aren't well-defined.Hyperinsulinemia has been implicated as one of the causative factors.The aim of this study is to explore the mechanisms by which insulin regulates the expression of local aromatase in the growth plate,thereby leading to accelerated epiphyseal closure.
Methods
Culturing and identification of primary chondrocytes from the growth plate of 20 - day - old Sprague - Dawley rats were performed.The CCK8 assay procedure was utilized to identify the optimal concentrations of leptin antagonist and PI3K inhibitor. After culturing primary chondrocytes for 4 days and subjecting them to serum starvation for 24 hours,the leptin antagonist and insulin were sequentially added. qPCR and Western blot were employed to analyze the effects of different action durations and concentrations of insulin on the mRNA and protein expression of CYP19A1. This step was to determine the optimal action time and concentration of insulin for subsequent signal pathway studies. The phosphorylation of AKT in chondrocytes was analyzed by Western blot, and the changes in AKT phosphorylation, CYP19A1 mRNA and protein levels following the addition of a PI3K inhibitor were examined. After the construction, the four recombinant plasmids (pGL3.0-CYP19A1-I.3, pGL3.0-CYP19A1-II, pGL3.0-CYP19A1-I.4, and pGL3.0-CYP19A1-I.6) containing different lengths ofthe aromatase promoter fragments were co-transfected with the the dual-luciferase reporter system (firefly luciferase and Renilla luciferase) into the target cells. The activity of each promoter was quantitatively evaluated by the Dual-Luciferase Reporter Assay Kit.
Results
qPCR and Western blot analysis showed that 12-hour treatment with 20 nmol/l insulin maximally upregulated CYP19A1 mRNA and protein expression in a dose and time dependent manner ($P<0.01$).Western Blot was employed to detect the phosphorylation of AKT at specific time points,namely 1, 5, 15, 30, and 60 minutes. The results indicated that AKT phosphorylation reached its peak at 30 minutes.In the PI3K inhibitor group, the degree of AKT phosphorylation was significantly decreased at 30 minutes ($P<0.01$). After insulin (20 nmol/l) acted for 12 hours, the expression of CYP19A1 mRNA and protein in the PI3K inhibitor group was significantly reduced ($P<0.01$). Luciferase reporter gene analysis showed that after 12 hours of incubation, insulin significantly increased the activity of aromatase promoters I.4/I.6.
Conclusions
Insulin not only promotes the expression of aromatase within growth plate chondrocytes through the PI3K/AKT signal transduction pathway, but also significantly upregulates the activity of aromatase promoters I.4/I.6.

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OC14.4

JOINT3277

Results of the foresiGHt trial support the efficacy and safety of once-weekly lonapegsomatropin in adults with growth hormone deficiency (GHD)

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Background
Adult growth hormone deficiency (aGHD) is characterized by metabolic abnormalities due to insufficient growth hormone (GH) production. Lonapegsomatropin was designed to provide release of unmodified somatropin, and once-weekly injection reduces the burden of daily GH replacement therapy.
Methods
ForesiGHt was a randomized, parallel-3-arm, placebo-controlled (double-blind) and active-controlled (open-label) trial to establish the efficacy and safety of lonapegsomatropin in aGHD. 259 adults with GHD across 21 countries who were GH treatment-naïve or not treated with GH in the prior year, randomized 1:1:1 to receive lonapegsomatropin, once-weekly placebo, or daily somatropin. Fixed dosing was based on age and oral estrogen intake, designed to be comparable across lonapegsomatropin and somatropin arms. Following a 12-week (w) titration to target maintenance dose, fixed doses were administered for 26w.
Results
Baseline characteristics were similar between arms. Lonapegsomatropin demonstrated superiority on the primary efficacy endpoint of change from baseline (CFB) in trunk percent fat at 38w vs placebo (lonapegsomatropin -1.7%, placebo 0.4%, LS mean difference -2.0%, $P<0.0001$) and key secondary efficacy endpoints of CFB in total body lean mass (lonapegsomatropin 1.6 kg, placebo -0.1 kg, LS mean difference 1.7 kg, $P<0.0001$) and CFB in trunk fat mass (lonapegsomatropin -0.5 kg, placebo 0.2 kg, LS mean difference -0.7 kg, $P=0.0053$). Mean total exposure and maintenance doses were similar for lonapegsomatropin and somatropin arms, with larger CFB in average IGF-I SDS mean at 38w in the lonapegsomatropin arm (1.4) vs somatropin arm (0.5). To assess outcomes at comparable weekly IGF-I exposure, a post-hoc analysis was done in participant subsets with average IGF-I SDS $\leq$1.75 SDS at 38w. Mean IGF-I SDS for these subsets were similar (lonapegsomatropin -0.1, somatropin -0.5), with comparable effects in fat and lean tissue compartments (CFB in trunk percent fat mean -2.4% and -2.6% respectively; CFB in total body lean mass mean 1.7 kg and 1.4 kg respectively). In the safety population, the incidence of severe AEs was low (lonapegsomatropin, 3.4%; placebo, 1.2%; somatropin, 2.3%) and the incidence of treatment-related AEs was similar (lonapegsomatropin 24.7%, somatropin 22.1%). Injection site reaction incidence was low and similar for lonapegsomatropin (4.5%), somatropin (5.8%) and placebo (4.8%), and A1c levels remained stable in all treatment arms.
Conclusions
The results of the foresiGHt trial indicate that lonapegsomatropin is an efficacious and tolerable replacement for endogenous GH. Once-weekly dosing may be impactful for adults with GHD who typically manage multiple other medical therapies.

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OC14.5

JOINT3101

Noonan syndrome in real life: Patient characteristics and response to growth hormone therapy in a genetically defined single-country multicentre cohort

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Background
The spectrum of genes associated with Noonan syndrome (NS) is growing and the real-life experience with management of these children is increasing; however, the genotype-phenotype correlation and a tailored management await further refinement.
Aim
To evaluate patient characteristics and the response to growth hormone (GH) therapy in a genetically defined large multicentre cohort of NS patients from a single country.
Patients and methods
Eighty-eight patients with NS (51 males) from five participating centres were included. Of these, 63 had a (likely) pathogenic variant in *PTPN11*; 10 in *SOS1*; and 15 in other genes (*BRAF* [2], *HRAS* [2], *KRAS* [3], *LZTR* [1], *MAP2K1* [1], *NRAS* [1], *RAF1* [3] and *SHOC2* [2]). All completed at least the first year of GH therapy while fifteen patients had already achieved their final height following GH administration.
Results
Not surprisingly, parental height was shorter than the population mean (fathers, -0.33 SDS [-1.33;0.57; median and IQR; $P=0.001$], mothers, -0.60 SDS [-1.47;0.12; $P<0.0001$]. The *SOS1*-patients were born earlier (GW 38 [32.5;38.3]) if compared to *PTPN11*-patients (GW 39 [38;40]; $P<0.001$). In the whole cohort of children, birth length was apparently lower (-1.26 SD [-1.78;-0.55] than the birth weight (-0.35 SD [-1.14;0.55; $P<0.0001$] demonstrating intrauterine bone growth restriction. Interestingly, both birth length and weight were lower in the *PTPN11* and *SOS1* patients if compared to the non- *PTPN11*-non- *SOS1* subcohort ($P<0.05$). GH stimulation testing was performed in 47/88 patients, with a peak GH of 7.8 mg/l [5.0;10.4]. Subsequently, GH therapy was started at age 5.7 years (3.8;9.3) with height-SDS -3.09 (3.74;2.59). The median annual height-SDS increments were 0.61 (year 1; $n=88$); 0.29 (year 2; $n=70$); 0.21 (year 3; $n=57$); 0.11 (year 4; $n=51$); and 0.09 (year 5; $n=34$), and were similar regardless the causative gene. The subcohort with final height already known ($n=15$) started GH therapy later (at 9.0 years [5.8;11.8] with height-SDS -3.48 (-3.86;-3.05). Following similar height increments, they reached height-SDS -2.00 (-3.26;-1.63) at pubertal onset (aged 12.5 years [11.5;14.3]), and final height-SDS -2.07 (-2.65;-1.08; aged 18.0 years [16.0-18.9]).
Conclusions
Growth restriction in NS has a prenatal component that is apparent in *PTPN11*- and in *SOS1*-patients, but not in the non- *PTPN11*-non- *SOS1* subcohort. GH therapy leads to a clinically significant improvement of statural height in all genetic subcohorts. In those with a known final height, the height increment occurred prior to pubertal onset; the pubertal portion of growth did not further improve final height. Thus, earlier initiation of therapy within childhood may optimize growth outcomes.

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OC14.6

JOINT185

Effects of navepegritide on growth in children with achondroplasia: 52-week results from the approach clinical trial

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Background
Navepegritide is an investigational prodrug of C-type natriuretic peptide (CNP), administered subcutaneously once weekly and designed to provide a low C_{max} through sustained release of active CNP. Continuous exposure to the released CNP stimulates natriuretic peptide receptor B (NPR-B) to counteract the constitutively active fibroblast growth factor receptor 3 (FGFR3) in achondroplasia (ACH). ApproaCH is a pivotal, randomized, double-blind, placebo-controlled trial evaluating navepegritide in children with ACH.
Methods
Children with ACH ($n=84$, aged 2-11 years) were stratified by age and sex and randomized 2:1 to receive navepegritide (100 μg/ kg/week) or placebo for 52 weeks. The primary endpoint was annualized growth velocity (AGV) at week 52. Secondary endpoints included ACH-specific height Z-scores. Safety and tolerability were evaluated through treatment-emergent adverse events (TEAEs), including injection site reactions (ISRs), and changes in bone age.
Results
The trial met its primary endpoint, demonstrating superiority of navepegritide over placebo in AGV at week 52. Children treated with navepegritide achieved a least square (LS) mean AGV of 5.89 cm/year compared with 4.41 cm/year in children who received placebo (LS mean treatment difference 1.49 cm/year, $P<0.0001$). Change from baseline in ACH-specific height Z-score at 52 weeks was also significantly greater in the navepegritide group than the placebo group (LS mean treatment difference 0.28, $P<0.0001$). In subgroup analyses of children aged ≥5 years ($n=53$), participants treated with navepegritide had a higher AGV at Week 52 (LS mean treatment difference 1.78 cm/year, $P<0.0001$) and a greater change from baseline in ACH-specific height-Z-score (LS mean treatment difference 0.31, $P<0.0001$) than those who received placebo. Most TEAEs were mild or moderate, with a low event rate of ISRs (all mild) across groups (0.41 events per person year of exposure with navepegritide vs. 0.15 with placebo). The incidence of treatment-related AEs was similar between the navepegritide (21.1%) and placebo (25.9%) groups. The mean bone age to chronological age ratio remained relatively unchanged from baseline (change of 0 in the navepegritide group and -0.01 in the placebo group).
Conclusion
Navepegritide demonstrated superiority over placebo in AGV at week 52 of the ApproaCH trial. Statistically significant improvements in ACH-specific height Z-scores in children treated with navepegritide compared with placebo were also observed. These findings suggest that the design of navepegritide – to provide continuous exposure to active CNP – improves growth in children with ACH while maintaining a safety and tolerability profile comparable to placebo.

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Oral Communications 15: Metabolism, Nutrition and Obesity

OC15.1

JOINT2287

Real-world setmelanotide changes in BMI in French patients with acquired hypothalamic obesity

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Introduction
Acquired hypothalamic obesity (aHO) results from physical hypothalamic damage due to trauma, tumours, treatment-related injuries, or inflammation, which can disrupt the melanocortin-4 receptor (MC4R) signalling pathway. aHO is characterized by rapid and excessive weight gain following the damage. A 16-week Phase 2 open-label trial, treating aHO with the MC4R agonist setmelanotide produced consistent and clinically significant responses, maintained or improved over a 12-month follow-up period. This report presents real-world data for 25 patients in France with aHO treated with setmelanotide under pre-marketing early access authorization.
Methods
For patients with aHO in France under early access treatment with setmelanotide for a minimum of 3 months changes in BMI are reported.
Results
Twenty-five patients (14 females), including 9 children, aged 7-42 years old, were included. Seventeen patients had craniopharyngioma, 3 astrocytoma, and 1 each AQP4 antibody encephalitis, ganglioma, Langerhans cell histiocytosis, neuroglial tumour or viral inflammation affecting the pituitary region. Patients started treatment at 0.25 to 2 mg/day. Depending on the duration of treatment, treatment response, and adverse events, patients received 1 to 3 mg/day at last included visit. For all 25 patients, mean BMI (SD) decreased from 40.6 (8.7) kg/m^2 to 36.2 (7.9) kg/m^2 after 3-month treatment, indicating a 10.8% decrease from baseline. For patients with 6-month data ($n=12$), mean BMI decreased from 42.5 (7.9) kg/m^2 to 37.6 (6.6) kg/m^2 to 34.9 (5.7) kg/m^2 after 3- and 6-month treatment, respectively, representing an 11.6% and 18.0% decrease from baseline. For patients with 9-month data ($n=7$), BMI decreased from 43.7 (7.9) kg/m^2 to 38.8 (7.0) kg/m^2 to 35.7 (6.0) kg/m^2 to 34.5 (6.0) kg/m^2 after 3-, 6- and 9-month treatment, respectively, indicating an 11.4%, 18.3% and 21.0% decrease from baseline. All patients except 1 had a lower BMI at each included time point. The patient with an increase in BMI, at Month 6, had surgery after 3 months due to disease progression and stopped treatment for 10 days. No new safety signals were observed.
Conclusions
This real-world evidence of 25 patients with aHO, including 3 with non-tumour-related causes, who received at least 3 months of setmelanotide under pre-marketing early access authorization in France showed consistent improvements in BMI in the majority of patients. Efficacy and safety outcomes are consistent with Phase 2 trial data that demonstrate beneficial outcomes of setmelanotide treatment in patients between 6 and 40 years of age with aHO.

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OC15.2

JOINT1568

Long-term results for diazoxide choline extended-release (DCCR) tablets in patients with prader-willi syndrome: developmental behaviour checklist 2 response and relationship to hyperphagia reductions

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Background
Prader-Willi syndrome (PWS) is a rare genetic neurobehavioural-metabolic disorder characterised by hyperphagia and behavioural/psychological complications. No approved therapy exists for treating hyperphagia in patients with PWS. DCCR is an oral, once-daily medication currently under development for treating patients with PWS who have hyperphagia.
Objective
The objective of this analysis was to characterise the long-term efficacy of DCCR on DBC2 questionnaire total and subscale scores and the relationship between

changes in behaviours and changes in hyperphagia in participants with PWS from 2 completed studies encompassing > 3 years of exposure to DCCR.
Methods
The population included 125 participants ≥4 years old with genetically-confirmed PWS who received DCCR in either of 2 sequential studies: a 13-week, placebo-controlled study (Study C601) followed by an open-label extension (OLE) study (Study C602-OLE). Baseline was defined as the last assessment prior to the first DCCR dose. The primary endpoint was change from baseline in hyperphagia assessed by Hyperphagia Questionnaire for Clinical Trials (HQ-CT) Total Score. Behavioural changes were assessed using the DBC2 questionnaire which evaluates behaviours using total score and 6 subscales: Anxiety, Communication Disturbance, Disruptive Behaviour, Self-Absorbed, Social Relating and a subscale associated with PWS. The relationship between change in HQ-CT and changes in behaviour were evaluated using correlations.
Results
At baseline, the median age of participants was 12.0 (range 4, 44) years, 69 (55.2%) were female, and the mean (SD) HQ-CT Total Score was 21.5 (6.7). Over 3 years of DCCR administration, there was a clinically and statistically significant improvement in HQ-CT total score at all assessments [LS mean change (SE, *n*) at 3 years -10.7 (0.76; 81); $P<0.0001$]. Administration of DCCR was also associated with significant improvements in DBC2 total score at all timepoints [LS mean change (SE, n) at 3 years -15.5 (2.06, 71); $P<0.0001$] and all subscales at all timepoints (all $P<0.0001$). At 3 years, improvements in DBC2 subscale scores ranged from 29% to 39%. The correlation between HQ-CT change and DBC2 total score change at 52 weeks was 0.53 ($P<0.0001$), and the correlations between HQ-CT changes and changes in DBC2 subscales ranged from 0.25 ($P=0.0159$, anxiety subscale) to 0.56 ($P<0.0001$, self-absorbed subscale).
Conclusions
Long-term administration of DCCR for up to 3 years in participants with PWS was associated with clinically significant improvements in hyperphagia and behaviours. Behavioural improvements appeared to be independent of hyperphagia improvements. These hyperphagia and behavioural improvements should benefit patients with PWS and their families.

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OC15.3

JOINT3694

Long-term outcomes of sleeve gastrectomy in paediatric and transition age patients with prader-willi syndrome: a 5-year longitudinal study

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Introduction
Prader Willi Syndrome (PWS) is a rare genetic disorder (1:20,000 live births) characterized by hypothalamic dysfunction, leading to endocrine complications including early-onset, and life-threatening obesity. Controlling weight is particularly challenging due to behavioural disorders and an intense hyperphagic drive. In cases of progressive obesity, bariatric surgery, such as laparoscopic sleeve gastrectomy (LSG), may be considered. While LSG is effective in non-syndromic adolescents and young adults with severe obesity, evidence of its long-term efficacy in PWS remains limited.
Patients and methods
We enrolled 16 patients affected by genetically confirmed PWS, and 32 sex-, age- and BMI-matched non-syndromic control subjects (OB) with severe obesity (BMI-standard deviation score [SDS] > 3), who underwent LSG. The whole cohort included 24 males (50%), with a median age at surgery of 16.2 years [range: 8.1-26.7]. All subjects underwent comprehensive endocrine and metabolic evaluation, received personalised nutritional counselling, as well as psychological assessment and multidisciplinary support before and after surgery.
Results
Baseline median weight, BMI and BMI-SDS were 117.6 [IQR 97.3-131.9] vs 122.3 [111.5-144.0] Kg ($P=0.130$), 47.0 [41.1-53.4] vs 44.3 [40.7-49.5] Kg/m^2 ($P=0.252$), and +5.2 [4.3-6.3] vs +4.5 [4.0-5.0] ($P=0.032$) in the PWS and OB groups, respectively. Patients were followed-up for a median of 4.8 [3.6-7.1] years. Changes in mean BMI-SDS at each year were significantly lower in PWS compared to OB patients: year 1 (-30.6±19.9% vs -55.7±23.6%, $P=0.008$), year 2 (-29.8±31.2% vs -65.5±28.5%, $P=0.008$), year 3 (-8.4±31.8% vs -65.0±33.4%, $P=0.006$), year 4 (-9.1±31.6% vs -62.1±30.4%, $P=0.006$), year 5 (-18.5±34.5% vs -58.5±35.1%, $P=0.014$). The number of comorbidities (intermediate hyperglycaemia or diabetes mellitus, hypertension, hypercholesterolemia, hypertriglyceridemia and obstructive sleep apnea) decreased from 2.6±1.5 to 1.9±1.2 in the PWS group ($P=0.051$), and from 1.1±0.9 to 0.5±0.2 in the OB group ($P=0.125$).
Conclusions
LSG results in less sustained weight loss in PWS than in OB over a 5-year period. LSG should be considered in PWS selected patients with complicated obesity when a rapid weight loss is needed. However, these findings highlight the need for alternative or adjunctive therapeutic strategies to address the complex pathophysiology of obesity in PWS and improve long-term outcomes.

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OC15.4

JOINT1571

FetuinA connects hepatic steatosis and islet lipid accumulation in HFD mice: inhibiting TLR4 to protect beta cell function therein

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Introduction
We and others have linked intracellular lipid accumulation in pancreatic islets with beta-cell dysfunction. Here, we report the effects of advancing hepatic steatosis on islet lipid accumulation during hyperlipidemic conditions. Increase in circulatory free fatty acids (FFA) enhances the expression and secretion of FetuinA (FetA) from the liver into the circulation. FetA, in combination with FFAs, activates TLR4, which induces insulin resistance and islet inflammation. This study thus targets TLR4 using its inhibitor C34 to investigate the regulation of islet lipid accumulation and beta cell function during the progression of hepatic steatosis.
Methods
C57BL/6J male mice were divided into 6 groups and given a standard diet (SD) for 20 weeks or a high-fat diet (HFD) for 4, 8, 12, 16 and 20 weeks. Another experiment had three groups receiving SD, HFD, HFD + TLR4 inhibitor C34 (1 mg/kg/day, i.p.) for 12 weeks. To assess the effects of FetA, mice on 4-week HFD received FetA i.p. injection for 5 days. Pancreatic islets from treated mice were subjected to immunoblot, qPCR and Nile Red staining. Immunofluorescence and H&E staining were performed on liver and pancreatic sections. Serum FetA level was measured using ELISA. Beta-cell function was evaluated by in-vivo GSIS.
Results
Results showed progressive increase in intracellular lipid accumulation in the pancreatic islet, along with hepatic steatosis and serum FetA levels, with HFD treatment from 4-16 weeks. However, in the 20-week HFD group, significant islet mass reduction with damage in islet morphology was observed. Increase in vesicular steatosis was seen in the liver with prominent adipocyte infiltration in the 20-week HFD, as evident from H&E-stained liver sections. Confocal images revealed higher lipid accumulation in islets of FetA-injected 4-week HFD mice compared to HFD (4-week) alone (~2-fold), suggesting the involvement of FetA in aggravating lipid accumulation. A concomitant increase in TLR4 expression and reduction in insulin content in the islet was observed in the HFD + FetA mice. TLR4 inhibition by C34 administration in HFD mice significantly reduced islet lipid accumulation and lowered circulating FetA (~0.4-fold) and IL-1β levels. Both lipid uptake and de-novo lipogenesis markers CD36 and SREBP1 were reduced in the islet of C34-treated HFD mice. Inhibiting TLR4 improved in-vivo GSIS, insulin gene expression and Pdx1 levels in HFD islets.
Conclusion
Elevated serum FetA level with advancing hepatic steatosis poses a significant increase in islet lipid accumulation and consequent dysfunction of beta cells in obese mice and could be prevented by early inhibition of TLR4.

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OC15.5

JOINT1000

SMG7 as a potential contributor to the progression of chronic liver disease to hepatocellular carcinoma

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Background
The SMG7 factor plays a key role in the nonsense-mediated mRNA decay (NMD), a cellular pathway that removes mRNAs containing common errors, such as premature termination codons (PTCs), to prevent their translation. Numerous NMD targets are involved in cellular stress responses. Additionally, SMG7 supports cell survival following genotoxic stress by activating the ATR-Chk1 pathway. Chronic exposure to lipotoxic free fatty acids (FFAs) in liver disease contributes to cellular stress and liver damage. This study focuses on investigating the role of SMG7 in the progression of metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated steatohepatitis (MASH) , and hepatocellular carcinoma (HCC).
Method
Expression (mRNA) of 22 NMD components was analyzed in two retrospective HCC cohorts (cohort 1 [$n=89$ HCC and non-tumor paired adjacent tissues (NTAT)] by microfluidic-based qPCR array and cohort 2 [$n=31$ HCC and $n=31$ NTAT] by RNA-seq), and validated in six external cohorts with healthy, MASLD, MASH, HCC, and/or NTAT samples. GSEA enrichment analysis was performed. Human (THLE2) and mouse primary hepatocytes (MPH) were treated with FFAs. Pharmacological (NMDI14, which blocks SMG7-UPF1 interaction) and genetic modulation of SMG7 were carried out in two liver-derived cell lines (Hep3B and SNU-387) to explore the functional effects in vitro.
Results
SMG7 is consistently overexpressed in samples of MASH, HCC, and MASH-derived HCC. In addition, hallmark pathways related to proliferation (mitotic spindle, G2M checkpoint, and E2F targets) are enriched in tumor samples with high SMG7 expression in the retrospective cohort 2 and an external cohort (TCGA or GSE164760). Furthermore, SMG7 (mRNA) expression was stimulated by FFAs (palmitate) in THLE2 and MPH cells, and its overexpression in liver cell lines enhances proliferation, as well as colony and tumorspheres formation. In contrast, SMG7 silencing reduced the proliferation and migration of SNU-387 cells, while having minimal functional effects on Hep3B cells, possibly due to a compensatory increase in UPF1, another key NMD factor. Notably, co-silencing SMG7 and UPF1 decreased tumor aggressiveness in both HCC cell lines. Consistently, treatment with NMDI14 led to a reduction in the aggressiveness of the HCC cell lines, while having no impact on MPH viability but reducing THLE2 proliferation.
Conclusion
The SMG7 factor could have a key role in the progression of MASLD-HCC, potentially opening new avenues for identifying biomarkers and/or therapeutic targets for these conditions.
Fundings
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OC15.6

JOINT266

Sex-specific molecular effects of semaglutide on cardiac and hepatic mitochondrial respiration and cellular redox state in HFpEF and MASLD

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Background
Glucagon-like peptide (GLP)-1 receptor agonists, such as semaglutide, are known to have beneficial effects on obesity-related diseases such as heart failure with preserved ejection fraction (HFpEF) and metabolic dysfunction-associated steatotic liver disease (MASLD). However, cellular mechanisms underlying these effects remain poorly understood. Moreover, the gender-specificity of these effects is unclear.
Methods
Male and female wistar rats were fed either standard chow **(CO)** or a high-fat/fructose **(HFD)** diet combined with L-NAME for 8 weeks to induce obesity, hypertension and associated comorbidities like HFpEF and MASLD. Following this regimen, the rats received either semaglutide **(SEMA)** or saline **(HFD)** for additional 8 weeks, with ad libitum access to either HFD or a low-fat/high-fructose diet. Echocardiography (ECG) was conducted at the end of treatment. Histological assessment for H.E., OilRed and CD3 was performed in hepatic tissue. Isolated cardiomyocytes were evaluated for mitochondrial redox state, while isolated cardiac and hepatic mitochondria were subjected to high-resolution respirometry to assess oxygen consumption (with carbohydrates and fatty acids as substrates) and redox state with an Oroboros Oxygraph-2k.
Results
In ECG, the male HFD group exhibited a significantly reduced E/A-ratio with preserved ejection fraction, indicating diastolic dysfunction and an HFpEF phenotype when compared to the healthy CO group. SEMA normalized the E/A-ratio, in line with a significantly improved mitochondrial redox balance compared to HFD. Cardiac mitochondrial respiration, was significantly reduced in the HFD group, and was fully restored by SEMA. In female HFD rats, ECG showed a significantly reduced E/A-ratio. However, the mitochondrial redox state remained similar to CO. Here, SEMA did not normalize the E/A-ratio and mitochondrial respiration was unaffected. Characteristic for MASLD, hepatic histological assessment in the male HFD group indicated increased lipid storage and inflammation. Hepatic mitochondrial respiration in males was significantly higher in the HFD group compared to CO. While SEMA improved histological parameters, only a partial reduction of mitochondrial respiration could be detected. In females, mitochondrial respiration was also significantly increased compared to CO. Here, SEMA treatment significantly reduced cellular respiration and redox state.
Conclusion
Semaglutide exhibits sex-specific effects in a diet-induced model of HFpEF and MASLD, improving cardiac mitochondrial function in males while providing less pronounced effects in females. Regarding hepatic mitochondrial respiration, semaglutide treatment led to stronger effects in females. These results highlight the critical need to incorporate sex-based analyses in research on HFpEF and MASLD, given the variations in responses to semaglutide between genders, potentially having implications for treatment strategies.

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Oral Communications 16: Reproductive and Developmental Endocrinology Part 2

OC16.1

JOINT2837

Human sex-determination and associated pathologies as a model to understand developmental gene regulation

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Background
Our analysis of patients with 46,XY gonadal dysgenesis and 46,XX DSD (Disorders/Differences in Sex Development) has identified many genes involved in mammalian sex-determination (SD) and gonadal differentiation. Despite extensive exome studies >50% of all cases remain idiopathic. We hypothesize that unexplained cases are due to variants in gene regulatory elements (GREs) that may define gene regulatory networks (GRNs). Consistent with this hypothesis, recently we defined a novel *SRY* enhancer and identified SNVs in it, associated with a spectrum of phenotypes including 46,XY gonadal dysgenesis and under virilized male (PMID: 38555298). We have extended this work to develop a multi-omic genome-wide approach to identify functional GREs in human SD and predict GRNs.
Methods
Single-cell RNAseq and ATACseq data from human fetal gonad atlas (PMID: 35794482) was reanalysed by Scenic+, to define candidate GREs (cGREs). Transcription factor (TF) binding-site enrichment and mutational constraint in cGREs were determined using pycistarget and Gnocchi respectively. We defined cGREs corresponding to human accelerated regions (HARs, PMID: 27667684). Rare/novel variants from genome sequences of >160 individuals with unexplained DSD were mapped to cGREs and functional variants prioritized using CADD, FinSurf and Fabian.
Results
We defined 18,932 and 18,200 cGREs in Sertoli and pre-granulosa cells with a mean Gnocchi score of 7.90 and 7.88 respectively. Using our pipeline, we observed an enrichment of binding-sites for known SD TFs in cGREs: e.g: SOX9

(Normalized Enrichment Score (NES) = 12.95), NR5A1 (NES = 10.98) in Sertoli and LHX9 (NES = 5.66) in pre-granulosa cells. As proof of principle, we identified a previously reported *SOX9* GRE (eSR-A (PMID: 30552336)).
Conclusions
Our approach dissects the role of GREs and GRNs in SD providing a unique model to further understand developmental gene regulation. This approach also provides a unique pipeline to understand the genetic causes of unexplained DSD due to gene regulatory variants.

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OC16.2

JOINT3303

Characterising the metabolism of 11Oxy-androgens in placental cell models, tissue homogenates and explants

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Maternal and fetal adrenal derived androgen precursors are trafficked through the placenta throughout human fetal development. Most of these androgen precursors are steroid substrates for the biosynthesis of estrogens in the placenta, which evades harmful androgen excess. The placenta therefore serves as a key organ in the fetal-(adrenal and liver)-placental unit. Androgens in the 11oxy-pathway have recently been profiled in placental tissue, amniotic fluid and in maternal and newborn serum, which underscores their importance during fetal development, but also their potential to cause damage if in excess. Adrenal androgen excess readily occurs in classic congenital adrenal hyperplasia (CAH), with CAH marked by 11oxy-androgen (11OxyA) excess. 11OxyAs are in addition not readily converted to estrogen metabolites. Therefore, the dynamic of 11OxyA metabolism in placental steroidogenesis requires investigation to better understand their role in fetal development, especially in the developing CAH fetus. In this study, 11OxyA metabolism was traced in placental cells models (BeWo and Jeg-3 choriocarcinoma cells), and in healthy term placental S9 fractions and explants. Steroid profiling using liquid chromatography-mass spectrometry enabled the quantification of precursor and downstream steroid metabolites following the addition of steroid substrates (1 μM) after 48 hrs in cells, 24 and 48 hrs in explants, and 15 min in S9 fractions. Looking at the cell models, directional 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) activity was favoured, producing 11-ketoandrostenedione (11KA4). 11KA4 was in turn converted to 11-ketotestosterone (11KT), while the opposite reaction did not readily occur. Conversions in placental S9 fractions showed the rapid metabolism of 11KA4 (92%), similar to the classic- and 16-hydroxyandrogens, however 11KT was not readily metabolised (25%). Furthermore, the 11βHSD2 activity in placental explants firstly converted 11β-hydroxyandrostenedione to 11KA4 (after 24 h), after which 11KT was produced (after 48 h). To summarise, our data show that the placenta is an active 11OxyA metabolising organ, favouring the biosynthesis and metabolism of 11KA4. We show that while 11βHSD2 and aromatase activities normally safeguard the fetus from glucocorticoid and classic androgen excess, these enzymatic activities either 'activate' or do not apply to the 11OxyAs, respectively. Therefore, if in excess, as in CAH, the 11OxyAs would be suitable steroid substrates for placental steroidogenesis, potentially producing active metabolites which prevail over classic androgens.

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OC16.3

JOINT3920

Exposure to phthalates at the masculinization programming window is associated with longer anogenital distance and reduced birth weight in healthy children: A COPANA cohort study of 589 infants

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Background
Phthalates are used widely in several consumer products. Previous studies suggest that phthalate exposure during the male programming window (MPW), gestational week (GW) 8-14, may disrupt gonadal and genital development with persistent effects. Most consistently, prenatal exposure to phthalates has been associated with reduced anogenital distance (AGD) in human and animal studies.
Primary aim
Exploratory assessment of prenatal exposure to phthalates was associated with changes in reproductive parameters in infancy.

Table 1

	Phthalate (ln2) Girls	Percent change	P value	Phthalate (ln2) Boys	Percent change	P value
Fetal outcomes						
Fetal AGD, mm	MEP	21.3	0.018	ΣDiBPm	-35.9	0.022
	ΣDiNPm	39.1	0.005	ΣDnBPm	-32.0	0.049
	ΣDINCHm	26.8	0.004			
Fetal AGD/EFW, mm/g	MEP	15.8	0.003	MMP	27.0	0.046
	MnHxP	16.5	0.0007			
	ΣDiBPm	14.5	0.033			
	ΣDnBPm	23.2	0.003			
	ΣDINCHm	12.7	0.021			
EFW, g (ln2)	MnHxP	-1.1	0.046	ΣDiBPm	-1.9	0.041
	ΣDnBPm	-2.1	0.022			
Infant outcomes						
AGDaf/ as, mm	ΣDINCHm	40.3	0.009	ΣDnBPm	94.0	0.049
AGDaf/ as per body weight, mm/kg	MnHxP	3.8	0.041	MBzP	9.6	0.022
	ΣDEHTPm	4.9	0.036	ΣDiBPm	12.6	0.019
	ΣDINCHm	5.4	0.016	ΣDnBPm	11.0	0.045
AGDac/ ap per body weight, mm/kg	ΣDEHTPm	11.2	0.004	MBzP	12.1	0.044

af = ano-fourchette. ac = ano-clitoral. as = ano-scrotal. ap = ano-penile.

Design
Prospective, observational pregnancy and birth cohort; The Copenhagen Analgesic Study (COPANA) (ClinicalTrials.gov NCT04369222).
Setting
Copenhagen University Hospital - Rigshospitalet (2020-2022).
Methods
Healthy, singleton pregnant women ($n = 685$) were enrolled during the first trimester, and 589 (287 boys) infants were examined. Metabolites of 15 phthalates and two substitutes were measured by LC-MS/MS in maternal urine samples collected in the first trimester (GW 14.1 ± 1.8 (mean ± SD)). Third-trimester ultrasound (GW 29-34): Fetal AGD and estimated fetal weight (EFW). Child examination (boys, mean age 3.1 months; girls, mean age 3.5 months): AGD by TIDES method, penile width and length, anthropometrics.
Statistics
Linear regression adjusted for maternal age, BMI, education level, and parity. Non-normally distributed data were ln2-transformed.
Results
Prenatal exposure to several phthalates in the first trimester was associated with longer fetal and infant AGD (raw and adjusted for weight), Table 1. In addition, exposure was associated with increased penile width and length. Metabolites of five different phthalates were associated with reduced birth weight and length in boys.
Conclusion
The results suggest endocrine-disrupting effects of phthalate exposure affecting early fetal development. We provide unique human data on phthalate exposure at MPW indicating androgenic effects. This may explain discrepancies with previous studies reporting reduced AGD after phthalate exposure in fetal life.

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OC16.4

JOINT999

Testosterone therapy and the risk of atrial fibrillation, venous thromboembolism and cardiovascular events in cisgender men with hypogonadism and transgender men

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Aim
Cardiovascular safety of testosterone therapy has been a subject of controversies. A recent trial showed an increased risk of pulmonary embolism and atrial fibrillation in men with hypogonadism. The issue of cardiovascular safety of testosterone therapy also concerns female-to-male transgenders, for whom there are limited evidence. The aim was to assess in a real-life setting the safety profile and cardiovascular risk of testosterone therapy in these two different clinical settings: cisgender men with hypogonadism and transgender men.
Methods
We used TriNetx Research Collaborative network, a global federated health research network with access to electronic medical records from participating health care organizations, to identify and included participants. Diagnosis was done using the International Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification (ICD-10-CM) codes, and medications. We used a 1:1 propensity-score matching for age and baseline characteristics to compare 117,908 cisgender men with hypogonadism treated with testosterone to 117,908 untreated cisgender men without a diagnosis of hypogonadism. Similarly, we compared matched 9,714 transgender men treated with testosterone to 9,714 untreated cisgender women treated with a contraceptive pill.
Results
After 5 years of follow-up, in cisgender men testosterone therapy was associated with a lower risk of myocardial infarction (HR: 0.94 95%CI [0.89-0.99], $P=0.01$) with no difference for stroke or total mortality. There was an increased risk of both atrial fibrillation (1.27 [1.22-1.32], $P<0.0001$) and acute pulmonary embolism/deep vein thrombosis (1.26 [1.18-1.34], $P<0.0001$). Transgender men treated with testosterone had a higher risk of acute myocardial infarction (2.82 [1.12-7.03], $P=0.02$) without significant difference for total mortality, stroke or atrial fibrillation compared to matched cis women treated with a contraceptive pill. Transgender men had a lower incidence of pulmonary embolism/deep vein thrombosis (0.46 [0.22-0.93], $P=0.03$) compared to matched cisgender women.
Conclusions
Testosterone treatment was associated in cisgender men with hypogonadism with a lower risk of myocardial infarction, but a higher risk of atrial fibrillation and venous thromboembolism as compared to men not treated with testosterone. Transgender men with testosterone therapy were at increased risk of myocardial infarction, without increased risk for atrial fibrillation or venous thromboembolism as compared to cisgender women.

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OC16.5

JOINT404

Histological markers of testicular health and spermatogenesis in transgender adolescent girls following puberty suppression and subsequent gender-affirming hormone therapy

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Background
Gender incongruence is a marked and persistent incongruence between an individual's experienced gender and their sex registered at birth. This may lead to a desire to medical transition. For adolescents, this usually includes puberty suppressing drugs and subsequent gender affirming hormone therapy (GAHT). For trans girls, pubertal hormones can be suppressed with GnRH analogues (GnRHa) or cyproterone acetate (CA), and subsequent feminisation induced with 17β-estradiol (E2). It is currently not known if long-term use of these medications may cause testicular damage or irreversibly affect gamete number and quality hampering evidence-based fertility preservation counselling.
Aim of this study
To assess the effect of puberty suppression and subsequent GAHT on markers of testicular health and fertility in trans girls via histological analysis of testicular tissue obtained at orchidectomy. Differences in outcomes between those who received GnRHa versus CA are explored.
Methods
The primary outcome was the developmental stage of the most mature germ cell visible by routine histological examination and overall advancement of spermatogenesis, expressed as a modified Johnsen score (MJS). Secondary outcomes were basal membrane thickness (BMT), open lumen, peritubular myoid cell pattern (α-SMA staining), edema, fibrosis, Leydig cell presence and Sertoli cell maturity (podoplanin staining). Serum levels of E2, follicle stimulating hormone, luteinizing hormone and Inhibin B at the last pre-operative follow-up consultation were obtained from the patient files.
Participants
Sixty-seven participants were identified; 21 had received GnRHa and 46 CA. GnRHa were generally started at Tanner stage II-III, while CA was started at Tanner stage IV-V. The median total treatment duration for those who had GnRHa+E2 was 67 (IQR: 57-73) months and for those who had CA+E2 33 (IQR: 28-44) months. All participants had received E2 for a median duration of 27 (IQR: 20-34) months. All treatments were interrupted 2 weeks prior to orchidectomy.
Results
As expected, most participants showed spermatogenic arrest at orchidectomy, although full spermatogenesis was observed in a small minority, all treated with CA. All but one had spermatogonial stem cells. A disconnected α-SMA staining pattern and (moderately or severely) increased BMT, both likely indicating testicular damage, were observed in 49,3% and 55,2%, respectively. MJS inversely correlated with BMT. GnRHa were associated with a more immature testicular morphology when compared to CA.
Conclusion
Long-term puberty suppression and subsequent GAHT induces testicular immaturity and spermatogenic arrest in most trans girls. It may in addition cause testicular damage, visible as increased BMT, which adversely correlates with MJS.

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OC16.6

JOINT531

Testicular function in young men and risk of cardiometabolic disease up to 20 years later – a register-based follow-up study of more than 5000

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Background
The role of testicular function may extend beyond reproduction, potentially serving as a biomarker of general health. In fact, poor semen quality has been linked with increased risk of cardiovascular morbidity, hospitalization, and mortality.
Objective
To investigate testicular function and its associations with cardiometabolic health from a longitudinal perspective by utilizing baseline data from a well-characterized cohort of Danish young men from the general population, coupled with register-based follow-up.
Material and methods
This register-based follow-up study includes 5,265 men from the Danish Young Men Study (DYMS), a cohort established to investigate reproductive function in young adulthood. At baseline, participants completed a questionnaire, provided a blood sample for the assessment of reproductive hormones and health markers, delivered a semen sample, and underwent physical examinations. After a median follow-up of 12.1 years (5th–95th percentile: 2.1–20.8), the men had a median age of 32.4 years (5th–95th percentile: 22.4–40.9). Baseline data were linked to the nationwide Prescription Register and National Patient Register to obtain information on cardiometabolic prescriptions and diagnosed diseases. Men were divided into quartiles based on semen quality parameters. The associations between semen quality in early adulthood and later cardiometabolic disease were analyzed using Cox regression analyses, with follow-up from baseline until the first cardiometabolic prescription or diagnosis, or censoring. Results are expressed as hazard ratios (HR).

Results

After adjustment for period of ejaculation abstinence, smoking and BMI, we observed that the lower the quartile of baseline total sperm count, the higher the risk of cardiometabolic conditions (Q4: reference, Q3: HR = 0.97, Q2: HR = 1.06, Q1: HR = 1.16; *P*-trend = 0.21). A similar dose-dependent pattern was observed for total progressive motile sperm count (Q4: reference, Q3: HR = 1.06, Q2: HR = 1.14, Q1: HR = 1.21; *P*-trend = 0.14). BMI modified the association, which was less pronounced in men with normal BMI but more pronounced and statistically significant in men with BMI $\geq$ 25 kg/m^2 (n = 898) (total sperm count: Q4: reference, Q3: HR = 0.93, Q2: HR = 1.34, Q1: HR = 1.59, *P*-trend = 0.01, and total progressive motile count: Q4: reference, Q3: HR = 0.72, Q2: HR = 1.20, Q1: HR = 1.47, *P*-trend = 0.01, respectively).

Conclusion

Semen parameters in youth were significantly associated with risk of cardiometabolic health in men with BMI $\geq$ 25 kg/m^2. Thus, semen quality could serve as an additional biomarker for future cardiometabolic health, enabling earlier intervention and prevention. Men seeking help for infertility may be a relevant target group for such preventive initiatives.

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Rapid Communications

Rapid Communications 1: Adrenal and Cardiovascular Endocrinology

RC1.1

JOINT1328

Role of postural test in differentiating from primary aldosteronism to low-renin hypertension

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Background
The concept of primary aldosteronism (PA) as a categorical disease has recently been revised; instead, PA may be considered as a continuous spectrum of disease, characterized by renin-independent aldosterone excess. The role of confirmatory tests in the diagnostic process of PA is still controversial. Among them, the postural stimulation test (PST) was proposed in the past for PA subtyping, however results were contradictory.
Objective
To assess PST role in differentiating from PA to low-renin hypertension (HTN).
Patients and methods
190 patients with arterial hypertension and at least one positive aldosterone to renin ratio (ARR) underwent confirmatory tests (saline infusion test and/or captopril challenge test). 80 were confirmed PA and 110 PA were identified as low-renin HTN. Baseline clinical and biochemical data and PST response were assessed. Principal component analysis (PCA), Partial Least Square-Discriminant Analysis (PLS-DA) and K-means clustering network were used to compute an integrated analysis.
Results
PST response showed 56/190 patients (29%) with suppressed renin levels both in clinostatism (clino) and orthostatism (ortho), 56/190 (29%) with desuppression of renin levels from clino to ortho, and 78/190 (42%) with non-suppressed clino renin which remained measurable in ortho. In the category of *always suppressed renin* 54/56 (92%) patients were PA, while 45/56 (80%) of patients in the category *renin from suppressed to measurable* were identified as low-renin HTN. Multivariable regression analysis showed increasing K levels (OR 12.5, 95% CI 3.4-42.5, $P<0.001$) and measurable ortho_renin (OR 351.6, 95% CI 31.35-3921, $P<0.001$) as significant predictors of low-renin HTN. Cluster analysis was able to distinguish PA from low-renin HTN. Cluster 1 correctly included 57/80 PA and Cluster 2 correctly included 104/110 low-renin HTN. Cluster 1 PA patients showed a higher frequency of suppressed renin levels at baseline and during PST, with a prevalence of clino_renin$_{suppressed}$ of 100% and a prevalence of ortho_renin$_{suppressed}$ of 95%. Cluster 1 low-renin HTN patients had lower potassium levels and a higher frequency of suppressed renin levels at diagnosis and during PST, compared to Cluster 2. LS-DA and PCA confirmed that ortho_renin, renin response to PST and presence of hypokalemia were the most accurate parameters to distinguishing PA from low-renin HTN.
Conclusion
PST demonstrated his role in the differential diagnosis of suspected PA, in particular regarding renin response during the test.

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RC1.2

JOINT2377

Clinical and biochemical determinants of left ventricular hypertrophy and its severity in primary aldosteronism: insights from the SPAIN-ALDO registry

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Introduction
Primary aldosteronism (PA) is the leading cause of secondary hypertension, strongly linked to left ventricular hypertrophy (LVH) and systolic dysfunction. Compared to essential hypertension, PA results in worse cardiac remodeling. However, data on factors influencing LVH at PA diagnosis remain scarce.
Methods
SPAIN-ALDO is a multicenter, national registry of patients with PA from 37 Spanish hospitals. This subgroup analysis included patients with an echocardiography within 24 months before or after diagnosis, excluding those who underwent PA surgery. Biochemical and clinical data at diagnosis were analyzed to identify independent factors associated with LVH.
Results
343 patients were included (women $n=119$, 35%) with a mean diagnosis age of 56 ± 12 yo. 188 patients (55%) had LVH from which, 108 (57%) had mild LVH severity, 69 (37%) moderate, and 11 (6%) a severe degree. Random forest analysis adjusted for age and sex identified patients with LVH as having longer durations of high blood pressure, a higher basal aldosterone index, higher BMI, elevated serum HbA1c levels, and increased 1mg overnight dexamethasone suppression test (ONDST) cortisol, along with lower glomerular filtration rates. Additionally, they were more likely to be male, active smokers, and have dyslipidemia and hypokalemia ($P=0.011$, $R^2=50.2\%$, $Q^2=0.73$, correctly predicted group: 73.9%). However, only glomerular filtration (OR = 0.12 [0.01 – 0.92]), active smoking (OR = 15.6 [1.79 – 37.2]), and hypokalemia (OR = 6.0 [1.3 – 16.8]) remained independent factors associated with LVH ($P=0.001$, $R^2=42.1\%$). The presence of type 2 diabetes mellitus (DM) was associated with LVH severity, with percentages of DM patients per group being 20%, 36%, and 46% in mild, moderate and severe LVH, respectively ($P<0.01$). Similarly, hypertensive retinopathy proportion of patients (mild = 4%, moderate = 17%, severe = 27%) and microalbuminuria (mild = 23%, moderate = 53%, severe = 67%) increased with LVH severity ($P<0.01$). Finally, basal aldosterone levels (ng/dl) increased with LVH severity: mild = 19.4 [13.9–31.5], moderate = 29.2 [20.7–47.6], severe = 27.6 [22.8–47.5] ($P=0.005$), as did ONDST cortisol levels (μg/d): mild = 1.5 [1.17–185], moderate = 2.10 [1.51–4.35], severe = 3.30 [1.40–4.50] ($P=0.014$).
Conclusion
Among patients with PA, those with active smoking, lower glomerular filtration and hypokalemia at diagnosis are at higher risk of developing LVH while higher levels of aldosterone and ONDST cortisol are associated with LVH severity.

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RC1.4

JOINT1041

Long-term cardiovascular outcomes after adrenalectomy in mild autonomous cortisol secretion: results from the multicentric ENSAT NAPACA outcome study

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Background
The efficacy of adrenalectomy in adenomas associated with Mild Autonomous Cortisol Secretion (MACS) is poorly investigated. A few small randomized trials and retrospective studies showed beneficial effects of adrenalectomy on hypertension. Long-term data on cardiovascular outcomes are missing.
Aim
To investigate cardiovascular outcomes in patients with unilateral adrenal adenomas and MACS after adrenalectomy.
Methods
Patients with MACS due to unilateral adrenal adenomas (serum cortisol after dexamethasone suppression test [DST] >1.8 mg/dl) from 14 ENSAT centers were included. Clinical data were retrieved at the time of initial evaluation (before adrenal surgery) and at last follow-up. From each center, MACS patients with and without surgery were matched 1:1. The control group belonged to a previously published study on long-term outcomes of MACS[1]. Matching was performed by propensity score using age and sex. We considered the following outcomes (occurring after adrenalectomy or after initial diagnosis in non-operated patients): new cardiovascular events (CVE), CVE and death from cardiovascular causes (composite-CVE), and death from all causes. We performed survival and multivariable Cox-regression analyses.
Results
We included 616 patients: 308 were treated by adrenalectomy and 308 underwent follow-up. Mean age was 58.1 ± 10.5 years for both groups ($P=0.927$). Prevalence of female sex was 67.2% ($n=207$) vs 67.9% ($n=209$) ($P=0.931$). The prevalence of hypertension and diabetes at baseline was not different between groups ($P=0.127$ and $P=1.000$, respectively). Values of post-DST cortisol were higher in operated patients than in non-operated ones (4.6 ± 3.7 vs 3.7 ± 3.2 mg/dl; $P<0.001$). After a median follow-up of 5 years (range 1 to 15 years), survival analysis showed significant differences between operated and non-operated patients for both new-CVE (HR: 0.554, 95%CI: 0.333-0.922, $P=0.023$) and composite CVE (HR: 0.581, 95%CI: 0.402-0.839, $P=0.004$). No significant differences were detected for all-cause mortality (HR: 0.772, 95%CI: 0.496-1.202, $P=0.251$). The multivariable Cox-regression analysis confirmed the significant beneficial effect of surgery on new CVE and composite-CVE after adjustment for cortisol after DST (HR: 0.565, 95%CI: 0.335-0.951, $P=0.032$ and HR: 0.573, 95%CI: 0.394-0.835, $P=0.004$, respectively).
Conclusion
Treatment of unilateral adenomas and MACS with adrenalectomy improves long-term cardiovascular outcomes.
Reference
1. Deutschbein, Lancet Diabetes Endocrinol Metab, 2022.
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RC1.5

JOINT895

Integrated liquid biopsy approach as disease monitoring tool in adrenocortical carcinoma: a preliminary study

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Background
Adrenocortical carcinoma (ACC) is a rare cancer with heterogeneous clinical outcome. Close disease monitoring is essential but relies on radiological imaging that comes with significant radiation exposure. Circulating cell-free DNA (ccfDNA) can contain tumour-derived somatic variants, representing a non-invasive tool for cancer monitoring. Similarly, tumour-derived steroid hormone metabolites can be detected in urine from patients with ACC and may provide an additional post-operative surveillance tool.
Aim
Evaluate the role of combined ccfDNA sequencing and urine steroid metabolomics (USM) to monitor disease recurrence in ACC.
Methods
We investigated 6 patients (1M/5F, median age 37.5yrs) with histologically confirmed ACC. Plasma and 24 h urine samples were collected before primary tumour resection (baseline), early post-operatively (28-42 days) and on 3-monthly follow-ups. ccfDNA and germline DNA (gDNA) were isolated with commercially available kits. Tumour DNA (tDNA) was isolated from paraffin-embedded tissue. ccfDNA/gDNA/tDNA were sequenced using a customized ACC-specific panel and by shallow (0.1×) whole genome sequencing (sWGS). Genetic alterations (including gene variants and copy number variations, CNV) were called following standard bioinformatic protocols. gDNA was used to discriminate somatic variants. 32 distinct adrenocortical steroid metabolites were quantified using gas chromatography/mass spectrometry and a previously developed generalised matrix learning vector quantisation algorithm was used to detect the presence of ACC.
Results
at tDNA level, 3/6 cases (50%) presented point mutations while all 6 cases (100%) had an altered CNV pattern at sWGS. tDNA-derived somatic alterations were detected in baseline ccfDNA from 4/6 patients (71%). USM demonstrated steroid profiles for ACC in 5/5 patients at baseline. Three patients developed radiological recurrence at 3 or 6 months, which coincided with detection of somatic alterations in follow-up ccfDNA samples in 2/3 cases (67%). In one case, sWGS gave a clear signal for recurrence that would otherwise be missed by targeted sequencing alone. USM detected ACC-diagnostic steroids at recurrence in all cases with available urine samples, one 3 months before radiological evidence of relapse. The other three patients remain tumour free at 2-year follow up. One case presented somatic alterations at baseline tDNA/ccfDNA that disappeared in follow-up ccfDNA. USM reliably showed no evidence of ACC-diagnostic steroids in both cases with available samples during the entire follow up.
Conclusion
Integrating molecular signatures from ccfDNA and USM could complement standard radiological surveillance in monitoring of patients with ACC. sWGS

seems to have an additional value beyond targeted sequencing alone. Validation in a larger cohort is required to confirm our promising findings.

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RC1.6

JOINT1779

Metabolic phenotype in non-aldosterone producing adrenal adenomas (NAPACAs) with co-existent polycystic ovaries syndrome (PCOS): a joint ENSAT project

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Non-aldosterone producing-adrenal-adenomas (NAPACAs) and polycystic ovaries syndrome (PCOS) are associated with hyperinsulinemia and insulin-resistance and thereby with increased prevalence of several aspects of the metabolic syndrome. Whether the co-existence of the two disease entities leads to accentuated prevalence of the metabolic syndrome remains unclear. Aim of the present study is the assessment of cardiovascular risk factors and insulin resistance indices in women with NAPACAs with and without PCOS. We conducted a retrospective multicenter study including adult premenopausal women categorized as NAPACA ($n=44$), PCOS ($=19$) or NAPACA+PCOS ($n=24$), excluding women with hormonally active adenomas other than mild autonomous cortisol excess (MACS), congenital adrenal hyperplasia, diabetes, systemic steroid medication or active malignancy and analyzed clinical, biochemical and hormonal data of the respective patients. As expected from the disease natural history, NAPACA patients were significantly older than the other two groups (NAPACA 41.02 ± 1.1, PCOS 31.05 ± 1.5, NAPACA+PCOS 33.83 ± 1.4 years old, $P<0.001$). PCOS patients displayed the lowest (26.88 ± 1.8 kg/m^2) and NAPACA+PCOS the highest body-mass-index (31.83 ± 1.9 kg/m^2, $P=0.05$), but patients of the three groups did not differ in their waist-to-height ratio ($P=0.12$), systolic ($P=0.51$) and diastolic blood pressure ($P=0.16$), HbA1c ($P=0.49$) and fasting plasma glucose levels ($P=0.51$). Interestingly, NAPACA+PCOS patients displayed significantly higher fasting insulin levels (NAPACA 9.38 ± 1.1, PCOS 12.93 ± 2.9, NAPACA+PCOS 25.52 ± 9.1 μU/ml, $P<0.05$). NAPACA+PCOS patients displayed significantly increased insulin resistance as calculated by the glucose-to-insulin ratio (GIR, $P<0.05$), the HOMA index ($P<0.05$) the QUICKI index ($P<0.05$) and the MATSUDA index ($P<0.05$). NAPACA+PCOS patients also presented lower HDL levels (NAPACA 58.67 ± 2.6, PCOS 58.21 ± 3, NAPACA+PCOS 48.05 ± 2.5 mg/dl, $P<0.05$). Although the cortisol levels upon 1 mg-dexamethasone suppression test (DST) did not differ among the groups ($P=0.1$), the DHEA-S ($P<0.05$), androstenedione ($P<0.01$) and testosterone levels ($P<0.01$) were significantly higher in the two groups including PCOS patients. Free androgen index levels positively correlated with the insulin resistance in NAPACA (GIR R -0.56, $P<0.01$, HOMA R 0.52, $P<0.05$, QUICKI R -0.52, $P<0.05$, MATSUDA R -0.49, $P=0.09$) and PCOS patients (GIR R -0.68, $P<0.01$, HOMA R 0.67, $P<0.01$, QUICKI R -0.67, $P<0.01$, MATSUDA R -0.82, $P<0.001$), while cortisol after 1mg-DST positively correlated with the insulin resistance in the NAPACA+PCOS group (GIR R -0.48, $P=0.05$, HOMA R 0.58, $P<0.05$, QUICKI R -0.58, $P<0.05$, MATSUDA R -0.67, $P<0.05$). These data provide hints that NAPACA+PCOS patients represent a distinct phenotype compared to NAPACA or PCOS patients, with a worse metabolic profile, and further studies with larger patient cohorts will be necessary to elucidate this observation.

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Rapid Communications 2: Diabetes and Insulin Part 1

RC2.1

JOINT1396

Stable age at diagnosis and persistently high incidence of inaugural diabetic ketoacidosis in children with type 1 diabetes: insights from french diabetic ketoacidosis observatory (2010–2023)

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Introduction

Diabetic ketoacidosis (DKA), a serious metabolic complication resulting from near-total insulin deficiency, is often associated with the initial presentation of type 1 diabetes (T1D) in children. Although DKA is transient at the time of diagnosis, it is associated with both medium- and long-term adverse outcomes. The incidence of DKA varies between countries. It is influenced by multiple factors including age, socioeconomic status and public awareness. The aim of this study is to evaluate for the first time the evolution of inaugural DKA in France over the past ten years.

Materials and methods

Data were collected from the national AJD (Aide aux Jeunes Diabetiques) registry, which collects data on paediatric patients with new-onset T1D (aged 0-15 years) from approximately 70% of the national clinics between 2010 and 2023. DKA was defined according to ISPAD criteria. Student's t-test, chi-squared test, or their non-parametric equivalents (Mann-Whitney U test and Fisher's exact test, Kruskall-Wallis) were used for statistical comparisons between groups and time periods.

Results

A total of 23108 children (46.7% female) were diagnosed with T1D at a mean age of 7.9 ± 5 years. The age at diagnosis and the distribution of patients across age groups (i.e., <5 years, 5-10 years and >10 years) remained stable over time. There was no significant increase in diagnoses in very young children (<5 years) (all $P>0.05$). DKA occurred in 39.1% of participants, with 43.2%, 36.1% and 39.5% in children <5, 5-10 and >10 years respectively. Between 2010 and 2019, the incidence of DKA remained consistently high in all years ($36.7\%\pm1.7\%$), with $12.9\%\pm0.9\%$ of children presenting with severe DKA ($P>0.05$). In participants without a first-degree relative (FDR) with T1D, DKA increased significantly after the COVID-19 pandemic (2016-2019 vs 2020-2023) from 39.7% to 46.5% ($P<0.0001$). This was accompanied by a significant increase in severe DKA (14.1% to 19.6%, $P<0.00001$). Children with FDR ($n=2523$) had a lower rate of DKA than children without FDR (18.8% vs. 41.6%, $P<0.000001$), but severe DKA persisted at diagnosis in 6.3% of this group.

Conclusion

Over the past decade, the age at diagnosis of T1D has remained stable. The incidence of DKA remains stable and elevated, with almost half of children with new-onset T1D who do not have an FDR presenting with DKA. While the rate of DKA was significantly lower in children with a FDR, there were still cases of severe DKA in this group. Increasing awareness for pediatric DKA is thus mandatory.

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RC2.2

JOINT1767

Migration background 2000-2023 in type 1 and 2 diabetes, analysis based on the DPV registry: children with Turkish background at increased risk to develop type 2 diabetes – independent of their BMI

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Introduction
Certain ethnicities – as native Americans and non-Hispanic Blacks in American cohorts- are known to have a higher risk to develop type 2 diabetes (T2D). As European cohorts differ substantially in migration background from American cohorts, we examined the migration background (mb) in a large pediatric German-Austrian-Suisse-Luxemburgish cohort.
Methods
The analysis was based on the DPV registry. Patients documented 2000-2023 with either type 1 (T1D) or T2D, younger than 18 years and diagnosed at the age of 6- 18 years were included. Mb is defined as either the child or one of the parents being born in another country. Mb was divided in the following groups: no mb, Turkish, African, East European, South European and Syrian/Iran/Irak/Jemen/Afghanistan (SIIJA). Statistical analysis was performed using the Wilcoxon rank sum test for continuous and Chi-square test for qualitative variables with adjustment for multiple testing (Bonferroni step-down). For longitudinal observations, adjusted regression models were used.
Results
70866 children with T1D and 2796 with T2D were included. Between 2000 and 2023, the rate of migration background increased in the total cohort from 3.2 to 29%. In the T2D group more children than in the T1D group had a migration background (33.7 vs 20.2%, $P=0.00$). Distribution of countries of origin differed between the two groups: More patients with T2D came from Turkey (8.9 vs 2.7%) , Africa (2.9 vs 1.7%), SIJJA (2.7 vs 1.6%) and Southern Europa (3.7 vs 2.6%) compared to T1D (all $P<0.0005$). At diagnosis, Turkish T2D patients were not more obese than patients with no mb, HbA1c and age were similar. In regression models adjusted for age, gender, diabetes duration and HbA1c, there was no significant difference in BMI between Turkish and no mb T2D patients ($P=0.48$).
Conclusion
Mb increased corresponding to the overall increase of mb in the general population (29% in Germany in 2023). We observe distinct differences in migration background between pediatric T1D and T2D cohorts. Pediatric T2D had more often a Turkish background. This difference could not be explained by differences in BMI. We hence postulate, that Turkish patients seem to have a higher genetic risk to develop T2D.

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RC2.3

JOINT1919

Islet cell autoimmunity and preclinical phase of type 1 diabetes in general population of 1-9 year old children in north-eastern region of Poland – a summary of the first 18 months of the study

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Aims
Assessment of islet autoimmunity and the prevalence of presymptomatic type 1 diabetes among children aged 1 to 9 years in a general population of North-Eastern Poland through a stepwise islet autoimmunity screening programme.
Methods
3575 children aged 1-9 years participated in the study. Venous blood samples have been collected and analysed in a stepwise procedure starting with 3 Screen Islet Cell Autoantibody ELISA and IAA ELISA. In the next step, samples found positive in either 3 Screen or/and IAAs, were verified for individual autoantibodies. Children with confirmed islet cell autoimmunity were invited for the first follow-up stage, that consisted of laboratory testing, metabolic staging and education.
Results
Among 3575 tested children 4.84% were found positive in 3 Screen test and 4.73% for IAA. Detailed antibody testing confirmed islet cell autoimmunity in 7.78% participants and 1.17% of the total number presented multiple positive islet autoantibodies (IAb). IAAs were the most frequently reported autoantibodies (50.75%), while IA-2As were the least frequent (8.4%). IAAs were observed more frequently in individuals with T1D family history compared to those without T1D in relatives ($P=0.04$) and in children aged 1-3 years compared to older ones ($P=0.02$). The frequency of IA2-As and ZnT8As increased with age ($P=0.035$ and $P=0.02$, respectively) and ZnT8As were observed more frequently in females than males ($P=0.024$). The prevalence of GADAs was similar in all age groups ($P=0.54$). The prevalence of multiple positive IAbs was almost 2.5-times higher among children with T1D family history than in other peers. 113 children with confirmed islet cell autoimmunity participated in metabolic staging. Within individuals with dysglycaemia (stage 2) almost 67% presented only a single autoantibody. Two participants (1.77%) presented stage 3 diabetes – both were diagnosed before DKA occurred.
Conclusions
Results of the study confirm the importance of screening for IAbs in general paediatric population as a method of prediction of T1D development. The study also shows that patients with a single positive islet autoantibody may have already developed dysglycaemia and need monitoring.

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RC2.4

JOINT2076

Transition of youth with type 1 diabetes from pediatric to adult care in Europe: Insights from centers participating in the international sweet initiative

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Introduction and objective
There is limited understanding of the heterogeneity in transfer of care from pediatric to adult services for youth with type 1 diabetes (T1D).
Aims
This study aims to examine T1D transition among European SWEET centers.
Methods
The SWEET (Better control in Pediatric and Adolescent diabete**S**: **W**orking to cr**E**ate **C**ent**E**r**T**ers of Reference) database was analyzed (2016-2023, >20

patients, > 5-year data). Transfer was assumed in patients 14-24 years without visits for ≥2 years. Age at transfer and sex, metabolic control, BMI-SDS, comorbidity, technology use (pump, continuous glucose monitoring [CGM], closed loop [CL], telemedicine [TM]) were evaluated across Western and Eastern Europe.

Results

19,123 patients (58 centers) were transferred (51% male, 93% T1D, mean DM duration 7.6 years). The median age at transfer was 18.7 years [Q1-Q3: 17.9-19.6]. Large centers transferred later, at 19.3 years [18.0-22.0], without gender differences. At patient level, the last visit mean age was 17.5 years [Q1-Q3: 13.6-18.9]. Mean HbA1c was 8% [6.9-8.7], BMI-SDS (WHO) 0.5 [-0.2-1.2]; 4% of patients had celiac disease (CD) and 3.8% Hashimoto thyroiditis. 5% of T1D patients were treated by CL, 41% with pump and 46% used CGM. Technology (as telemedicine, CGM, pump) was used by 60% of patients. Compared to patients not transferred ($n=23,947$), HbA1c was higher (7.6% vs 8%; $P<0.0001$), without differences in BMI-SDS. T1D females left earlier (-0.13 years; $P<0.0001$), patients with longer T1D and followed at larger centers left later. CD and thyroiditis did not affect age at transfer. Higher BMI z-score was associated with earlier transfer (-0.07, $P<0.0001$) as well as worse metabolic control (-0.1, $P<0.0001$). A model including interactions showed that only metabolic control, center size and diabetes duration remained associated with age at transfer. Pump, CL, CGM users were transferred earlier (-0.2, -0.3, -0.2; $P<0.0001$), while telemedicine was associated with later transfer (+0.7, $P<0.0001$). The interaction between technology use, HbA1c and BMI-SDS did not change the results. Age at transfer was similar in East and West Europe, with some differences in transition-related factors. For West Europe CGM was not associated to age at transfer. Considering East Europe, gender and metabolic control didn't affect age at transfer, while CL and technology use were associated with earlier transfer (-0.1, p 0.03).

Conclusion

This study highlights the significant heterogeneity of age at transfer of youth with T1D across Europe and some notable differences between European regions that warrant further exploration.

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RC2.5

JOINT2621

Developing a multicentre surveillance system for hyperosmolar hyperglycaemic syndrome: a framework for implementation and findings

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Background

Despite guidelines, significant variation in Hyperosmolar hyperglycaemic syndrome (HHS) diagnosis, management, and outcomes persists due to inconsistent protocol adherence. We developed and implemented a multicentre surveillance system to evaluate HHS management across hospitals, identify barriers to guideline adherence, and provide real-time feedback to optimise care pathways.

Methods

We conducted a prospective multicentre study (January 2021–November 2024) across 12 hospitals. Data were collected on demographics, precipitating factors, biochemical profiles, treatment practices, and outcomes. The surveillance system was modelled on the DEKODE (Digital Evaluation of Ketosis and Other Diabetes-related Emergencies) framework, incorporating standardised electronic data collection tools aligned with Joint British Diabetes Societies guidelines. The surveillance system facilitated the comparison of data from a hospital with median values from all participating hospitals and against a hospital of similar size and capacity. We assessed variations in management and mortality outcomes. Structured surveys and focus groups involving clinicians, diabetes specialist nurses, and acute care teams explored barriers and facilitators to guideline implementation.

Results

A total of 245 HHS episodes were captured, with 218 cases meeting diagnostic criteria (median age: 77 years (IQR 64–85)). Participation varied across the 12 hospitals due to various logistical and capacity issues. The leading precipitating factors were intercurrent illnesses (49.5%) and infections (16.0%). The median time to diagnosis was 2 hours, with 7.8% of cases diagnosed > 24 hours post-admission. Fluid resuscitation and insulin regimens varied widely, contributing to discrepancies in HHS resolution time (48.2 hours (IQR 24.9–74.2), [$n=149$]) and hospital length of stay (10.3 days (IQR 6.0–17.0), [$n=156$]). Mortality was 16.1% overall but significantly lower at Hospital A (2.3%) vs Hospital B (16.3%, $P=0.024$). Interestingly, Hospital A had higher insulin use and more frequent glucose monitoring than Hospital B. Key barriers to guideline adherence included reported staffing shortages, inconsistent glucose/ketone monitoring, and interdepartmental coordination issues. Facilitators included diabetes specialists' early involvement during acute admission, structured educational programs, and continuous real-time feedback throughout the year. Staff in one of the NHS trusts participating in the surveillance reported that a simplified, colour-coded HHS management algorithm improved adherence.

Conclusions

A standardised multicentre surveillance system identified care variations in HHS management, reinforcing best practices and refining guideline implementation. Integrating such surveillance into routine quality improvement frameworks could facilitate national benchmarking to drive improvements in management and future updates to HHS guidelines.

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RC2.6

JOINT282

Isolated glucosuria in adolescence and early-onset type 2 diabetes: a nationwide cohort study of 1.6 million adolescents

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Background

Identifying populations at risk for early-onset type 2 diabetes (T2D) is crucial due to its rising incidence, delayed diagnosis, aggressive course, and deleterious socioeconomic sequelae.Isolated glucosuria is an uncommon but well-recognized hereditary condition caused by variants in *SLC5A2* encoding sodium-glucose co-transporter 2. Data regarding its long-term glycemic outcomes are scarce.

Objective

To assess the risk of developing T2D in young adulthood among adolescents with isolated glucosuria in a large nationwide cohort of 1.61 million adolescents.

Research design and methods
Israeli adolescents (ages 16–19 years) examined prior to compulsory military service between 1993 and 2015 were included. Evaluations comprised medical and socio-demographic assessments. Isolated glucosuria was defined based on persistent findings in at least two repeated urine dipstick tests and normal results from a comprehensive evaluation, including a morning fasting glucose test, a 2-hour 75-gram oral glucose tolerance test, and a biochemistry panel. Data were linked with the Israeli National Diabetes Registry, where incident T2D was defined as an outcome. Cox proportional hazard models were applied.
Results
The study included 1,611,467 individuals (42.5% women), of whom 755 (0.05%) were diagnosed with glucosuria during adolescence. Adolescents with versus without glucosuria were predominantly male (75.0% vs. 57.5%; $P<0.001$) and had lower rates of overweight and obesity (10.4% vs. 16.3%; $P<0.001$). During a cumulative follow-up of 23,848,350 person-years, 10,328 T2D cases were recorded, with a mean age at the end of follow-up of 32.6 years (SD 6.8). Ten (1.3%) and 10,318 (0.6%) T2D cases were observed among those with and without glucosuria, respectively, with incidence rates per 100,000 person-years of 87.5 and 43.3. No significant differences in mean BMI ($P=0.11$) or eGFR ($P=0.67$) at T2D diagnosis were observed between groups. Individuals with isolated glucosuria had an HR of 2.17 (95% CI, 1.17–4.04) following adjustment for sex, BMI, age, year of study entry, and sociodemographic confounders. The association was accentuated in individuals with lean BMI (i.e. BMI<85th percentile) at baseline and in those without coexisting illness at baseline. Results were consistent in sub-analyses limited to T2D before age 40, stricter outcome definition, and logistic regression [adjusted OR of 2.33 (95% CI, 1.26–4.27).
Conclusions
Isolated glucosuria during adolescence is associated with an increased risk of early-onset T2D, particularly in populations with lean BMI and unimpaired health at baseline. This suggests caution in viewing isolated glucosuria strictly as a benign condition.

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Rapid Communications 3: Metabolism and Aging

RC3.1

JOINT809

Genotype-histotype-phenotype correlations in atypical congenital hyperinsulinism

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Background
Hyperinsulinaemic hypoglycaemia (HH) is a heterogeneous disease entity characterized by failure to suppress insulin secretion from the pancreatic beta cells during hypoglycaemia. Persistent non-syndromal CHI can be caused due to inherited mutations in a number of known genes. But in 40 – 50% of affected patients the genetic basis is unexplained. The two main histologically forms are diffuse and focal CHI. The diffuse form is an apparently normally structured islet. The focal form is characterized by the presence of a small endocrine lesion in the pancreas. The histology in some patients differ from these main forms. This form is referred to as CHI with atypical histology. We present molecular characterization of variants in this latter group. Atypical congenital hyperinsulinism (CHI) is characterized by distinct pancreatic histology that differs from classical KATP-channel diffuse or focal CHI and Beckwith-Wiedemann Syndrome (BWS). Its genetic basis remains largely unclear.
Aim
To explore genotype-histotype-phenotype correlations in atypical CHI within a single-center cohort.
Methods
Genetic analysis involved sequencing CHI-related genes in blood and pancreatic tissue, with BWS testing when appropriate. For negative cases, a targeted 140-gene panel, including the non-coding *HK1* region, was performed on blood, pancreatic tissue, and laser-microdissected (LCM) islets. Pancreatic tissue was evaluated through histological, immunohistochemical, and morphometric studies.
Results
Atypical CHI was observed in 5/70 (7.1%) surgically treated patients. Median birth weight was 2965 g (range: 2650–3385 g), with disease onset at a median of 93 days (range: 1–259 days). 18F-DOPA PET/CT showed diffuse labeling in all cases. Genetic findings revealed low-grade mosaic *HK1* intron 2 mutations in three patients: de novo germline, somatic mosaic in the whole pancreas, or isolated islets. One patient had a *CACNA1D* frameshift mutation of uncertain significance, while no abnormalities were identified in another. Histological analysis revealed lobule-specific enlarged islets with increased insulin-producing cell volume, interspersed with diffusely distributed shrunken islets. Nuclear enlargement was observed in isolated islets from one patient.
Conclusion
This is the first study to describe how low grade de novo variants in the beta-cell of the pancreatic islet can explain the atypical form of Hyperinsulinaemic hypoglycaemia. Rare atypical CHI cases display unique histological patterns restricted to specific lobules and are frequently associated with *HK1* intron 2 mosaic variants. Detection of low-grade mosaicism may necessitate laser-microdissected islet analysis.

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RC3.2

JOINT734

An ongoing phase 2 study of efpegerglucagon: promising results on safety and efficacy in subjects with congenital hyperinsulinism

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Introduction
Congenital hyperinsulinism (CHI) is a rare disease affecting 1 in 25,000 to 50,000 newborns, characterized by severe hypoglycemia that can lead to neurological damage or death. Current treatments, which include dietary management, medications, and surgical interventions, are often limited by suboptimal efficacy and significant side effects, highlighting the urgent need for novel therapeutic approaches.
Methods
Efpegerglucagon (HM15136), a long-acting glucagon analogue, is being evaluated in a Phase 2 open-label, multicenter trial across five countries (ACHIEVE, NCT No. 04732416, EUCT No. 2024-515290-98-00). The study targets CHI patients aged two years and older with recurrent hypoglycemia (>3 episodes/week) despite standard care. The trial includes two dosing cohorts: Cohort 1 (0.04 mg/kg) and Cohort 2 (0.06 mg/kg). Each cohort consists of 8 subjects receiving weekly subcutaneous injections over an 8-week period. Enrollment for Cohort 1 ($n=8$, median age: 16 years, equal male-to-female ratio) has been completed, and Cohort 2 is currently ongoing.
Results
The most frequent adverse events were gastrointestinal (e.g., upper abdominal pain, diarrhea, vomiting, nausea) and metabolic(e.g., hyperglycemia, decreased appetite) in nature. These events were predominantly mild or moderate, with no treatment discontinuation, adverse events of special interest, or deaths reported. Efficacy analysis based on the data from eight patients in Cohort 1 showed significant reductions in level 1 or level 2 hypoglycemia events (blood glucose< 70 mg/dl [<3.9 mmol/l]). After 8 weeks of treatment, the mean weekly level 1 or level 2 hypoglycemia events measured by 7-point self-monitored blood glucose (SMBG) decreased from 10.1 ($\pm$8.5, standard deviation) at baseline to 2.8 ($\pm$ 2.3), representing a 72.3% reduction. Home monitoring SMBG data also reflected a significant decline in weekly level 1 or level 2 hypoglycemia events decreasing from 16.0 ($\pm$19.4) at baseline to 3.6 ($\pm$6.5) at Week 8, indicating a 77.5% reduction. Notable improvements were demonstrated, including reductions in the weekly number and rate of level 2 hypoglycemia events (blood glucose<54 mg/dl [<3.0 mmol/l]) at Week 8, as measured by 7-point SMBG, and improvements in nutritional parameters such as total carbohydrate intake during treatment compared to baseline.
Conclusion
Efpegerglucagon demonstrated a favorable safety profile and clinically meaningful efficacy. After eight weeks of treatment, CHI patients experienced significant reductions in hypoglycemia events. These findings emphasize its therapeutic potential as a safe and effective treatment for CHI and support the continued enrollment of Cohort 2.

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RC3.3

JOINT157

Modulation of SIRT1-related microRNAs in differentiating adipocytes and their relationship with inflammation

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Background
Chronic low-grade inflammation in adipose tissue is closely linked to metabolic diseases and organ complications in overweight and obese individuals. Dysfunctional adipocytes that release inflammatory adipokines are responsible for initiating and maintaining this inflammation. Although it is a low-grade inflammation, it adversely affects distant organs and contributes to obesity-related complications. Sirtuin 1 (SIRT1), a crucial nutrient-sensing histone deacetylase, is enhanced by caloric restriction and attenuated by overfeeding. When SIRT1 levels drop, inflammatory factors are produced in white adipose tissue, suggesting that reduced SIRT1 connects overnutrition with adipose tissue inflammation.
Aim
This study aimed to identify microRNAs that negatively regulate SIRT1 expression and are upregulated in differentiated and hypertrophied adipocytes and explore their relationship with inflammatory parameters.
Methods
A bioinformatics study was conducted to discover microRNAs conserved among mammals, targeting the 5'-UTR of SIRT1. 3T3-L1 cells were cultured in DMEM medium containing 10% FBS and differentiated into mature and hypertrophied adipocytes using MDI induction medium (comprising 1-methyl-3-isobutyl-xanthine, dexamethasone, and insulin). The differentiation cycle continued for 14 days in a culture medium containing 10% FBS. The expression of selected miRNAs was evaluated by real-time PCR. The microRNA with the highest expression was selected for subsequent experiments. Transfection of 3T3-L1 cells was performed using polyethyleneimine (PEI) and confirmed by fluorescence microscopy. Real-time PCR and Western blotting analyzed SIRT1 gene and protein expression levels, respectively. Luciferase reporter gene assay assessed the direct interaction between microRNA and SIRT1. The gene expression of inflammatory cytokines was measured by real-time PCR.
Results
Bioinformatics analysis identified mmu-miR-448, mmu-miR-181-5p, mmu-miR-186-5p, mmu-miR-653-5p, and mmu-miR-199-5p aligning with the 5'-UTR of SIRT1. Among these, miR-186 had the highest expression in differentiated and hypertrophied adipocytes. Upregulation of miR-186 by its mimic oligonucleotide led to decreased SIRT1 levels, while inhibition by miR-186 anti-sense sequence increased SIRT1 expression. miR-186 caused a significant elevation in the expression of inflammatory genes, including IL-6, IL-1β, TNF-α, and MCP-1, indicating a strong relationship between miR-186-induced SIRT1 inhibition and inflammation.
Conclusion
Differentiation and hypertrophy of adipocytes are accompanied by changes in microRNA expression, affecting various biological outcomes. Notably, inhibition of SIRT1 by microRNAs such as miR-186 may contribute to the increased inflammation observed in obesity. These findings suggest that overcoming the negative regulation of SIRT1 by miR-186 could be a promising strategy to alleviate obesity-associated inflammation.

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JOINT2396

Sensitivity to thyroid hormones and glomerular hyperfiltration in children and adolescents with overweight or obesity

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Background
Glomerular hyperfiltration (GHF) is an early manifestation of obesity-related glomerulopathy, with an estimated prevalence of 7 to 31% in childhood. GHF in obesity has been hypothesized to be a physiological adaptation mechanism to the changes the organism undergoes, including increased absolute mass of adipose tissue and body mass, increased cardiac output, increased glomerular pressure. A reduction in GFR has been correlated with a modification in sensitivity to thyroid hormones (THs), particularly a reduction in central sensitivity to THs, both in adults and youths with obesity. However, no data are available regarding the possible correlation between GHF and sensitivity to THs.
Objective
The aim of this study is to evaluate the association between sensitivity to TH and GHF in euthyroid non-diabetic youths with overweight (OW) and obesity (OB).
Material and methods
This cross-sectional study included 654 Caucasian youths with OW or OB (aged 6-18 years) recruited at seven Italian centers for the care of OW/OB. Inclusion criteria were: THs within the normal range in each center, anti-thyroid antibody negativity. Exclusion criteria were: diabetes mellitus, thyroid diseases, renal disease, subclinical hypothyroidism, genetic or endocrine obesity, chronic diseases, pharmacological treatment. Estimated glomerular filtration rate (eGFR) was calculated using Pottel's formula. Youths with reduced eGFR ($<$ 90 ml/min/1.73 m^2) were excluded. GHF was defined by eGFR $>$ 120 ml/min/1.73 m^2. Pulse pressure (PP) was calculated as: systolic blood pressure (BP) minus diastolic BP. The fT3/fT4 ratio was evaluated to assess peripheral sensitivity, while TSH index (TSHI), Thyrotroph T4 Resistance Index (TT4RI), Thyroid Feedback Quantile-based Index (TFQI) and Parametric TFQI (PTFQI) were calculated to assess central sensitivity.
Results
Youth with GHF ($n=203$) had significantly higher values of peripheral sensitivity to THs (FT3/FT4 ratio 0.46 ± 0.11 vs 0.44 ± 0.09 vs; $P=0.004$), fasting glucose (89.2 ± 9.0 mg/dl vs 85.5 ± 9.6 vs; P0.0001) and PP (47.5 ± 11.8 vs 45.4 ± 12.8 vs mmHg; $P=0.047$) compared to youths with normal eGFR. No significant differences were observed for indices of THs central sensitivity. Odds ratio of hyperfiltration rose of 1.04– and 13.16–fold for each increase of 1 mg/dl of fasting glucose ($P<0.0001$) and 1 mIU/l in FT3/FT4 ratio ($P=0.004$), respectively, independently of centers, PTFQI and PP.
Conclusions
GHF was associated with an increased peripheral sensitivity to THs in youths with OW/OB. GHF could be an allostatic adaptation mechanism in obesity and may represent early expression of obesity-related glomerulopathy. Further studies are needed to confirm these results.

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RC3.5

JOINT192

Delivery mode is associated with persistent changes of steroid hormone levels in boys at three months of age - a COPANA study of 508 healthy infants

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Table 1. Levels of steroid hormones at three months of age in boys ($n=243$) according to delivery mode

Hormone SDS	ECS ($n=26$)	VD ($n=207$)	ELCS ($n=10$)	KW *P*-value	Pairwise MWU *P*-value		
	Median (IQR)	Median (IQR)	Median (IQR)		ECS/VD	VD/ELCS	ECS/ELCS
CORT	-0.64 (-1.87-1.64)	0.22 (-2.74-1.96)	0.68 (1.73-1.29)	**0.034**	0.026	0.239	**0.023**
17-OHPreg	-0.49 (-1.92-1.03)	-0.07 (-3.43-3.57)	0.56 (-1.70-2.19)	**0.015**	0.034	0.068	**0.006**
17-OHP	-0.38 (-1.77-1.01)	0.24 (-3.30-2.27)	0.55 (-0.88-1.53)	**0.006**	0.005	0.190	**0.007**
11-DOC	-0.46 (-1.99–1.29)	0.17 (-2.93-2.71)	0.58 (-1.19-1.23)	**0.026**	0.013	0.376	**0.031**
Cortisol	-0.38 (-1.71–1.79)	0.34 (-2.48-2.46)	0.81 (-0.67-1.60)	**0.008**	0.019	0.058	**0.003**

Background

Epidemiological studies suggest that delivery mode is associated with numerous long-term conditions, including atopy and asthma, potentially associated with altered levels of cortisol. Emergency caesarean section is associated with increased levels of cortisol in the umbilical cord, and animal studies suggests that perinatal stress cause persistent changes in hypothalamic-pituitary-adrenal (HPA) axis activity. However, human data on the long-term impact of delivery mode on steroid hormone profiles during infancy remain limited.

Objectives

To evaluate the association between delivery mode and circulating levels of steroid hormone metabolites in healthy infants at three months of age.

Design

Prospective, observational pregnancy and birth cohort; The Copenhagen Analgesic Study (COPANA) (ClinicalTrials.gov NCT04369222).

Setting

Copenhagen University Hospital – Rigshospitalet, Denmark (2020-2022).

Methods

Healthy, singleton pregnant women recruited early in pregnancy ($n=685$) and 589 infants (287 boys) were examined (age 3.31 months (0.67) mean ($\pm$SD)). Infants with available hormone values and information on delivery mode ($n=508$) were included and stratified according to delivery mode: 1) emergency caesarean section (ECS), $n=50$ (26 males), 2) vaginal delivery (VD), $n=437$ (207 males), 3) elective caesarean section (ELCS), $n=21$ (10 males). Steroid hormones: progesterone (PRO), 11-deoxycorticosterone (DOC), corticosterone (CORT), aldosterone (ALDO), 17alfa-hydroxypregnenolone (17-OHPreg), 17-hyroxyprogesterone (17-OHP), 11-deoxycortisol (11-DOC), cortisol, cortisone, dehydroepiandrosterone (DHEA), androstenedione (Adion), testosterone (T) and dihydrotestosterone (DHT) were analyzed (LC/MS-MS), and age-related standard deviation scores (SDS) were calculated. Statistics: Kruskal-Wallis (KW) and Mann-Whitney U (MWU) tests.

Results

In boys, ECS was associated with consistently lower levels of: CORT, 17-OHPreg, 17-OHP, 11-DOC and cortisol compared to both VD and ELSC at three months of age (Table 1). Delivery mode was not associated with steroid hormone levels in girls.

Conclusions

The present study suggests that delivery mode has long-term impact on HPA axis activity. Whether effects on steroid hormone levels contribute to adverse long-term health outcomes associated with delivery mode remains to be examined.

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JOINT3352

Efficacy and safety results from a pivotal phase 3 trial of DTX401, an AAV8-mediated liver-directed gene therapy, in individuals with glycogen storage disease type Ia (GSDIa)

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Background

GSDIa is a rare, potentially life-threatening inborn error of carbohydrate metabolism caused by biallelic *G6PC* pathogenic variants, resulting in glucose-6-phosphatase deficiency. DTX401 is an investigational adeno-associated virus serotype 8 vector containing the human *G6PC* gene.

Methods

DTX401-CL301 (GlucoGene Study; ClinicalTrials.gov: NCT05139316), is an ongoing, pivotal, phase 3, double-blind, randomized, placebo-controlled trial in patients $\geq$8 years old with GSDIa. Participants were randomly assigned (1:1) to receive blinded DTX401 or placebo. At Week 48, participants entered a 48-week Crossover Period when, in a blinded manner, those randomized to DTX401 received placebo and placebo received DTX401. The primary endpoint was change from Baseline to Week 48 in daily cornstarch intake, DTX401 versus placebo.

Results

The study met the primary endpoint: at Week 48, the Primary Efficacy Analysis Period (PEAP), DTX401 treatment resulted in a mean (standard deviation [SD]) daily cornstarch intake reduction of 41.0% (18.4) versus a 10.1% (18.0) reduction with placebo; P <0.0001 based on mixed model of repeated measures. In the Crossover Period, greater reductions in total daily cornstarch were observed in both the ongoing DTX401 group and the Crossover Placebo to DTX401 group (Table). Glycemic control was maintained in participants treated with DTX401 despite significant reductions in daily cornstarch intake. Patient experience data support cornstarch reduction clinical meaningfulness, with Week 48 Patient Global Impression of Change Moderately or Much Improved corresponding to a 34% mean reduction in daily cornstarch intake. Anticipated vector-induced liver enzyme elevations were manageable with prophylactic corticosteroids. Elevations in triglycerides were observed in individual participants, requiring adjustments of cornstarch and dietary intake.

Conclusion

Treatment with DTX401 resulted in statistically significant and clinically meaningful reductions in cornstarch intake in the 48-week PEAP versus placebo. Greater reductions in cornstarch were observed in both groups in the Crossover Period after Week 48. Experience with disease management post-gene therapy and confidence that all participants had been treated with DTX401 likely contributed to improvements in the Crossover Period (Year 2) versus the PEAP (Year 1). DTX401 had an acceptable safety profile.

Mean (SD)	Week 96 *n*	DTX401	*n*	Crossover Placebo to DTX401*
Daily cornstarch, % change from baseline	13	-60.9 (18.9)	13	-64.7 (24.9)
Nighttime cornstarch, % change from baseline	12	-66.1 (33.5)	10	-74.2 (26.5)
Percent glucose values <70 mg/dl, change from baseline	17	3.78 (4.96)	16	2.33 (3.23)
Percent glucose values <54 mg/dl, change from baseline	17	0.85 (0.88)	16	0.27 (0.47)

*Data at 48 weeks after DTX401 treatment

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Rapid Communications 4: Pituitary, Neuroendocrinology and Puberty Part 1

RC4.1

JOINT313

Targeted correction of plasma sodium in hospitalized patients with chronic hyponatremia

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Background

Chronic hyponatremia is associated with increased mortality and rehospitalization rates, but it remains unclear whether this relationship is causal. The aim of this study was to evaluate the effects of targeted hyponatremia correction versus routine care on mortality and rehospitalization rates.

Methods

Pragmatic, randomized controlled, parallel-group, international multicenter trial with blinded outcome assessment. Hospitalized participants with plasma sodium <130 mmol/l from nine European centers were assigned to undergo either targeted correction of hyponatremia according to guidelines (intervention) or routine care for hyponatremia (control). The primary outcome was the combined risk of death or rehospitalization within 30 days of study inclusion.

Results

2173 patients were included in the primary analysis of whom 1079 (49.7%) were randomized to the intervention and 1094 (50.3%) to the control group. Normonatremia was reached in 641 (60.4%) patients in the intervention group compared to 492 (46.2%) patients in the control group. Within 30 days after inclusion, the primary outcome occurred in 20.5% (218/1065 patients) in the intervention group and 21.8% (234/1073 patients) in the control group (estimated absolute difference in proportions [95% CI] -1.3% [-4.9, 2.2], $P=0.45$). Death occurred in 86 (8.0%) and rehospitalization in 141 (13.2%) patients in the intervention group compared to 88 (8.0%) and 151 (14.1%) patients in the control group. These findings were consistent in the per-protocol analysis and no evidence of effect modification was found for hyponatremia etiology and severity.

Conclusion

In hospitalized patients with chronic hyponatremia, targeted correction of plasma sodium did not reduce 30-day mortality and rehospitalization rates.

Trial registration

ClinicalTrials.gov (NCT03557957)

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RC4.2

JOINT591

Melatonin as a possible stimulus to unmask an oxytocin deficient state in hypopituitarism and hypothalamic damage

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Introduction

Emerging evidence supports the presence of oxytocin deficiency (OXT-D) in patients with hypopituitarism and hypothalamic damage (HHD). However, the lack of reliable diagnostic tests for OXT-D remains a critical gap. Melatonin might be a candidate for such a test as melatonin receptors are located in the hypothalamus where OXT is synthesized, and melatonin regulates OXT release in animals. This study aimed to examine plasma OXT dynamics in response to oral melatonin in patients with HHD compared to healthy controls (HC) and explore its associations with psychopathology, sexual function, and quality of life (QoL).

Methods

This proof-of-concept study (NCT05319301) included 20 participants with HHD (11 females) and 20 HC (11 females). Melatonin (1.95 mg) was administered sublingually between 8-9 am. Blood samples were collected over 120 minutes. Additionally, participants were asked to complete questionnaires to assess psychopathology, sexual function and QoL. Linear mixed-effects regression model controlled for body mass index (BMI) was used to evaluate the change in OXT over time in HHD compared to HC.

Results

Both groups were comparable in age and gender distribution. The median BMI was higher in the HHD compared to the HC group (30.20 (3.79) vs. 22.91 (7.34) kg/m^2, $P=0.02$). Baseline OXT levels were similar across groups (HHD 56.75 ± 4.13 vs. HC 57.05 ± 3.99 pg/ml, $P=0.86$). In HC, melatonin significantly increased OXT at T90 vs. T0, whereas no such increase was observed in the HHD group (68.95 ± 4.37 vs. 54.07 ± 4.37 pg/ml, respectively; difference 14.57 pg/ml 26% increase, 95%IC 1.90 to 27.23, $P=0.02$); however, with high interindividual variability. Similar results were found in the subgroup of patients with HHD and arginine vasopressin deficiency (AVP-D) ($n=17$), with HC showing a greater OXT increase at T90 (HC 68.95 ± 4.37 vs. AVP-D 55.52 ± 6.85 pg/ml; difference 13.30 pg/ml, 95%CI 0.95 to 25.65, $P=0.03$). HHD group had more depression and alexithymia symptoms, impaired sexual function and worse QoL in comparison with HC. The mean percentage change in OXT from T0 to T90 was negatively associated with depressive and alexithymia symptoms in HHD and anxiety in both groups.

Conclusion

The reduced OXT response to melatonin in HHD, supports the existence of an impaired OXT response in a subset of patients with HHD. The associations between OXT changes and psychopathology suggest its role in mood and QoL. These findings provide support for a clinically significant OXT-deficient state in HHD. Future studies could examine different doses of melatonin as a diagnostic tool to address OXT-D.

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RC4.3

JOINT2654

Clofutriben inhibits 11ß-hydroxysteroid dehydrogenase type 1 and improves ACTH-dependent cushing's syndrome compared with placebo in a phase II trial (RESCUE)

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Introduction
Tissue-specific 11β-hydroxysteroid dehydrogenase type 1 (HSD-1) reactivates glucocorticoids increasing binding to intracellular receptors. HSD-1 deficiency suppresses Cushing syndrome (CS) phenotype despite hypercortisolism.[1-3] Treatment with clofutriben (C), a potent and specific inhibitor of HSD-1, might improve CS comorbidities by decreasing intracellular cortisol.
Methods
Seventeen adults with ACTH-dependent CS (16 pituitary, 1 ectopic), and type 2 diabetes (T2D), impaired glucose tolerance (IGT), hypertension (HTN), hyperlipidemia, or osteopenia were randomized to a total of 12 weeks of oral C 6mg/d and 12 weeks of matching placebo (P) in 2 blinded sequences (PCCP, CCPP; "P" or "C" representing 6-week periods). Patients were offered open-label C treatment on completion. Primary endpoint was urinary ratio of cortisol and cortisone metabolites at Week 6 (hepatocellular HSD-1 activity biomarker). Key exploratory endpoints (and applicable population) at Week 6 were HbA1c (T2D), systolic blood pressure (>120 mmHg), LDL cholesterol (>100 mg/dl), osteocalcin (<7.5 mg/l), and normalization of elevated (>1.5×ULN) urinary free cortisol.
Results
Mean baseline HSD-1 ratio was 1.95±0.171. At Week 6, mean ratio was 0.21±0.091 with C and 2.01±0.263 with P. HbA1c decreased by 0.6% for C and 0.2% for P. Systolic blood pressure in C and P decreased by 8 and 3 mmHg. LDL in C decreased by 25 mg/dl but increased in P by 29 mg/dl. Osteocalcin increased by 6 mg/l for C and by 0.1 mg/l for P. Urinary free cortisol normalized with C in 3 of 8 patients, but in none of 6 patients with P. Concomitant medications for T2D were reduced in 4 C-treated, but increased in 2 P-treated patients. For HTN there were also 4 reductions for C-treated and 1 increase for P-treated patients. One patient succumbed to ectopic Cushing's due to cervical carcinoma after trial discontinuation. Four patients discontinued for non-adverse event (AE) reasons. One serious AE of vomiting (possible glucocorticoid withdrawal syndrome per investigator) led to temporary drug interruption. Common AEs (≥ 3 patients) included Arthralgia, Fatigue, Headache, and Nausea, but only Headache was more common in C during the P-controlled period. There was no evidence of adrenal insufficiency, clinically or biochemically (low cortisol). All 13 patients completers elected to enter the open-label extension (current treatment duration 3-15 months).
Conclusions
Clofutriben decreased hepatic HSD-1 activity adequately to confer clinical benefit while maintaining safety and overall tolerability. These limited data support clofutriben's potential for clinical improvement without adrenal insufficiency.
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RC4.4

JOINT1743

Results from the core phase of the open-label, phase 3 ACROINNOVA 2 trial: CAM2029, a subcutaneous octreotide depot, achieves sustained, long-term biochemical control in acromegaly

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Background
Effective biochemical control of excess insulin-like growth factor-I (IGF-I) and growth hormone (GH) is essential to alleviate symptoms and associated conditions of acromegaly. CAM2029, an octreotide subcutaneous depot designed with FluidCrystal® technology to be long-acting, is conveniently self-administered using an autoinjector pen. In ACROINNOVA 1, a 24-week, Phase 3 trial (NCT04076462), CAM2029 demonstrated superior biochemical control versus placebo (72.2% vs 37.5%; $P=0.0018$) in patients previously controlled (IGF-I ≤ upper limit of normal [ULN]) on standard-of-care somatostatin receptor ligands (SoC; octreotide long-acting repeatable/lanreotide Autogel). ACROINNOVA 2 (NCT04125836), a 52-week, open-label, Phase 3 trial (plus 52-week extension), assessed long-term safety and efficacy.
Methods
ACROINNOVA 2 included patients from ACROINNOVA 1 (prior-placebo and prior CAM2029 groups) and directly-enrolled patients with IGF-I ≤2×ULN (on SoC for ≥3 months). Patients received CAM2029 20 mg every 4 weeks (±1 week) for 52 weeks (prior-placebo: week [W] 24–52). The primary endpoint characterised safety; secondary endpoints included the proportion of patients with IGF-I ≤ULN (W50/52 mean) and both IGF-I ≤ULN (W50/52 mean) and GH < 2.5 µg/l (W52 mean).
Results
In total, 135 patients were enrolled: 54 completing ACROINNOVA 1 (prior-placebo, $n=18$; prior-CAM2029, $n=36$) and 81 directly-enrolled. Overall, 127 patients (94.1%) completed treatment (prior-placebo, $n=18$; prior-CAM2029, $n=35$; directly-enrolled, $n=74$). CAM2029 was well tolerated; no new safety signals were identified. The most common adverse events (AEs) were injection-site erythema and injection-site swelling, occurring in 27.4% (37/135) and 14.8% (20/135) of patients, respectively. All injection-site AEs were mild-to-moderate (Grade 1–2); new injection-site AEs decreased throughout the study. AEs leading to treatment discontinuation occurred in 1.5% (2/135) of patients. The proportion of patients with biochemical control are presented in the Table.
Conclusions
CAM2029 treatment resulted in biochemical control being regained in prior-placebo and sustained in prior-CAM2029 patients. Biochemical control was notably improved in directly-enrolled patients previously uncontrolled on SoC. These long-term findings support CAM2029 as an effective new treatment for acromegaly with a safety profile consistent with SoC.

Table Proportion of patients with biochemical control

Endpoint(s)	Timepoint	Prior-placebo	Prior-CAM2029 n/NaII* (%)	Directly-enrolled
	SoC baseline	17/18 (94.4)	33/36 (91.7)	12/81 (14.8)
IGF-I ≤ULN	Placebo baseline†	5/18 (27.8)	–	–
	W50/52 mean	17/18 (94.4)	31/35 (88.6)	27/74 (36.5)
	SoC baseline	17/18 (94.4)	33/36 (91.7)	12/81 (14.8)
IGF-I ≤ULN and GH <2.5 µg/l	Placebo baseline†	5/18 (27.8)	–	–
	IGF-I: W50/52 mean			
	GH: W52 mean	16/17 (94.1)	29/33 (87.9)	23/74 (31.1)

*Patients with available data at timepoint; †IGF-I: W22/24, GH: W24.

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RC4.5

JOINT356

Efficacy and safety of once-weekly somatrogon in adults with growth hormone deficiency: a phase 3 study

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Objective
To evaluate the efficacy and safety of once-weekly somatrogon, a long-acting recombinant human growth hormone, in adults with growth hormone deficiency (GHD) (NCT01909479). Somatrogon has been approved in many countries for treatment of pediatric GHD.
Methods
This randomized, double-blind, placebo-controlled Phase 3 study enrolled adults with GHD across 52 sites in multiple countries. The study included a 26-week double-blind period (Period 1), a 26-week open-label extension (OLE; Period 2) (Main Study = Periods 1 and 2, lasting up to 60 weeks, including a 2–8-week washout period), and a multi-year long-term OLE (Period 3) to evaluate long-term safety. In Period 1, patients were randomized 2:1 to somatrogon or placebo, with dosing based on gender, age, and estrogen therapy. During Periods 2 and 3, all patients received somatrogon. The primary endpoint was change (baseline–Week 26) in trunk fat mass (FM). Secondary endpoints included changes (baseline–Weeks 26 and 52) in total FM, lean body mass (LBM), percentage change in trunk FM, and trunk FM (baseline–Week 52 only). A post-hoc supplemental efficacy analysis evaluated changes (baseline–Week 26) in percent trunk FM relative to the total trunk mass (FM + LBM), trunk LBM, and appendicular skeletal muscle mass. Safety assessments included adverse events (AEs), vital signs, and laboratory evaluations.
Results
In Period 1, 389 patients were screened, 202 randomized and 198 received treatment (somatrogon:133; placebo:65). Change in trunk FM from baseline to Week 26 (primary endpoint) was not significantly different between somatrogon vs placebo (-0.37 vs 0.03 kg; $P = 0.0821$). Change in LBM from baseline to Week 26 was significantly higher in somatrogon vs placebo (1.35 vs 0.02 kg; $P < 0.0001$). The somatrogon group showed significant improvements in percentage change in trunk FM (baseline-Week 26) and the 3 supplemental endpoints (baseline-Week 26). Mean IGF-1 SDS at baseline was $\leq$-2.6 in both groups; IGF-1 SDS normalized following initiation of somatrogon in either Period 1 or 2. The incidence of all-causality AEs was similar between patients originally randomized to somatrogon vs placebo (Period 1: 63.9% vs 69.2%; Period 2: 56.4% vs 60.0%; Period 3: 64.9% vs 60.0%); most AEs were mild to moderate in severity. The most frequently reported AEs (somatrogon vs placebo) were injection site pain (9.0% vs 13.8%) in Period 1, and nasopharyngitis in Periods 2 (7.5% vs 6.2%) and 3 (11.7% vs 10.0%).
Conclusions
Once-weekly somatrogon treatment significantly improved most body composition parameters and was well tolerated in adults with GHD.

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RC4.6

JOINT1879

Comparison of long-acting and short-acting GLP-1 receptor agonists on copeptin in euvolemic participants - a secondary analysis of three prospective trials

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Introduction
Glucagon-like peptide-1 (GLP-1) plays an important role in regulating sodium and water balance. Long-acting GLP-1 receptor agonist (RA) treatment reduces fluid intake, diuresis, and copeptin levels, a surrogate marker for vasopressin. In contrast, short-acting GLP-1 RA induces natriuresis, but their effects on copeptin remain unknown. The aim of this analysis was to compare the effects of long-acting and short-acting GLP-1 RA on copeptin levels.
Methods
This analysis combined data from three prospective trials conducted at the University Hospital Basel, Switzerland. The primary objective was to compare the effect of a three-week treatment with dulaglutide (GOLD & GATE trials) to a single dose of exenatide (FAST trial) on plasma copeptin release in euvolemic adults. In the GOLD & GATE trials, 34 and 20 participants were randomly assigned, respectively, to first receive a three-week treatment with either dulaglutide (1.5 mg) or placebo (0,9% sodium chloride) subcutaneously once a week. After a wash-out period of at least three weeks, participants received the opposite intervention. In the FAST trial, 10 participants received a single dose of Exenatide (10ug) intravenously.
Results
In total, 64 participants in the three trials were included. The median age was 27 (IQR, 24 to 37) years in the GOLD & GATE cohorts, whereas participants in the FAST cohort were modestly older with 38 [33 to 41] years. The body mass index (BMI) was 23 (IQR 20.8-24.8) in the GOLD & GATE cohorts, compared to 27(IQR 24.8-30.4) in the FAST cohort. Participants in the FAST cohort were predominantly male (72%), whereas gender distribution was more balanced in the GOLD & GATE cohorts.Long-term treatment with dulaglutide resulted in a significant suppression of copeptin in both GOLD & GATE trials ($P = 0.04$) compared to placebo [GATE: treatment effect: -1.4 pmol/l and GOLD: treatment effect: -0.4 pmol/l]. In contrast, short-term treatment with exenatide in the FAST trial resulted in an increase of copeptin ($P = 0.06$) compared to baseline [FAST: treatment effect: + 0.34 pmol/l]
Conclusion
Long- and short-acting GLP-1 RA differ in their effects on copeptin regulation. Long-acting GLP-1 agonists significantly suppress copeptin, likely through a synergistic mechanism, while short-acting GLP-1 RAs appear to stimulate copeptin release. These differing effects may also extend to other GLP-1-related mechanisms with potential high clinical relevance.

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Rapid Communications 5: Reproductive and Developmental Endocrinology Part 1

RC5.1

JOINT1612

Excess adrenal androgen secretion is a consequence of in utero androgen excess in an ovine model of PCOS

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Background
Exogenous androgenic steroid applied to pregnant sheep, or directly to developing sheep fetuses, programmes a PCOS-like metabolic phenotype in female offspring. We hypothesised that such androgen excess during development would alter postnatal adrenal steroidogenic capacity.
Methods
Using both indirect androgenic overexposure (Prenatal androgen excess; PA) (maternal testosterone propionate treatment (100 mg twice weekly) from day (d) 62 to d102 of gestation; maternal injection – M-PA) and direct fetal androgen treatment (from d62, F-PA), we examined postnatal female adrenal gland function. A subset of animals directly treated during fetal life with estrogen receptor agonist DES (F-DES), or synthetic glucocorticoid dexamethasone (F-DEX) were studied to examine specificity of androgenic effects observed. Adrenal function testing, and qPCR measurement of adrenal steroidogenic genes were the outcome measurements.
Results
During fetal life, in terms of a panel of steroidogenic and related genes examined in the adrenal cortex, we observed some sexual dimorphism, but there was no evidence of prenatal androgen excess causing masculinisation of the developing female adrenal. Prior to puberty, (11 weeks postnatal age), we observed no functional alterations in terms of either cortisol or testosterone secretion in response to synthetic (Synacthen) ACTH stimulation. However, in post-pubertal female offspring (11 months old) from both M-PA and F-PA models, we observed increased expression of *StAR*, *HSD3B1* and *HSD17B* mRNA in animals exposed to excess androgens during fetal life ($P < 0.05 – 0.001$ compared to vehicle treatment). These post-pubertal adrenal gene expression changes were

accompanied by a markedly exaggerated testosterone secretory response to ACTH stimulation in M-PA and F-PA animals as compared to vehicle controls ($P < 0.05$), in the absence of any alterations in cortisol secretion. This effect was specific to prenatal androgen excess alone.

Conclusion

We conclude that the postnatal, post pubertal adrenal gland develops a hyperandrogenic phenotype as a consequence of prenatal androgen excess. The adrenal cortex may be a secondary source of increased androgens found in PCOS due to excess androgen exposure during development.

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RC5.2

JOINT3757

Comparison of oxytocin and incretin dynamics in response to food intake in women with polycystic ovary syndrome and healthy controls

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Objective

The role of oxytocin and its potential relation with incretin hormones in regulation of food intake is not known in polycystic ovary syndrome (PCOS). This study aims to investigate the dynamics of oxytocin and incretins (GLP-1, GIP) in response to a mixed meal test (MMT) in women with PCOS compared to healthy controls and to examine their associations with appetite regulation, including hunger, satiety, and food craving behaviors.

Methods

Thirty-six women with PCOS (mean age: 21.6 ± 2.6y; mean BMI:25.5 ± 4.6 kg/m^2) and 36 age- and BMI-matched healthy controls were included. Each participant underwent a standardized MMT with blood samples collected at baseline and at 30, 60 and 120 minutes after meal ingestion to measure plasma concentrations of oxytocin, GLP-1, GIP, insulin, and glucose. All tests were performed during early follicular phase of the menstrual cycle. Appetite regulation was assessed using validated tools, including the Visual Analog Scale (VAS) to measure hunger and satiety levels during the test, and the "Food Craving Questionnaire" to evaluate the urge to overeat.

Results

Baseline oxytocin levels were significantly lower in the PCOS group compared to controls(1294 ± 92.5 pg/ml vs 1580 ± 83 pg/ml respectively; $P = 0.024$). Oxytocin levels showed a significant decrease within the first 30 minutes after food intake in the control group, whereas in the PCOS group this physiological decrease was absent and no significant change in oxytocin levels were detected throughout the test. Baseline GLP-1 and GIP levels were significantly lower in the PCOS group compared to controls ($P < 0.001$, $P = 0.022$ respectively) and remained consistently lower throughout the test. The AUC values for GLP-1 and GIP were also significantly reduced in the PCOS group, indicating impaired incretin responses ($P < 0.001$, $P = 0.033$ respectively). Significant correlations between oxytocin and GLP-1 levels were observed both at baseline and during the test in the entire cohort. In the control group, the 0–30 minute change in oxytocin correlated negatively with the hunger score ($r = -0.361$, $P = 0.031$) and positively with the satiety score ($r = 0.370$, $P = 0.027$). However, this pattern was not observed in the PCOS group. Notably, women with PCOS exhibited higher scores on the Food Craving Questionnaire, reflecting a greater propensity for food cravings ($P < 0.001$).

Conclusion

Women with PCOS show lower fasting oxytocin, GLP-1 and GIP levels and impaired response of these hormones to food intake. Altered dynamics of oxytocin, incretins and their interactions might play a role in regulation of appetite and weight in PCOS.

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RC5.3

JOINT3133

The kisspeptin/nNOS/GnRH (KiNG) neuronal network: regulating reproductive function through a dual activation-inhibition mechanism

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Gonadotropin-releasing hormone (GnRH) is the master regulator of the hypothalamic-pituitary-gonadal (HPG) axis, orchestrating reproductive function through its pulsatile and surge release patterns. While kisspeptin has been extensively studied as a primary excitatory input to GnRH neurons, the precise mechanisms regulating GnRH pulsatility remain debated. We have previously proposed a theoretical model of the Kisspeptin/nNOS/GnRH (KiNG) network as a critical regulatory circuit, in which neuronal nitric oxide (NO) acts as a dynamic modulator of GnRH secretion—opposing kisspeptin's excitatory drive and providing an essential "OFF" signal for pulse generation. This study aimed to experimentally validate the KiNG network, examining the interplay between kisspeptin, NO, and GnRH neurons in the preoptic hypothalamic area, in shaping the pulsatile and surge release of GnRH/lH. By employing a combination of neuroanatomical, genetic, chemogenetic, and pharmacological approaches, including a novel viral tool for highly sensitive NO/cGMP detection, we extensively assessed the functional role of NO signaling in GnRH pulse generation. Our study reveals the existence of a functional network formed between the nNOS-expressing neurons of organum vasculosum of the lamina terminalis (OV) and the median preoptic nucleus (MePO), and the kisspeptin and GnRH neurons. Kisspeptin directly stimulates GnRH neurons while simultaneously engaging nNOS neurons to induce NO release. NO, in turn, is necessary to fine-tune the kisspeptin response, shaping both the GnRH pulse and surge. Our findings reveal that NO production from nNOS neurons is not merely a modulatory factor but an essential component of the network, acting as a gatekeeper for the dynamic regulation of GnRH secretion in a cycle- and sex-dependent manner. This study provides experimental validation of the KiNG network as a fundamental mechanism governing GnRH/lH pulsatility. By acting as the Yin to kisspeptin's Yang, NO ensures the proper balance between excitation and inhibition, allowing for the precise control of reproductive hormone release. Understanding this interplay offers new perspectives on the neuroendocrine control of fertility and potential targets for reproductive disorders.

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RC5.4

JOINT1320

Kisspeptin-54 accurately identifies the cause of delayed puberty

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Background

Most young people with delayed puberty have self-limited delayed puberty (SLDP), but ~10% have congenital hypogonadotrophic hypogonadism (CHH). Differentiating between these two conditions is challenging, with the diagnosis typically made retrospectively, particularly in the absence of 'red flag' features of CHH e.g. anosmia. Kisspeptin stimulates hypothalamic GnRH neurons, and in turn LH release in healthy individuals, however patients with CHH have a minimal hormonal response to kisspeptin. Early evidence suggests that kisspeptin-10 could differentiate the cause of delayed puberty, however no data exists using kisspeptin-54, which could be advantageous. Kisspeptin-54 is reported to cross the blood brain barrier to access GnRH neuronal cell bodies, and a single bolus induces a greater LH rise than kisspeptin-10. We therefore investigated whether kisspeptin-54 could differentiate children with SLDP from those with CHH.

Methods

Fourteen young people with delayed puberty (12 boys and 2 girls) were categorised into three groups (Group 1: likely SLDP, Group 2: likely CHH, Group 3: indeterminate pending follow-up) according to pre-determined criteria including clinical history, auxology, and longitudinal Tanner staging. Participants received an intravenous bolus of kisspeptin-54 and GnRH on two separate occasions. Reproductive hormone levels were assessed every 15 min for 6 h (kisspeptin visit) , and for 2 h (GnRH visit). LH rises between the three groups were compared by Kruskal Wallis test with post-hoc Dunn's multiple comparisons. The LH rise between SLDP and CHH was compared by Mann Whitney U test.

Results
The mean age (±SD) of participants at time of assessment was 15.9±1.8 years. Five boys had likely diagnosis of SLDP, four young people (2 boys and 2 girls) had likely CHH, whilst the remaining five were indeterminate (Group 3). Kisspeptin-54 induced different maximal LH rises in the three groups (SLDP: 3.91±1.38, CHH: 1.29±0.91, Indeterminate 2.46±0.70 IU/l; *P*-value<0.0001). By contrast, the LH responses following GnRH were not significantly different between the groups (*P*-value=0.36). The LH-rise at two hours following administration of kisspeptin-54 fully differentiated participants with SLDP from those with CHH (area under ROC curve 1.0; *P*-value 0.0094). LH at both 30 and 60min post-GnRH had a poorer performance (auROC 0.58; *P*-value 0.72).Summary: Kisspeptin-54 demonstrates promise as a diagnostic test and performs better than GnRH, in young people with delayed puberty to help differentiate SLDP from CHH. Accurate and early identification of the cause of delayed puberty would remove uncertainty, aid in counselling, and could direct prompt appropriate management.

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RC5.5

JOINT2797

The predictive value of AMH and FSH concerning spontaneous vs induced puberty: a retrospective, longitudinal study of 50 girls with Turner Syndrome

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Background
Turner syndrome (TS) is characterized by early onset of premature ovarian insufficiency (POI). In prepubertal patients, predicting ovarian function is essential for counselling of puberty guidance and potential ovarian cryopreservation. During infant minipuberty, HPG axis activation allows ovarian function assessment, with FSH remaining elevated in 45,X patients until around age 6 yrs. AMH, produced by small antral follicles, is unaffected by central HPG axis inhibition, keeping circulating levels measurable in all healthy prepubertal girls. While low AMH and elevated FSH are established markers of POI in adolescence, their predictive value in childhood for ovarian function at pubertal onset remains unexplored.
Aim
To evaluate the predictive value of AMH and FSH for POI in TS.
Setting
Copenhagen University Hospital – Rigshospitalet (1995-2022).
Design
Single-center, retrospective, longitudinal study.
Method
Turner syndrome (TS) patients (ICD10 Q96–Q96.9) were categorized into a) spontaneous puberty (*n*=13) or b) induced puberty by hormone replacement therapy (HRT) due to POI (*n*=37). Karyotypes: 45X (*n*=20), 45X/46XX (*n*=16), miscellaneous (*n*=14). AMH and FSH levels were analyzed by immunoassays. We assessed the predictive value of low AMH (<3pmol/l) as well as elevated FSH (>+2SDS) concerning induced pubertal onset (Tanner B2) at different timepoints prior to pubertal onset. ROC curves were used for data analysis.

Table 1. AMH<3 pmol/l and FSH >+2SD as predictors of the requirement for HRT to induce puberty

	Age (yrs)	*n* (total patientsin this age range)	Sensitivity	Specificity	PPV	NPV
AMH <3 pmol/l	0-1	4	NA	NA	NA	NA
AMH <3 pmol/l	1-6	11	100	75	88	100
AMH <3 pmol/l	>6 *	38	100	100	100	100
FSH >+ 2SD	0-1	6	NA	NA	NA	NA
FSH >+ 2SD	1-6	22	88	60	88	60

*age 6yrs to time of pubertal onset (spontaneous or induced by HRT)

Results
50 patients had blood samples prior to pubertal onset: 221 blood samples (mean 4, range 1–14 per patient). ROC curves: AMH cut off <3pmol/l provided the best combination of sensitivity and specificity.
Conclusion
From the age of 6yrs, AMH accurately predicted the patients who required HRT to induce puberty and the patients who underwent spontaneous pubertal onset. Thus, prepubertal AMH is a valuable clinical tool for guiding puberty management as well as future fertility counseling in TS girls. Further follow up is necessary to evaluate the predictive value of hormone levels in minipuberty.

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RC5.6

JOINT1434

Low prolactin levels as a risk factor for gestational diabetes mellitus: a longitudinal cohort study

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Rationale
Pregnancy induces profound metabolic adaptations to support fetal development, including increased insulin resistance and significant hormonal changes. However, when insulin production is inadequate to overcome pregnancy-induced insulin resistance, glucose impairment may occur thus increasing the risk of developing gestational diabetes mellitus (GDM). Emerging evidence highlights the role of early biomarkers, including hormonal profiles, in predicting GDM risk. Prolactin (PRL) plays a pivotal role in these adaptive changes, particularly in glucose homeostasis.
Objective
This study aimed to investigate the trajectory of PRL levels during pregnancy and their association with metabolic and glycemic outcomes.
Methods
A total of 120 pregnant women (67 with GDM, and 53 healthy controls) were assessed for anthropometric, hormonal (serum PRL) and metabolic parameters, including HbA1c, fasting glucose and glucose levels during the oral glucose tolerance test (OGTT). Women diagnosed with GDM underwent a follow-up OGTT between 4 and 12 weeks postpartum.
Results
PRL levels progressively increased across pregnancy but were significantly lower in patients with GDM, particularly in the third trimester (*P*=0.027). Early pregnancy PRL levels negatively correlated with fasting glucose (*P*=0.02; *r*=-0.4), whereas second-trimester PRL levels were inversely correlated with HbA1c levels in both the second (*P*=0.035; *r*=-0.5) and third trimesters (*P*<0.001; *r*=-0.9), respectively. Lower third-trimester PRL levels were associated with higher pre-pregnancy (*P*=0.02; *r*=-0.3) and postpartum weight (*P*=0.01; *r*=-0.6), whereas higher PRL levels correlated with better metabolic outcomes and longer breastfeeding duration. Subsequently, women were stratified into two groups based on the median third-trimester PRL level (183.8 μg/l). Ninety-six % of women with PRL<183.8 μg/l developed GDM, compared to 62% of those with PRL>183.8 μg/l (*P*<0.001). A one-unit decrease in third-trimester PRL predicted a 0.301-unit increase in 2-hour OGTT glucose (*P*=0.016; t=-2.81), reinforcing its potential role in GDM risk prediction. Adverse outcomes, including preterm delivery<37 weeks (5%) and infants large (LGA, 2.5%) or small (SGA, 5%) for gestational age, rarely occurred. No significant difference emerged between groups in breastfeeding duration, neonatal weight or length. Among patients retested after pregnancy, 22.3% had impaired glucose regulation, including 1 (1.5%) with type 2 diabetes mellitus, 7 (10.4%) with IFG and 7 (10.4%) with IGT.
Conclusions
PRL might represent a valuable biomarker for GDM risk stratification and maternal cardiometabolic health assessment during pregnancy. A sustained increase in PRL levels appears to support glucose homeostasis, whereas lower PRL levels are associated with increased GDM risk. Early monitoring of PRL levels could help identify women at high-risk, enabling timely interventions to improve maternal and fetal outcomes.

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Rapid Communications 8: Diabetes and Insulin Part 2

RC8.1

JOINT264

Study of predictive markers determining poor response to finerenone therapy in the management of diabetic kidney disease

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Background
Diabetic kidney disease (DKD) is a leading cause of end-stage renal disease. Finerenone, a non-steroidal mineralocorticoid receptor antagonist (MRA), has demonstrated renoprotective effects in patients with DKD. However, not all patients respond equally to finerenone therapy. Identifying predictive markers for poor response is crucial for personalized management. This study aimed to investigate potential predictive markers associated with suboptimal response to finerenone in patients with DKD.
Methods
This prospective cohort study included 140 patients with DKD (estimated glomerular filtration rate [eGFR] 25-75 ml/min/1.73 m^2 and urinary albumin-to-creatinine ratio [UACR] $\geq$30 mg/g) who were initiated with finerenone therapy. Patients were followed for 12 months. Poor response was defined as a less than 15% reduction in UACR or a decline in eGFR of more than 5 ml/min/1.73 m^2 at end of one year. Baseline clinical and laboratory parameters, including age, sex, HbA1c, blood pressure, eGFR, UACR, serum potassium, sodium, uric acid, and inflammatory marker (high-sensitivity C-reactive protein [hs-CRP]), were analyzed as potential predictors. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of poor response.
Results
Of the 140 patients, 45 (32.14%) were classified as poor responders to finerenone therapy. Univariate analysis revealed that baseline eGFR (OR 0.95, 95% CI 0.92-0.98, $P=0.001$), UACR (OR 1.001, 95% CI 1.000-1.002, $P=0.03$), hs-CRP (OR 1.25, 95% CI 1.08-1.45, $P=0.003$), and uric acid (OR 1.15, 95% CI 1.02-1.30, $P=0.02$) were significantly associated with poor response. In multivariate analysis, baseline eGFR (OR 0.96, 95% CI 0.93-0.99, $P=0.01$) and hs-CRP (OR 1.20, 95% CI 1.03-1.40, $P=0.02$) remained independent predictors of poor response to finerenone.
Conclusion
This study suggests that baseline eGFR and hs-CRP are independent predictors of poor response to finerenone therapy in patients with DKD. These findings highlight the importance of considering these markers in clinical practice to identify patients who may require closer monitoring or alternative treatment strategies. Further prospective studies are needed to validate these findings and explore the underlying mechanisms contributing to the observed associations.
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RC8.2

JOINT142

Efficacy and safety of finerenone in people with chronic kidney disease and type 2 diabetes by treatment goal attainment: A FIDELITY analysis

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Background
Finerenone significantly reduced cardiovascular and kidney risk versus placebo in patients with chronic kidney disease and type 2 diabetes in FIDELITY, a prespecified pooled analysis of the FIDELIO-DKD and FIGARO-DKD trials. Whether the benefits of finerenone on cardiovascular and kidney outcomes are observed independently of the number of American Diabetes Association-recommended treatment goals (HbA1c $\leq$7.0%, SBP $<$130 mmHg and DBP $<$80 mmHg, LDL cholesterol $<$70 mg/dl, and use of SGLT-2is or GLP-1RAs) achieved by patients at baseline remains to be determined.
Methods
Patients included in FIDELITY were on optimised RASi and were randomised 1:1 to finerenone or placebo. Composite cardiovascular (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for heart failure) and kidney (kidney failure, sustained $\geq$57% estimated glomerular filtration rate [eGFR] decrease from baseline over $\geq$4 weeks, or kidney-related death) outcomes, and treatment-emergent adverse events (TEAEs) were assessed according to the number of treatment goals achieved at baseline.
Results
At baseline, 29%, 40%, 24% and 7% of patients achieved 0, 1, 2 and $\geq$3 goals, respectively. Larger proportions of patients achieved a higher number of goals in Asia and Western Europe versus other regions. Median urine albumin-to-creatinine ratio and mean eGFR at baseline decreased with an increasing number of goals achieved. No significant heterogeneity in the effect of finerenone versus placebo on the composite cardiovascular or kidney outcomes was observed between treatment goal achievement subgroups ($P_{interaction}$ of 0.75 and 0.61, respectively; Table). The safety profile of finerenone (versus placebo) was generally similar across treatment goal attainment subgroups, although patients who achieved a higher number of treatment goals tended to have slightly higher TEAE rates.

Table. Effect of finerenone versus placebo on efficacy outcomes by number of treatment goals achieved at baseline (Cox proportional hazards model)

		Treatment goals (*n*)			
		0 (*n*=3732)	**1 (*n*=5208)**	**2 (*n*=3091)**	**≥3 (*n*=959)**
			Composite cardiovascular outcome		
Incidence (n/N)	**Finerenone**	295/1905	299/2534	182/1568	47/491
	Placebo	307/1827	388/2674	194/1523	49/468
HR (95%CI)		0.90 (0.76–1.05)	0.79 (0.68–0.92)	0.88 (0.72–1.08)	0.89 (0.59–1.37)
$P_{interaction}$	0.75				
			Composite kidney outcome		
Incidence (n/N)	**Finerenone**	128/1905	144/2534	63/1568	21/491
	Placebo	155/1827	202/2674	89/1523	19/468
HR (95%CI)		0.77 (0.60–0.97)	0.71 (0.57–0.88)	0.70 (0.50–0.97)	1.11 (0.56–2.18)
	$P_{interaction}$	0.61			

CI, confidence interval; HR, hazard ratio.

Conclusion
Overall, the beneficial effect of finerenone on the composite cardiovascular and kidney outcomes was observed irrespective of the number of treatment goals achieved by patients at baseline.
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RC8.3

JOINT2775

Deviations in guideline implementation lead to severe hypoglycemia in diabetic ketoacidosis management

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Background
The Joint British Diabetes Societies (JBDS) guidelines provide evidence-based recommendations to prevent complications during Diabetic Ketoacidosis (DKA)

Table 1 Comparison of various parameters among cases with TDT having NGT (normal glucose tolerance) and altered glucose metabolism

		Altered glucose metabolism				
	NGT ($n=73$) Mean±SD/ Median [25th to 75th percentile]	**IFG ($n=35$) Mean±SD/ Median [25th to 75th percentile]**	**IGT ($n=6$) Mean±SD/ Median [25th to 75th percentile]**	**Diabetes ($n=2$) Mean±SD/ Median [25th to 75th percentile]**	**Total ($n=37$) Mean±SD/ Median [25th to 75th percentile]**	***P* value NGT vs altered glucose metabolism**
Mean fasting glucose (mg/dl)	91.05±6.34	106.6±6.07	122.33±19.4	142.5±20.51	108.51±70	**<0.001^**
Mean Serum fasting Insulin (uU/ml)	4.73±2.72	8.37±5.54	10.68±6.25	11.26±9.11	8.53±5.64	**<0.001^**
Median Serum Insulin (uU/ml) at 30 minutes (of OGTT)	13.5[7.9 to 21.98]	19.40[11.70 to 39.23]	28.20[13.47 to 66.35]	36.38[28.20 to (*]	22.35[13.37 to 40.76]	**0.004^**
Mean HOMA-IR	1.06±0.64	2.23±1.56	3.35±2.33	4.19±3.78	2.34±1.7	**<0.001^**
Median Insulinogenic Index	0.27[0.14 to 0.74]	0.46[0.23 to 1.08]	0.25[0.04 to 0.73]	0.26[0.0 to *]	0.46[0.23 to 1.08]	0.084

*2 subjects diabetes, 75th percentile not estimated, ^ p value<0.05 significant

management. Despite their established protocols, deviations from these guidelines remain prevalent, primarily due to errors in insulin administration. One significant consequence of these errors is severe hypoglycaemia, a potentially life-threatening condition affecting 5–25% of patients annually.

Aims

1. To evaluate adherence to JBDS guidelines in DKA management.
2. To explore the characteristics of severe hypoglycemia associated with DKA treatment.

Methods

This study was conducted at a large tertiary care centre from October 2024 to January 2025. A retrospective analysis was performed using data from all DKA episodes between August 2023 and September 2024. Episodes where severe hypoglycaemia (blood glucose <3.9 mmol/l) did not occur were excluded from the analysis. Patient demographics, episode characteristics, adherence to JBDS guidelines, and details regarding the hypoglycaemic events were extracted from electronic health records. Statistical analysis was conducted using Microsoft Excel and results are presented as frequencies or proportions as appropriate.

Results

Of the 304 DKA episodes during the study period, 68 hypoglycaemic episodes across 32 patients met the eligibility criteria for inclusion in this study. The median age of the patients was 42 years, with an equal male-to-female distribution. 68.8% had Type 1 Diabetes Mellitus (T1DM) (median age:38.8 years, CCI:1.5). 75% of the episodes lacked hourly glucose monitoring, 28% did not initiate the correct insulin infusion rate (0.1 unit/ kg/hour), 54% failed to introduce 10% dextrose when glucose levels fell below 14 mmol/l, and 69% did not halve the insulin infusion rate under these conditions. 60% of hypoglycaemic episodes were attributed to multifactorial causes. 19.1% of the episodes were classified as level three hypoglycaemia.

Conclusions

This audit underscores the substantial deviations from JBDS guidelines in managing DKA, particularly in relation to insulin administration, glucose monitoring, and dextrose supplementation. These gaps contribute to the high incidence of severe hypoglycaemia in DKA patients. The findings highlight the urgent need for targeted interventions, such as implementing standardised checklists and reinforcing clinical protocols, to improve adherence to guidelines and ultimately optimise patient outcomes. These interventions could be crucial in reducing hypoglycaemic events and enhancing the safety and effectiveness of DKA management.

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RC8.4

JOINT1391

Congenital hyperinsulinism and diabetes later in life –dominant variants causing both phenotypes

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Background & aim

It is unclear which genes causing congenital hyperinsulinism (HI) can also cause diabetes later in life due to possible beta-cell exhaustion from excess insulin secretion. To test this, we screened for pathogenic variants in the three most common dominant HI genes in a large cohort of individuals with diabetes referred for MODY testing and in a large population cohort.

Methods

We examined dominantly acting pathogenic HI-causing variants in *ABCC8*, *GCK*, *GLUD1* in 2,413 individuals with early-onset diabetes (<40 y) referred for MODY genetic testing. We repeated the analyses in 24,203 individuals with late-onset diabetes from the UK Biobank (UKB). We examined enrichment of pathogenic variants in these cohorts compared to total of 395,625 controls.

Results

We did not find pathogenic HI-causing *GCK* or *GLUD1* variants in individuals with early- or late-onset diabetes, suggesting these etiologies do not increase diabetes risk. In contrast we found a significant enrichment of dominant *ABCC8* HI variants in the MODY cohort compared to control population (odds ratio 43, 95%CI 4–375, $P=0.0023$). The phenotype of the 9 individuals with diabetes and a dominant *ABCC8* HI variant in MODY cohort was not suggestive of type 1 or 2 diabetes and they lacked pathogenic variants in all known monogenic diabetes genes. They were diagnosed at median age of 16 years [IQR, 12.5;16.0]. All were negative for islet auto-antibodies and had low Type 1 diabetes Genetic Risk Score (<15thcentile). Their median BMI was 26.7 kg/m^2, seven (78%) had family history of diabetes, and only 2 (22%) neonatal-HI. A dominant *ABCC8* HI variant was detected in only 1 of 24,203 individuals with diabetes in the UKB.

Conclusion

Our results suggest that dominant loss-of-function HI variants can cause diabetes later in life but this is limited only to the *ABCC8* gene. Although further understanding is needed about treatment, these variants should be screened to determine the aetiology of early-onset diabetes.

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RC8.5

JOINT2397

Assessment of derangements in glucose metabolism in children with transfusion dependent thalassemia: a cross sectional analytical study

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Introduction

The mechanisms of abnormal glucose homeostasis in children with transfusion dependent thalassemia (TDT) are complex and multifactorial.

Objective

To assess the prevalence and spectrum of deranged glucose metabolism in children with TDT in comparison with age and sex matched controls.

Methods

Cross-sectional analytical study conducted in 110 children (aged 5-18 years) with TDT (cases) and equal number of age and sex matched controls. Proportion of children with deranged fasting blood glucose and fasting insulin levels were assessed in both cases and controls. Impaired glucose tolerance and insulin resistance were evaluated using oral glucose tolerance test (OGTT) and Homeostatic model assessment of insulin resistance (HOMA-IR) levels respectively in children with TDT.

Results

Altered glucose metabolism was observed in 33.6% children with TDT. Prevalence of impaired fasting glucose (IFG), impaired glucose tolerance and diabetes was 31.8%, 5.45% and 1.8% respectively. Proportion of children with IFG [31.8% vs 0], fasting insulin deficiency [19% vs 5.5 %] and raised HOMA-IR [17.3% vs 1.82%] were higher in cases as compared to controls ($P<0.001$). The mean fasting glucose, fasting insulin, 30-minute insulin on OGTT and HOMA-IR were significantly higher in children with TDT and altered glucose metabolism than with normal glucose tolerance (table 1). Significant predictors of altered glucose metabolism in TDT cases were delayed puberty, raised ALP and high BMI for age.

Conclusions

1/3rd of children with TDT had altered glucose metabolism. Underlying mechanisms include both insulin resistance and insulin deficiency.

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RC8.6

JOINT1996

Inherited stress vulnerability exacerbates obesity-induced metabolic alterations through dysfunctional adipose tissue

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Background
Obesity is a significant risk factor for developing cardio-metabolic diseases and is associated with increased mortality. However, there is substantial variability in the severity of metabolic abnormalities among obese individuals. The exact mechanisms contributing to this heterogeneity remain unclear.
Objective
This study aims to investigate whether differences in stress response affect metabolic health and to explore underlying mechanisms, hypothesizing that impaired stress resilience affects adipose tissue function.
Methods
The study utilized a selectively bred mouse model with inherent social dominance (Dom) and submissiveness (Sub), representing stress resilience and vulnerability, respectively. Mice were fed either a high-fat diet (HFD) or standard diet (STD), followed by physiological and molecular analyses. To manipulate stress response, a stress inoculation paradigm involving chronic mild stress (CMS) was employed (14 days of 5-minute daily restraint)[1]. Epididymal and inguinal white adipose tissue (eWAT and iWAT, respectively) were isolated for RNA-seq analysis, insulin sensitivity assessment, and determination of adipogenic potential.
Results
HFD-fed Sub mice exhibited hyperinsulinemia, hyperleptinemia, severe glucose intolerance, and fatty liver, whereas Dom mice showed minimal effects. CMS reduced HFD-induced glucose intolerance in stress-vulnerable mice, with similar positive effects observed in C57BL/6 mice. Adipose tissue analysis revealed impaired adipokine expression in HFD-fed Sub mice, with higher leptin and lower adiponectin mRNA levels compared to Dom mice. Additionally, an impaired pro-inflammatory gene expression profile was observed in Sub mice. Further investigation focused on differences in adipose tissue function between Sub and Dom mice, showing impaired insulin-induced Akt phosphorylation and glucose uptake in Sub mice. RNA-seq analysis demonstrated distinct clustering of genes in WAT of Sub and Dom mice, even under STD-feeding conditions, indicating fundamental differences in adipose tissue function between strains. Pathway analysis revealed that adipogenic pathways were enriched in eWAT but reduced in iWAT of lean Sub mice, suggesting impaired adipogenic potential in iWAT of Sub. Functional analysis of adipogenesis in isolated stroma-vascular fraction (SVF) from iWAT confirmed lower proliferation and differentiation rates in Sub mice compared to Dom mice. Furthermore, differentiated adipocytes from Dom mice exhibited a higher UCP1 and adiponectin-to-leptin expression ratio, compared to adipocytes from Sub.
Conclusion
Stress vulnerability contributes to increased susceptibility to metabolic alterations, with impaired adipogenic potential and impaired function in stress-vulnerable mice, potentially exacerbating metabolic abnormalities observed in this model.
Reference
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Rapid Communications 9: Endocrine Related Cancer

RC9.1

JOINT3173

Hereditary duodenopancreatic neuroendocrine tumors, what genetic analysis? a retrospective analysis on 410 patients

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Background
Duodenopancreatic Neuroendocrine Tumors (dpNETs) have an estimated prevalence of approximately 5 per 100,000, with less than 5% presenting as hereditary cases. Tumor growth is generally slow, but metastases can appear quickly. DpNETs can sometimes be the first symptom of syndromic diseases, diagnosed thanks to the identification of a pathogenic genetic variants. In France, the last recommendations of germinal genetic analysis in case of dpNETs focused only on *MEN1* and *VHL* analysis in isolated and familial cases or in isolated dpNETs before 50 years except for gastrinomas.
Objectives
Objectives was to update the list of candidate genes and to estimate the prevalence of these newly identified genes in order to update the decision tree for genetic analyses in dpNETs.
Methods
We conducted a literature review of genes implicated in dpNETs. Once identified, we performed a retrospective analysis of genetic and clinical data of patients diagnosed with dpNETs and analyzed using the Endocrine Tumor library at the laboratory of molecular biology APHM between 2018 and 2024.
Results
The literature review identified 3 additional syndromic diseases including dpNETs : neurofibromatosis type 1 (*NF1*), multiple endocrine neoplasia type 4 (*CDKN1B*), and tuberous sclerosis (*TSC1*, and *TSC2*). We include 410 patients, 306 with isolated dpNET and 104 syndromic dpNETs. A total of 15 had familial of dpNETs and 395 were sporadic. All (likely) pathogenic variants ((L)PV) of *MEN1*, *VHL*, *NF1*, *CDKN1B*, *TSC1* and *TSC2* identified by NGS in the 410 patients were collected. Overall, 36 (L)PV were identified, including 27 in *MEN1* (75%), 6 in *NF1* (16,7%), 3 in *VHL* (8,3%), and none in *CDKN1B* and *TSC1/2*. A (L)PV was identified in 28.8% (30/104) of patients with syndromic dPNETs while in only 2% (6/306, 5 *MEN1* and 1 *NF1*) of patients with isolated dpNETs. Among the 6 *NF1* cases, 3 (50%) had pancreatic gastrinomas, and in one case, dpNET was the first manifestation of the disease. An earlier onset of dpNET was observed in *VHL* patients with a mean age of 23 years, compared to 44 years for *MEN1* and *NF1* patients.
Conclusion
In patients with dpPNET, not only MEN1 and VHL but also *tuberous sclerosis*, and NF1-related lesions should be assessed to identify syndromic genetic predisposition. In case of isolated and sporadic dpNET, mutation detection rate is very low ($<2\%$); a better definition of the targeted population remains required to avoid an over genetic exploration.

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RC9.2

JOINT1986

Dysregulation of a RNA exosome component: a driving force behind prostate cancer progression

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New diagnostic, prognostic and therapeutic strategies for different endocrine-related cancers are urgency required, especially in highly common types of malignancies affecting millions of subjects worldwide. Prostate cancer (PCa) represents a major endocrine health issue, with its progression influenced by intricate molecular factors, being the acquisition of an androgen-independent phenotype by prostate cancer cells a death sentence for patients [metastatic PCa (mPCa)]. In this context, recent evidence from our group indicates a profound

dysregulation in the RNA-Exosome complex (REC), a molecular machinery responsible for 3′-5′ RNA processing and degradation, in PCa vs. non-tumoral samples which might be implicated in driving oncogenic processes associated with tumour progression and aggressiveness. This study focuses on characterizing the levels and pathophysiological role of a REC component (REC-C) in PCa. Analysis of seven independent cohorts of patients with PCa and/or mPCa (three internal and four external) revealed that REC-C was consistently up-regulated in PCa and mPCa vs. control tissues, being this overexpression directly correlated with different clinical features of aggressiveness, including high Gleason scores, recurrence, and metastasis. Functional studies in different preclinical models, both *in vitro* [using normal-like prostate (PNT-2) and mPCa (LNCaP, DU145, and 22Rv1) cells] and *in vivo* (xenografted mice) demonstrated the impact of REC-C silencing in critical cancer hallmarks, including significant reductions in cell proliferation, migration, colonies or tumourspheres formation and tumor growth. Mechanistically (employing RNAseq and phosphoarray approaches), REC-C actions were mediated through the modulation of key inflammatory-related RNAs (e.g., interferon-gamma response) and critical oncogenic signalling pathways (e.g., MAPK and TGFβ). Remarkably, microscopy studies indicated that REC-C was predominantly localised in the nucleolus of normal and low-aggressiveness mPCa cells, whereas it was found to be enriched in the nucleoplasm of highly aggressive mPCa cells suggesting a cellular localization-dependent role of REC-C in prostate cells. In fact, this study demonstrated that the general expression and nucleoplasmic-guided accumulation of REC-C in the PNT2 normal prostate cell model induced metastasis-associated morphological changes (e.g. loss of nucleolar circularity) and increased cellular aggressiveness, including enhanced migration and invasion capacity. Finally, cross-linking and analysis of cDNA (CRAC) technique revealed **that** the enhanced aggressiveness features linked to REC-C might be associated to its potential interaction with critical long non-coding RNAs. These findings underscore REC-C as a driving force behind prostate cancer progression and as a promising therapeutic target for PCa/advance-state PCa.

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RC9.3

JOINT74

Defining the clinical value of circulating splicing factors in prostate cancer: SRRM1 as a novel predictive biomarker and exploitable therapeutic target

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Prostate cancer (PCa) is the second most prevalent endocrine-related cancer among men worldwide. The main screening method, based on prostate-specific antigen (PSA) determination, exhibits significant limitations, including poor specificity and restricted prognostic value. Thus, the identification of accurate non-invasive diagnostic biomarkers, with potential prognostic and therapeutic applications, remains a critical need in PCa. In this context, dysregulation of the splicing process has emerged as a hallmark in PCa development and progression, with several splicing factors (SFs) playing key roles in PCa pathophysiology. However, despite discrete SFs have been reported to be potentially secreted by cancer cells, this event has not been addressed in PCa. Therefore, we aimed to explore the presence and potential clinical value of SRRM1, SNRNP200, and SRSF3 (previously reported SFs with a key pathophysiological role in PCa) in human plasma samples. Thus, plasma levels of these SFs were measured (using ELISAs) in control individuals ($n=40$) and PCa patients ($n=166$). We identified, for the first time, that these SFs were detectable in human plasma samples, being corroborated in an independent cohort of healthy individuals ($n=313$). Notably, plasma levels of SRRM1 and SNRNP200, but not SRSF3, were significantly elevated in PCa patients compared to controls. Furthermore, plasma and tissue SRRM1 levels were associated with relevant features of castration-resistant PCa (CRPC), a lethal disease stage, and positively correlated with androgen-receptor (AR) and AR-splicing variant 7 (AR-V7) expression and activity in PCa tissues. Furthermore, *in vivo* SRRM1 silencing in CRPC-derived xenografted tumors reduced aggressiveness features and AR/AR-V7 activity. Taken together, our findings suggest that circulating SRRM1 levels could serve as a valuable non-invasive diagnostic and prognostic biomarker in PCa. Additionally, SRRM1 may hold a promising therapeutic value, offering a clinically relevant opportunity for further exploration in human studies. Also, this study set the groundwork to thoroughly evaluate the presence and clinical utility of circulating SFs for clinical management of PCa patients.

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RC9.4

JOINT3581

Adipsic arginine vasopressin deficiency in CNS tumour patients: clinical management challenges

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Introduction
Arginine vasopressin deficiency (AVP-D), formerly central diabetes insipidus, results from inadequate production of arginine vasopressin (AVP), also called antidiuretic hormone (ADH). It can be congenital or acquired, often resulting from tumours affecting the hypothalamic-pituitary region. The condition is marked by excessive urine output (polyuria), usually offset by increased water intake. Adipsic arginine vasopressin deficiency (AAVP-D), a rare form affecting hypothalamic osmoreceptors, impairs thirst perception, leading to an increased risk of dehydration and hypernatremia. This study retrospectively analyses patients with AAVP-D among those diagnosed with central nervous system (CNS) tumours in our centre.
Cases
Among 383 paediatric patients with CNS tumours, 34 were diagnosed with AVP-D, including 4 with AAVP-D. Of these, 2 (50%) were male. In most cases, AAVP-D was identified shortly after the CNS tumour diagnosis, except for one patient who developed symptoms 9 years later. Case 1: A girl diagnosed with a germinoma at 3 years, treated with multiple surgeries and chemotherapy, presented at age 12 with somnolence, hypernatremia (serum sodium: 157 mmol/l, osmolarity: 311.3 mOsm/kg), and concurrent panhypopituitarism. Given the potential influence of adrenal insufficiency on ADH secretion, she was hospitalized for initiation and titration of desmopressin therapy, followed by hydrocortisone. Case 2: A 13-year-old female with a hypothalamic germ cell tumour treated with radiotherapy developed adipsia, anorexia, and hypernatremia (serum sodium: 159 mmol/l, osmolarity: 325 mOsm/kg). Panhypopituitarism was diagnosed, requiring desmopressin, hydrocortisone, and levothyroxine. Due to persistent inadequate hydration, nasogastric tube feeding was attempted but ineffective, necessitating chlorpromazine therapy, which successfully improved hydration and thirst perception. Case 3: An 18-year-old male with a germinoma developed panhypopituitarism and AAVP-D following CNS radiotherapy but achieved good sodium control after initiating desmopressin. Case 4: An 6-year-old male presenting with vomiting, severe headache, and hydrocephalus due to intraventricular haemorrhage developed polyuria and hypernatremia (serum sodium: 155 mmol/l). Initial management was difficult due to high sodium from low water intake. Increasing desmopressin and setting a fixed water intake plan with school teacher support improved symptoms.
Conclusion
AAVP-D is a rare form of arginine vasopressin deficiency, in which the lack of polydipsia poses a challenge for both diagnosis and management. Effective treatment requires a personalized approach, with acute management involving fixed doses of ADH analogues and carefully controlled water intake. For patients with concurrent endocrine deficiencies, hormone replacement is essential. In refractory cases, chlorpromazine may be considered to enhance thirst perception, offering a potential adjunctive therapy.

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RC9.5

JOINT2913

Preclinical development and first clinical use of a radioiodinated CYP17 inhibitor for adrenal theranostics

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Background
The CYP11B1/2-selective tracers iodometomidate and IMAZA have been used for theranostics in adrenocortical carcinoma (ACC), but only ~40% of ACC patients show sufficient uptake, limiting their diagnostic and therapeutic utility. Since CYP17 is more frequently and highly expressed in ACC than CYP11B1/2, we designed several radiolabeled CYP17 inhibitors.
Methods
We designed and synthesised fluorinated and iodinated derivatives of known CYP17 inhibitors and evaluated their adrenostatic potential on CYP17-related enzymatic steps in NCI-H295 cells. Steroid concentrations of 17-OH-progesterone, DHEA and androstenedione were measured by LC-MS in supernatant after coincubation with the respective compounds and IC50 values were calculated. After successful establishment of the radiochemistry, the tracers were investigated in cell uptake experiments, cryosection binding studies and biodistribution analyses in hsCYP17-humanised mice.
Results
Ten derivatives of the known CYP17-inhibitor CFG920 showed single-digit nanomolar inhibition of at least one target steroid. Tracers showed up to 40% intracellular uptake, accumulating mainly in the endoplasmic reticulum fraction. Cryo-binding studies identified several tracers with high and specific tissue binding, with the radioiodinated compound IPIMA standing out. In animal studies, IPIMA exhibited high, sustained accumulation in CYP17-expressing tissues. Initial clinical studies in IMAZA-negative ACC patients showed that IPIMA effectively visualized tumor lesions undetected by IMAZA.
Conclusion
The CYP17-targeting radioiodinated compound IPIMA is a promising theranostic agent for adrenocortical tumors.

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Rapid Communications 10: Pituitary, Neuroendocrinology and Puberty Part 2

RC10.1

JOINT645

Recessive truncations in a previously uncharacterized gene, CCDC149, are a novel cause of congenital hypopituitarism

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Background
Congenital Hypopituitarism (CH) is a complex developmental disorder characterized by a variable combination of defects in pituitary function, including deficiencies in growth hormone (GHD) (most frequent), gonadotropins, ACTH, TSH, prolactin and vasopressin. To date, a molecular basis has been identified in ~10-15 % of patients, but the majority remain unexplained.
Methods
Next generation sequencing was performed in two unrelated pedigrees including three patients with GHD, hypogonadotropic hypogonadism, and developmental delay/autism. MRI studies were performed to visualize morphological defects in the spinal cord and the pituitary. In situ hybridisation was conducted to generate an expression profile of *CCDC149* in the human embryonic brain at different Carnegie stages of development. A null *Ccdc149* mouse model was generated for phenotypic characterization.
Results
Two novel homozygous frameshifts were identified in *CCDC149*, c.832G>T p.G278* and c.665T>A, p.L222* respectively, in the two unrelated pedigrees with CH. Severe scoliosis was present in two out of the three patients, with the third unrelated patient having a small anterior pituitary on MRI. *CCDC149* mutations have not been reported previously. Human embryonic expression of *CCDC149* was localised to the developing hypothalamo-pituitary (HP) region at Carnegie stages (CS) 16, 19, 20 and 23. Preliminary murine data suggest that *Ccdc149*-knockout mice exhibit growth impairment and reduced fertility compared to their wildtype littermates.
Conclusion
We report the first genetic variant in a novel gene, *CCDC149*, associated with CH, scoliosis and learning difficulties/autism. We present clinical and molecular data in two pedigrees with CH, as well as gene expression in human embryonic sections and murine data to confirm the association between *CCDC149* variations and CH. *CCDC149* is therefore a novel candidate gene that should be considered for analysis in patients with unsolved CH. Previous studies in C.elegans report expression of the *CCDC149* orthologue in the basal bodies of ciliated neurons, supporting the possibility of impaired ciliary function as an underlying mechanism in this complex disorder.

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RC10.2

JOINT2027

Transcriptomic classification of PIT1-lineage PitNETs reveals distinct molecular groups associated with tumor differentiation and treatment resistance

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Objective
PIT1-lineage PitNETs are the most common pituitary tumors, encompassing lactotroph, somatotroph and thyrotroph tumor types. At a molecular level, several questions about their biology remain open. Among these, the molecular mechanisms of resistance to medical treatments remain largely unknown. The aim of this study was to better characterize PIT1-lineage PitNETs based on bulk transcriptome analysis, refining their molecular classification and deciphering molecular signatures associated with treatment resistance.
Methods
The transcriptome of 121 patients with PIT1-lineage PitNETs was evaluated. Clinical and histological data were collected, including those about response to dopamine agonists in prolactinomas, and to first-generation somatostatin analogs in acromegaly. Unsupervised transcriptome classifications were generated, both in the overall cohort and within subtypes, and tested for association with clinical data and treatment response.
Results
Unsupervised classification mainly discriminated PIT1-lineage PitNETs according to tumor histopathology (χ_2 $P<10_{-22}$ and $P<10_{-4}$ for WHO 2017 tumor type and granulations, respectively), secretion (χ_2 $P<10_{-22}$), and *GNAS* mutational status (χ_2 $P<10_{-6}$). Compared to previous classifications, a clear separation between sparsely granulated somatotroph PitNETs and thyrotroph/plurihormonal PIT1 PitNETs emerged. Moreover, a majority of aggressive PitNETs cumulated in a distinct transcriptomic subgroup, defined by a signature of mesenchimal differentiation, irrespective of histotype. Among prolactinomas, sensitivity to

dopamine agonists was the main driver of transcriptomic classification. Sensitive tumors cumulated in a distinct molecular subgroup. Resistant tumors were classified into three different clusters, with specific expression profiles (dedifferentiated, proliferative, and immune-rich). Among tumors causing acromegaly, three main transcriptomic groups were observed: sparsely granulated somatotrophs, densely granulated somatotrophs with *GNAS* somatic mutation, and densely granulated somatotrophs with PIT1/SF1 co-expression. Moreover, three smaller clusters were also observed, lacking the hallmark features of the three main ones: one of proliferative tumors with aggressive behavior; one of giant invasive tumors with atypical histology but otherwise indolent growth; and one of smaller tumors with limited extrasellar extension. Sensitivity to first-generation somatostatin analogs was associated with these molecular classes, with resistant tumors grouping within the sparsely granulated, proliferative, and giant invasive tumor clusters.

Conclusions

This transcriptomic study unravels important new aspects of the biology of PIT1-lineage PitNETs and further refines their molecular classification. The transcriptomic classification of prolactinomas recognizes the sensitivity to dopamine agonists as its main driver. The transcriptomic classification of tumors causing acromegaly primarily reflects their histological heterogeneity and identifies distinct molecular clusters associated with treatment response.

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RC10.3

JOINT3777

TNIP1 as a key regulator in sparsely granulated somatotropinomas: a combined proteomics and bioinformatics approach

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Background

Histopathologically somatotropinomas are classified as sparsely granulated (SG) and densely granulated (DG). Compared to DG, SG displays aggressive clinical behaviour, including a younger presentation, a higher percentage of invasiveness, therapy resistance, and recurrence (after total removal). A quantitative proteomics-based approach can dissect the signalling pathways between SG and DG subtypes and can potentially leads to new therapeutic targets in SG subgroups.

Method

Surgically resected 8 sporadic somatotropinoma (SG ($n=4$) and DG ($n=4$)) were subjected to high-throughput label-free quantitative mass spectrometry-based (Orbitrap Exploris mass spectrometer, Thermo Scientific) proteomics analysis in triplicates. Functional enrichment was conducted to identify the biological pathways and functions of the identified proteins. Topmost significantly differentially expressed proteins (cut-off = 1.5 fold-change) were considered for validation by immunofluorescence (IF) ($n=10$; SG = 5, DG = 5) and western blot ($n=8$ SG = 4, DG = 4).

Results

Mass spectrometry analysis identified 41,786 peptides corresponding to 5,163 proteins. Of these, 4,037 proteins were detected with ≥ 2 unique peptides. Statistical analysis showed significant differential expression of 1014 proteins, with overexpression of 44 proteins and under expression of 970 proteins. TNIP1($P=0.0001$) was the most overexpressed followed by PRSS29P ($P=0.001$), HPN ($P=0.001$) and DTNP ($P=0.002$) while COQ6 (0.00004) was the most under expressed protein. Functional enrichment analysis showed significant enrichment of glutathione synthesis pathway ($P=0.004$) and integrin signalling pathway ($P=0.004$) for overexpressed while mRNA processing ($P<0.0001$) and splicing ($P<0.0001$) pathways were significantly enriched for under expressed proteins. TNIP1 plays important role in EGFR mediated signalling cascade and inhibition of ERK2 mediated trancription[1,2]. ELK, a transcription factor regulated by ERK2, was found to be significantly enriched in our dataset ($P=0.04$). Notably, 122 proteins identified as targets of ELK exhibited under expression, suggesting a potential ELK-mediated transcriptional repression by TNP1. Furthermore, western blot analysis showed 5.9-fold increase ($P=0.007$) in TNIP1 expression in SG tumours as compared to DG tumours while there was no significant difference in the COQ6 levels between two groups. Immunofluorescence showed overexpression and nuclear localisation of TNIP1 in SG tumours as compared to DG.

Conclusion

Our findings suggest a potential role of TNIP1 in modulating ERK2-ELK signalling in SG tumours.

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RC10.4

JOINT2387

Sustained DNA methylation changes despite biochemical remission in cushing's disease

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Background

Glucocorticoids (GC) modulate the epigenetic machinery, thereby influencing gene expression. In cases of Cushing's disease (CD) in remission, the persistence of some comorbidities, such as hypertension, obesity, and diabetes, may be related to epigenetic changes. Our objective was to evaluate a) the reversibility of GC-induced changes in DNA methylation (DNAm) in patients with CD after at least one year of disease remission and b) the impact of DNAm on the persistence of comorbidities.

Methods

Forty-six patients diagnosed with CD and 59 BMI and gender-matched control subjects were included. Blood samples were collected during the active phase of CD (active_CD) ($n=40$) and at least one year of remission (remission_CD) ($n=30$, mean 49.76 ± 20.02 months), including 24 paired samples. Methylation levels of leukocyte-derived DNA were assessed using the Illumina Infinium Human Methylation 850K array. A difference in beta values of 0.05 with a Benjamini-Hochberg adjusted p-value of <0.05 was used to define differentially methylated probes/CpGs (DMPs).

Results

A total of 4264 DMPs were detected between control and active_CD (hypomethylated $n=2195$ and hypermethylated $n=1349$), 184 in control vs remission_CD (hypomethylated $n=150$ and hypermethylated $n=34$), and 2384 in active_CD vs remission_CD (hypomethylated $n=453$ and hypermethylated $n=1931$). Unsupervised hierarchical clustering revealed 3 main clusters; Cluster 1 comprised almost entirely of controls, the adjacent Cluster 2 included predominantly remission_CD, whereas most active_CD clustered in the distal Cluster 3. Analysis of DMPs associated with gene promoter regions yielded similar results. These results suggest that differences in methylation persist between the control and remission groups despite disease remission. Gene set enrichment analysis (GSEA) using DMPs revealed enrichment of cellular metabolic processes by comparing active CD or remission with controls, whereas immune processes were primarily enriched by comparing active CD and remission. A sub-analysis of 24 patients with paired samples from active disease and remission showed similar results. No association was observed between DMPs and comorbidities, such as diabetes, hypertension, obesity, and dyslipidemia. Using a random forest model, we could classify control, active, and remission samples in our cohort with an overall error rate of 14% (%; controls = 0, active_CD = 23.5, remission_CD = 22).

Conclusion

Cortisol excess in active CD is associated with a spectrum of methylation changes in leukocyte-derived DNA, which are not completely reversible after long-term remission. This indicates that cortisol has sustained effects on the epigenetic machinery. Future studies should explore prolonged epigenetic changes in other cell types in CD and examine their relation to persistent morbidities.

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RC10.5

JOINT1241

Histotype is not associated with short- or long-term remission of somatotroph tumours

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Introduction
Pituitary surgery is the first-line treatment for acromegaly in most cases. While clinical and radiological predictors of remission have been extensively evaluated, few studies have analysed pathological prognostic factors, and evidence regarding histotype remains conflicting. Acromegaly histotypes mainly include pure GH adenomas, which can be either densely (DG) or sparsely granulated (SG), as well as GH-PRL adenomas.
Objectives
The primary objective was to assess the impact of histotype on acromegaly remission, defined as normal IGF-1 levels without treatment 3 months after surgery and at last follow-up. The secondary objective was to evaluate the influence of histotype on acromegaly control at last follow-up, defined as IGF-1 $\leq 1.2\times$ the upper limit of normal (ULN) with or without medical treatment.
Methods
Monocentric retrospective study including 162 patients with GH or GH-PRL adenomas who underwent endoscopic transsphenoidal surgery performed by an expert surgeon between 2012 and 2022.
Results
Among 162 patients, 63 (38.9%) had GH-PRL adenomas, while 99 (61.1%) had pure GH adenomas, including 59 DG (36.4%) and 40 SG (24.7%). Median age (48 years [IQR: 34-58]), IGF-1 (2.9×ULN [IQR: 2.1-3.7]), maximum tumour diameter (14 mm [IQR: 10-21]), and invasion rate (38%) did not significantly differ between GH and GH-PRL groups. Compared to pure GH adenomas, GH-PRL adenomas were more frequently p53-positive ($P<0.01$), had a higher mitotic count ($P<0.05$), and higher SST2 expression ($P<0.01$). Trouillas grade did not differ significantly between GH and GH-PRL adenomas. Compared to SG adenomas, DG adenomas had a lower Trouillas grade ($P<0.05$), lower SST5 expression ($P<0.01$), higher SST2 expression ($P<0.001$), and were more frequently SF1-positive (50% versus 0%, $P<0.01$). The 3-month remission rate was 52% for pure GH and 49% for GH-PRL adenomas, with no significant difference. At last visit, after a median follow-up of 33 months [IQR: 17-61], remission rates remained comparable between pure GH (63%) and GH-PRL adenomas (62%). The control rate at last follow-up for pure GH (89%) was not significantly different from GH-PRL adenomas (95%). Among patients requiring medical treatment, all controlled pure adenomas received monotherapy, while 35% of GH-PRL adenomas required combined therapy. In pure GH adenomas, no significant difference in remission was observed between DG and SG adenomas at 3 months or last follow-up. Similarly, control rates did not differ significantly.
Conclusion
Our results indicate that histotype is not significantly associated with remission or control of acromegaly and do not support the WHO classification, which considers SG high-risk pituitary adenomas.

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RC10.6

JOINT1431

Hypothalamic obesity following craniopharyngioma surgery; what is the role of hypothalamic inflammation?

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Background
Childhood craniopharyngioma (cCP) poses significant risks of hypothalamic damage, leading to severe obesity in up to 75% of survivors. Despite hypothalamus-sparing surgical techniques, hypothalamic obesity remains a prevalent issue. Emerging evidence suggests a link between hypothalamic inflammation (HI) and obesity. In this study, we aimed to investigate the presence of HI before and after cCP surgery using MRI and to study the association between HI and BMI change.
Methods
We conducted a retrospective analysis of two childhood craniopharyngioma cohorts; the Dutch cohort (diagnosed between 2018-2023, $n=40$), and the German cohort (diagnosed 2019-2023, $n=67$). Preoperative and postoperative MRI scans were scored, focusing on increased T2 signal intensity (SI) changes on FLAIR, indicative of hypothalamic inflammation(HI). Change of SI in the hypothalamus after surgery was tested and the effect of clinical and radiological variables on post-operative SI was evaluated. In addition, we estimated the correlation between the change in SI and the change in BMI at 3 months postoperatively and quantified the effect of clinical and radiological variables on BMI change at 3 months with a multivariate linear regression model. Lastly, in a subgroup of patients ($n=40$), post-op signal intensity ratios were compared between patients with or without hypothalamic syndrome (HS) at 6 months.
Results
Both left ($P<0.001$) and right ($P<0.05$) hypothalamic SI increased after surgery, indicative of HI. High post-operative SI was associated with increased pre-operative SI, older age, less cystic tumors, and post-operative grade of hypothalamic lesions (Muller score). A positive correlation was found between the change in SI and BMI change at 3 months ($r=0.56$, 95% CI: 0.29–0.74). SI increase was associated with an increase in BMI Z-score ($\beta=1.02$, SE$=0.35$) after adjusting for age, tumor composition, and postoperative Muller score. Post-operative SI ratios of patients with hypothalamic syndrome ($n=17$) were found significantly higher than in those without hypothalamic syndrome ($n=23$, $P<0.01$).
Conclusion
Our data suggests that HI may contribute to the BMI increase and development of hypothalamic dysfunction observed after CP surgery. These insights offer a valuable step toward understanding the pathophysiology underlying hypothalamic dysfunction. Prospective studies are needed to confirm our findings.

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Rapid Communications 11: Thyroid Part 1

RC11.1

JOINT2292

Medullary thyroid carcinoma and pathogenic ret proto-oncogene variants in children: clinical outcomes following prophylactic/therapeutic thyroidectomy

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Introduction
Medullary thyroid carcinoma (MTC) is a rare but aggressive endocrine malignancy, often associated with variants in the *RET* proto-oncogene. *RET* variants are responsible for multiple endocrine neoplasia (MEN) syndromes (MEN2A, MEN2B). In addition to MTC, these patients may develop other MEN components, including pheochromocytoma and primary hyperparathyroidism. This study aims to evaluate the clinical outcomes of pediatric patients with MEN syndromes who has undergone either prophylactic or therapeutic thyroidectomy; and their long-term surveillance for pheochromocytoma and hyperparathyroidism.
Methods
Retrospective review of medical records of patients (aged <18 years) diagnosed with a pathogenic variant in the *RET* proto-oncogene between 2000-2024. Collected data included clinical information, biochemical markers, genetic analysis, imaging, and long-term outcomes. Histopathological evaluation classified patients as having benign (benign findings, C-cell hyperplasia) or malignant (micromedullary, multicentric MTC) pathology. Risk stratification was based on *RET* mutation status according to the 2015 American Thyroid Association (ATA) guidelines for MTC, and recurrence was defined by elevated calcitonin levels and/or radiological evidence of disease.

Results
Twenty-two *RET* variant carriers were included in the study; 54.5% ($n=12$) were male. Mean age at presentation was 6.8 ± 0.9 years (95% confidence interval [CI]: 4.8-8.9). According to risk stratification, 22.7% ($n=5$) were identified as moderate risk, 72.7% ($n=16$) as high risk, and 4.5% ($n=1$) as highest risk. All patients underwent total thyroidectomy at a mean age of 8 ± 0.9 years (95% CI: 5.9-10). Histopathological evaluation revealed benign findings in 22.7% ($n=5$), C-cell hyperplasia in 13.6% ($n=3$), micromedullary MTC in 50% ($n=11$), and multicentric MTC in 13.6% ($n=3$). No statistically significant difference was found between preoperative calcitonin levels and postoperative pathology outcomes in the benign and malignant groups ($P=0.111$). During postoperative follow-up, 27.3% ($n=6$) experienced recurrence. A significant association was found between pathology results (benign vs. malignant) and recurrence status ($P=0.041$), indicating a higher recurrence rate in malignant cases. During the follow-up period (mean: 5·9 $\pm$ 0·8 years) no cases of pheochromocytoma or hyperparathyroidism were observed.
Conclusions
Close monitoring of *RET* variant carriers is essential for early detection and management of MTC. Despite prophylactic thyroidectomy and subsequent diagnosis of MTC, recurrence occurred in some patients, highlighting the necessity of long-term follow-up. Preoperative calcitonin levels did not serve as a reliable predictor of malignancy, thus further research is needed to identify alternative biomarkers. Family screening enables the early identification of at-risk children, allowing prophylactic thyroidectomy to effectively prevent MTC.

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RC11.2

JOINT3378

Different thyroid hormone profiles in women with euploid compared to aneuploid pregnancy loss – a prospective cohort study

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Background
Thyroid dysfunction is associated with adverse reproductive outcomes including pregnancy loss. Approximately 55% of pregnancy losses are due to lethal chromosome abnormalities (aneuploid losses), whereas fetuses with a normal number of chromosomes (euploid) are potentially viable. Euploid pregnancy loss is suspected to be due to maternal comorbidity, e.g. thyroid dysfunction, although this has not previously been studied. We investigated if thyroid function and autoimmunity were associated with the risk of euploid pregnancy loss.
Methods
Prospective cohort study of women experiencing pregnancy loss at three Danish University hospitals (2020–2024). Blood was drawn at the time of pregnancy loss and at follow-up four to eight weeks after. Analyzes included thyroid stimulating hormones (TSH), free and total thyroxine (FT4, TT4), total triiodothyronine (TT3), human chorionic gonadotropin (hCG), thyroid peroxidase and thyroglobulin antibodies (TPOAb, TgAb). Antibody positivity: >60 kIU/l. Fetal chromosome status was determined by cell-free fetal DNA or fetal tissue sequencing to detect aneuploidy. Logistic regression models were adjusted for age, gestational week, body mass index, and thyroid medication use.
Results
A total of 1,031 out of 2,018 (51%) pregnancy losses were euploid. The euploid pregnancy loss risk did not differ according to TSH (adjusted odds ratio (aOR) 0.9, 95% confidence interval (CI) 0.8;1.1), FT4 (aOR 1.0, 95%CI 1.0;1.0), TPOAb positivity (aOR 0.99, 95%CI 0.68;1.43), or TgAb positivity (aOR 0.96, 95%CI 0.66;1.41). In contrast, the euploid loss rate was higher in women with TT3 >2.6 nmol/l (laboratory cut-off) vs TT3 ≤ 2.6 nmol/l ($n=61/85$, 71.8% vs. $n=470/1,521$ 48.6%, $P<0.001$) and TT4 >140 nmol/l (laboratory cut-off) vs ≤ 140 nmol/l ($n=248/425$ 58.4% vs. $n=552/1,180$ 46.8%, $P<0.001$). Also, in the adjusted regression models the euploid pregnancy loss risk was positively associated with TT3 concentration (aOR) 2.0, 95%CI 1.5;2.6) and TT4 concentration (aOR 1.09, 95%CI 1.05;1.13). This remained significant when further adjusting for TSH, TPOAb, TgAb, and hCG concentrations (TT3 aOR 2.7, 95%CI 1.44;5.33, and TT4 aOR 1.16, 95%CI 1.06;1.27). Noteworthy, 15 of 18 (83%) women with high TT3 and TPOAb- or TgAb-positivity had a euploid pregnancy loss. The majority of women with high TT3 or TT4 at inclusion had normalized hormone concentrations at follow-up ($n=49/52$, 94.2% for TT3 and $n=256/291$, 88.0% for TT4).
Conclusion
Women experiencing a euploid pregnancy loss have higher TT3 and TT4 concentrations at the time of the loss, but not outside of pregnancy. The mechanisms, including a potential interplay with thyroid antibody-positivity, needs further exploration.

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RC11.3

JOINT2350

Proteomics-based identification of novel biomarkers for assessing severity and predicting recurrence in graves' thyrotoxicosis

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Background
Graves' disease (GD) is an autoimmune disorder causing hyperthyroidism, primarily assessed by TSH-receptor-stimulating antibodies (TRAb). However, TRAb variations (blocking or neutral) can lead to misjudgments in disease severity and treatment duration. This study aims to identify novel biomarkers for GD severity and recurrence using proteomics analysis of blood samples.
Methods
We analyzed 121 plasma samples from 63 patients diagnosed with GD (first-time or recurrent after ≥ 2 years remission) between March 2019 and June 2023 at Skåne University Hospital, Sweden. Proteomics analysis was performed at baseline, 3- and 12-months post-antithyroid drug (ATD) treatment.
Results
A total of 758 proteins were identified. Independent of GD severity and recurrence status, the following proteins were significantly upregulated at 3 and 12 months post-treatment: SERPINA7 (Thyroxine-binding globulin, TBG) – a key thyroid hormone transport protein; Transthyretin (TTR) – essential for thyroid hormone and vitamin A transport; Apolipoprotein D (APOD) – involved in lipid transport; Adipocyte plasma membrane-associated protein (APMAP) – associated with metabolic processes. Conversely, significantly downregulated proteins at 3 and 12 months included: Cadherin 5 (CDH5) – vital for endothelial cell adhesion; Factor H-related protein 5 (FHR5) – regulator of the complement immune system; Coagulation Factor XIII B chain (F13B) – a key component in blood coagulation; Sex hormone-binding globulin (SHBG) – regulates sex hormone bioavailability.
Conclusion
Proteomics analysis identified significant protein alterations post-ATD treatment in GD patients. Upregulated proteins are linked to hormone transport and metabolism, while downregulated proteins are associated with vascular integrity, immune regulation, and hormone bioavailability. These findings suggest potential biomarkers for monitoring GD progression and treatment response, warranting further validation.

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RC11.4

JOINT1029

The role of ferroptosis as a novel alternative cell death model in thyrocytes from Hashimotós thyroiditis patients

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Introduction
Autoimmune thyroid disorders (AITD) are organ-specific diseases that result from the dysregulation of the immune system homeostasis, leading to an immune response against self-thyroid antigens. The main AITD are Hashimotós thyroiditis (HT) and Graveś disease (GD). Ferroptosis is an intracellular iron-dependent form of cell death that involves the generation of reactive oxygen species, which increases oxidative stress and lipid peroxidation. Glutathione peroxidase 4 (GPX4) has a key role in reducing lipid peroxides into lipid alcohols, preventing ferroptosis. The high oxidative stress and the thyroid folicular cells (TFCs) death that takes places in HT patients suggests that ferroptosis could represent an alternative cell death pathway in HT pathogenesis.
Methodology
We analyzed lipid peroxidation with a sensor for lipid peroxidation (BodipyTM 581/591 C11) in a human thyroid follicular cell line stimulated with HT-associated proinflammatory cytokines (IFN-γ and TNF-α), ferroptosis inductors (RSL3 and erastin) and inhibitors (ferrostatin-1). At the same time, we evaluated cell death with the 7-AAD Staining Solution. We evaluated the levels of ferrous ion (Fe^{2+}), a ferroptosis inductor, in cellular models with an iron sensing dye (FerroOrange). We measured the expression of GPX4 and lipid peroxidation products, such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) in thyroid tissue and *in vitro* models by Western Blot (WB) and image.
Results
We observed an increase of lipid peroxidation and cell death in thyrocytes stimulated with IFN-γ and TNF-α. This increase was similar with the ferroptosis inductors RSL3 and erastin and, interestingly, this effect was reverted by ferrostatin-1. Furthermore, IFN-γ and TNF-α decreased GPX4 expression and increased Fe2+ levels. In thyroid tissue, GPX4 expression was downregulated in TFCs from HT patients compared to controls or GD. Although MDA expression did not change between conditions, the levels of 4-HNE, a lipid peroxidation product, were increased in HT, suggesting a relationship between ferroptosis and HT pathogenesis.
Conclusions
Our data indicates that ferroptosis may constitute a novel alternative cell death model in HT pathogenesis because of the proinflammatory microenvironment.

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RC11.5

JOINT2037

Thyrosense – a sensing device for monitoring of thyroid-stimulating hormone

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Introduction
Hypothyroidism affects 200 million people globally, with 4 million new diagnoses annually. Despite thyroid-stimulating hormone (TSH)-guided levothyroxine (LT4) replacement therapy, many patients experience persistent symptoms and impaired quality of life. TSH monitoring is recommended every 4-8 weeks upon diagnosis or treatment modification, with increased frequency during pregnancy and 1-2 times per year for maintenance. However, up to 50% of patients show TSH levels outside the reference range, increasing the risk of symptoms, pregnancy complications, and comorbidities associated with dysregulation. Current laboratory-based testing is costly and inconvenient, limiting patient compliance, and delaying treatment adjustments.
Objective
We present data on the ThyroSense prototype, a point-of-care (POC) home monitoring device that provides real-time, quantitative TSH measurements. This technology aims to improve disease self-management, reduce healthcare visits, and enhance treatment precision.
Methods
The ThyroSense system comprises a handheld reader, a single-use cartridge containing a test strip, and a companion mobile application. It utilizes a novel proprietary sensing chemistry for TSH detection. Analytical performance was assessed using electrochemical impedance spectroscopy, ELISA (for the selectivity tests), and anonymous clinical plasma samples. Clinical samples were pooled for biological normalization to TSH concentrations of 1, 5, and 10 mIU/l, respectively.
Results
The ThyroSense sensor demonstrated high specificity for TSH, with no significant cross-reactivity to luteinizing hormone, follicle stimulating hormone, and human chorionic gonadotropin hormone, showing relative signal levels of 3%, 4%, and 3%, respectively, at equivalent TSH concentrations. TSH was quantified within a range of 0-10 mIU/l with a detection limit of 0.2 mIU/l and a coefficient of variation of 10.7-13.0%. Results were obtained within 5 minutes of sample application.
Conclusions
There are currently no quantitative home-based TSH monitoring devices available. ThyroSense offers a cost-effective (aimed at <5£/test), user-friendly solution that can enhance treatment adherence and personalized care, particularly for newly diagnosed patients, before and during pregnancy, treatment adjustments, and long-term monitoring. Additionally, this device may facilitate research on TSH kinetics and treatment responses, potentially improving hypothyroidism management.

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RC11.6

JOINT2486

Evaluation of congenital hypothyroidism cases diagnosed through newborn screening and predictive factors for transient forms

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Introduction
Congenital hypothyroidism (CH), a leading cause of preventable intellectual disability in children, can be identified early in life through newborn screening (NBS) programs. This study aims to analyze the clinical and biochemical characteristics of CH patients and identify predictive factors for transient CH (T-CH) in children diagnosed through NBS.
Methods
This retrospective study included a total of 322 term neonates (M/F = 163/159) diagnosed through NBS and initiated on levothyroxine therapy between 2006 and 2020. Patients were classified as thyroid dysgenesis (TD) or gland in situ (GIS) (dyshormonogenesis, DH) based on ultrasonography. Exclusion criteria included T-CH due to maternal factors, prematurity; syndromic and central CH. Cases with T-CH and permanent CH (P-CH) were compared based on gender, baseline thyroid hormone levels, and levothyroxine dosage at presentation and during follow-up (at 6 months, 1 year, 2 and 3 years). P-CH was diagnosed in patients whose TSH >10 μIU/ml following the discontinuation of levothyroxine therapy after at least 3 years of follow-up. Predictive factors for T-CH were identified.
Results
Among the cases, 22.7% ($n=73$) were categorized as TD, and 77.3% ($n=249$) as DH. Overall, 60.2% ($n=194$) of the patients were identified as having T-CH, while 39.8% ($n=128$) were classified in the P-CH group. Ultrasonography revealed thyroid agenesis in the majority (53.4%, $n=39$) of cases in the TD group. Screening TSH levels, initial venous TSH levels, initial treatment doses, and treatment doses at 6 months, and at 1, 2, and 3 years were significantly higher in the TD group ($P=0.001$ for all except the initial treatment dose, $P=0.006$). In DH group, after re-evaluation, 55 patients (23%) required restarting levothyroxine treatment and were diagnosed of P-CH. Among DH cases, mean heel blood TSH levels were significantly higher in the P-CH group (50.4 ± 30.7 mIU/l) compared to the T-CH group (28.2 ± 20.4 mIU/l) ($P=0.001$). Furthermore, in the P-CH group, treatment doses at the 1st, 2nd, and 3rd years were significantly higher than in the T-CH group ($P<0.001$ for all). ROC analysis identified levothyroxine dose thresholds for predicting T-CH as 2.1, 1.9, and 1.5 mg/kg/day at 1, 2, and 3 years, respectively.
Conclusion
This study identifies levothyroxine dose thresholds during first 3 years of life, to distinguish transient and permanent CH. Systematic re-evaluation, especially in DH cases at 3 years or even earlier, is crucial for minimizing unnecessary treatments and optimizing long-term follow-up plans. These findings support a tailored approach to CH management.
Key words: Congenital hypothyroidism, Newborn screening, Transient congenital hypothyroidism

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Rapid Communications 13: Adrenal and Cardiovascular Endocrinology Part 2

RC13.1

JOINT2848

Constitutional duplication of PRKACA causes primary pigmented nodular adrenocortical disease (PPNAD) and generates new chromatin interactions

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Objective

Constitutional duplications of the *PRKACA* gene locus (encoding the catalytic subunit of the Protein Kinase A) have been described in rare cases of Cushing's syndrome due to bilateral nodular adrenocortical diseases (BNAD). The pathological description according to the current WHO definition of adrenal tumors still needs to be reported. The objective here was to evaluate the results of the systematic screening of PRKACA constitutive duplication in BNAD and to specify the associated hormonal and pathological phenotype.

Methods

Between 2020 and 2024, 781 index cases diagnosed with BNAD: bilateral macronodular adrenal disease (BMAD) ($n=693$) or primary pigmented nodular adrenocortical disease (PPNAD) ($n=88$) (14% of isolated PPNAD) were genotyped with a targeted Next Generation Sequencing (NGS) panel including the exonic and intronic flanking regions of the *ARMC5*, *KDM1A*, *MEN1*, *PRKAR1A* and *PRKACA* genes, or by whole genome sequencing. Familial screening was offered to relatives. In situ Hi-C libraries were generated from three patients' tumors and chromatin conformation analysis were performed.

Results

Constitutional duplications of *PRKACA* were identified in 8 index cases and 7/11 screened relatives (sex-ratio = 1 male/2.5 female), supporting the involvement of the *PRKACA* oncogene through a constitutional copy gain mechanism. The whole genome sequencing performed on 4 index cases did not find any other gene involved in human pathology in the duplicated region, nor any other alteration in genes implicated in adrenal pathology. *PRKACA* tandem duplications generated neo-Topologically Associating Domains (TADs) (150kb), self-interacting genomic regions, in patient derived tumor Hi-C maps compared to Micro-C data from human embryonic stem cell line. All index cases and 6/7 relatives had PPNAD responsible for ACTH-independent hypercorticism, diagnosed at a median of 21 years old (range 9-35) and treated by bilateral adrenalectomy. The resected adrenals contained micronodules, composed mainly of large eosinophilic cells containing lipofuscin vacuoles, separated by patches of atrophic cortex, making the diagnosis of PPNAD. Similar staining was found with PRKACA and PRKAR1A antibody in these nodules and adjacent cortex, whereas in patients with PRKAR1A pathogenic variants, PRKAR1A staining was decreased in the nodule, compared to adjacent cortex.

Conclusion

Constitutional duplication of PRKACA is causing PPNAD (9% of index cases with PPNAD in this cohort), but no other forms of BNAD. Immunohistochemistry may differentiate the genetic background of PPNAD (*PRKAR1A* pathogenic variants *versus PRKACA* duplications). *PRKACA* tandem duplications generated neo-TADs in patient derived tumor Hi-C maps, pointing to specific regions of gene expression dysregulation induced by *PRKACA* duplication in BNAD.

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RC13.2

JOINT955

Imaging bias in patients with adrenal adenomas

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Background

Although an association between adrenal adenomas and various cardiovascular and metabolic risk factors has previously been noted, it is suspected that patients with pre-existing comorbidities are more likely to be diagnosed with incidental adrenal adenomas due to increased frequency of imaging.

Methods

Historical case-control population study was performed. Patients diagnosed with adrenal adenoma between 2005-2017 with no evidence of overt hormone excess were paired with two different age- and sex-matched control groups without diagnosis of adrenal adenoma. To represent the general population, the first control group was randomly chosen from the same population matched on age and sex. The second control group only included patients who had a CT/MRI scan performed within 5 years prior to the index date (date of adrenal adenoma diagnosis). The prevalence of various social and metabolic risk factors present within 10 years prior to index date was compared across groups.

Results

Total of 670 cases identified. Patients with adrenal adenoma had a higher median body mass index (BMI) at 10 years prior to index date compared to the general population as well as the control group with prior imaging (30.1 kg/m^2 vs 27.4 kg/m^2 and 28.2 kg/m^2, respectively $P<0.001$). Cases were in a lower socioeconomic (SES) percentile based on Area Deprivation Index (ADI) at 10 years prior to index compared to controls (36.7% in poverty (ADI national percentage 51-100) vs 34.4% in the general population group and 31.1% in the control group with imaging, $P=0.116$). Compared to the general population control group, patients with adrenal adenoma were found to have higher prevalence of tobacco use, substance use, obesity, hypertension, dyslipidemia, pre-diabetes, and diabetes at 5-10 years prior to index date. However, when compared to the control group with prior cross-sectional imaging, the only differences that persisted were higher prevalence of obesity, tobacco use, and diabetes in patients with adrenal adenoma.

Conclusions

Previously noted associations between some cardiovascular/metabolic risk factors and adrenal adenomas are likely confounded by imaging bias. When compared to controls who had cross-sectional imaging performed within the past 10 years, patients with adrenal adenomas still had higher prevalence of obesity, tobacco use, and diabetes prior to index date.

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RC13.3

JOINT502

Adrenal aldosterone synthase (CYP11B2) histopathology and its association with disease-induced sudden death

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Background

//tgcqSudden death is a high-priority public health concern, affecting at least 249,500 individuals each year in the European Union. Unidentified cardiovascular risk factors may account for approximately half of sudden deaths, a devastating event with limited preventive tools. We investigated whether adrenal histopathology suggestive of primary aldosteronism could explain part of the risk for disease-induced sudden death (DSD).

Methods

In this cross-sectional study, autopsies and histopathological analyses, including aldosterone synthase staining of adrenal glands, were performed on 403 consecutive individuals who experienced sudden death. These individuals were classified into 258 cases of DSD and 144 deaths caused by trauma, suicide, or intoxication, i.e., non-disease-induced sudden death (nDSD). Histopathological analysis followed the HISTALDO consensus. A four-grade classification of CYP11B2 positivity was used in the analyses with the following categories:1) aldosterone-producing adenomas

(APA) or nodules (APN), 2) aldosterone-producing micronodules (APMs) <20, 3) APMs ≥20, or 4) diffuse CYP11B2 positivity. This trial was registered at ClinicalTrials.gov (NCT05446779).

Findings

Adrenal histopathology revealed changes in 31 (7·7%) subjects of the cohort. Of these, the most prevalent findings [25 (6·2%)] were APA or APN, which were associated with myocardial infarction and atherosclerosis at autopsy. Individuals in the DSD group and the subgroup with sudden cardiac death (SCD) were more likely to have APA or APN than individuals in the nDSD group [23 (8·9%) vs. 2 (1·4%), $P=0·002$; 16 (8·8%) vs. 2 (1·4%), $P=0·003$, respectively]. Among all study subjects, heart weight, left ventricular wall thickness and the degree of aortic atherosclerosis showed an increasing trend with decreasing CYP11B2 continuity. In logistic regression analyses APA or APN were explanatory factors for DSD (odds ratio [OR] 6·47, 95% confidence interval [CI] 1·40-29·88, $P=0·017$) and SCD (OR 10·68, 95% CI 2·02-56·43, $P=0·005$).

Conclusions

Histopathological findings of APA or APN were observed more frequently in DSD and SCD cases than in nDSD cases and emerged as significant independent predictors of sudden death. The presence of APA or APN, along with a reduction in CYP11B2 continuity indicative of potential autonomous aldosterone production, was associated with markers of cardiovascular morbidity at autopsy. Timely diagnosis and effective treatment of PA may help extend the lifespan of individuals with CYP11B2-positive adrenal pathology. However, whether systematic biochemical screening for PA, targeted MRA therapy, or a combination of both should be implemented to reduce the risk of sudden death requires further investigation.

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RC13.4

JOINT744

Primary adrenal insufficiency in the young, consider APS-1

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Background

Autoimmune polyendocrine syndrome type-1 (APS-1) is a rare severe organ-specific autoimmune disease often presenting in childhood. A clinical diagnosis is made by the presence of at least two of the main manifestations: chronic mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency (PAI). Other relatively specific manifestations are enamel hypoplasia and severe alopecia. The phenotypic variation is huge overlapping with the much more common autoimmune polyendocrine syndrome type-2 (APS-2). Thus, there is a significant risk of delayed or missed diagnosis.

Objective

We investigated presentation of PAI in patients with APS-1 and -2 and isolated PAI to look for overlapping features, and to see if the diagnosis APS-1 had been missed.

Methods

Forty-eight Norwegian patients with APS-1 (age range 2-79 years) were compared with 1001 patients with isolated PAI or APS-2 (age range 5-100 years). APS-1 was confirmed by presence of disease-causing mutations in the autoimmune regulator gene (*AIRE*). Clinical examinations and assay of autoantibodies were conducted longitudinally.

Results

PAI was present in 35/48 (73%) APS-1 patients with a mean onset of 14.9 years (range 4-55 years) compared with 35 years (range 1-86 years) in the isolated PAI/APS-2 group. PAI was diagnosed after 20 years of age in 5 APS-1 patients and 55 years of age in one patient. Three of these already had developed hypoparathyroidism and therefore were clinically diagnosed with APS-1. The other three had no apparent APS-1-like manifestations, but they were positive for interferon omega autoantibodies on screening. The APS-1 diagnoses were subsequently confirmed by finding disease-causing mutations in *AIRE*.

Conclusions

PAI can present late in APS-1 without the other main manifestations. In patients younger than 30 years of age at PAI debut, APS-1 should be suspected by searching for other autoimmune manifestations and ideally by testing for interferon omega autoantibodies.

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RC13.5

JOINT3318

Crinecerfont improves reproductive hormones in classic congenital adrenal hyperplasia: 1-year results from the phase 3 CAHtalyst™ adult study

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Background

//tgcqGonadal dysfunction with classic congenital adrenal hyperplasia (CAH) is due to testicular adrenal rest tumors and/or poor hormonal control (males) and to high adrenal androgens and progesterone (P4) (females). Crinecerfont, a corticotropin releasing factor type 1 receptor (CRF1) antagonist, is FDA-approved for adjunctive treatment to glucocorticoid (GC) replacement to control androgens in patients with CAH. In CAHtalyst™ Adult (NCT04490915), least-squares mean (LSM) percent changes in GC dose at Week 24 (end of double-blind placebo-controlled period) indicated a significant reduction with crinecerfont (-27.3% vs -10.3% for placebo; LSM difference -17.0%; $P<0.0001$) while androstenedione (A4) was maintained/improved relative to Day 1 baseline (BL). At Month 12 (end of open-label period), mean percent decreases from BL were -24.6% in participants continuing crinecerfont (CFT/CFT) and -29.7% in those switching from placebo (PBO/CFT).

Objective

To evaluate reproductive hormone changes in adults with CAH who received up to 1 year of crinecerfont, in the context of substantial GC dose reductions.

Methods

Analyses conducted at Week 24 and Month 12 were as follows: luteinizing hormone (LH), follicle stimulating hormone (FSH), A4-to-testosterone ratio (A4/T) in males; testosterone (T) and P4 in females. Males included for analysis had abnormal (low or high) LH, abnormal FSH, or A4/T ≥0.5 at BL. Females had elevated T or P4 at BL, with analysis conducted without regard to menstrual cycle phase. In participants with abnormal values at BL, results are presented as % (n/N) (n=number achieving normalisation; n=number with available assessments).

Results

The percentages of males achieving normal/target levels at Week 24 with crinecerfont vs placebo were: LH (47.4% [9/19] vs 22.2% [2/9]); FSH (13.3% [2/15] vs 14.3% [1/7]); A4/T (18.9% [7/37] vs 4.5% [1/22]). Results at Month 12 for CFT/CFT and PBO/CFT were: LH (64.7% [11/17], 44.4% [4/9]); FSH (35.7% [5/14] , 14.3% [1/7]); A4/T (23.5% [8/34], 23.8% [5/21]). The percentage of females achieving normal levels at Week 24 were: T (10.7% [3/28] vs 0% [0/11]; P4 (13.5% [5/37] vs 5.9% [1/17]). Results at Month 12 for CFT/CFT and PBO/CFT were: T (3.7% [1/27], 9.1% [1/11]); P4 (8.6% [3/35], 18.8% [3/16]).

Conclusion

Crinecerfont has been shown to reduce ACTH, androgens, and androgen precursors in paediatric and adult patients with CAH. These analyses from CAHtalyst Adult indicate potential normalisation of reproductive hormones with crinecerfont, even with substantial GC dose reductions. CRF1 antagonism may be a promising therapeutic approach for improving reproductive hormones in adults with CAH.

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RC13.6

JOINT3270

Crinecerfont enables glucocorticoid dose reductions while maintaining/improving androstenedione in paediatric patients with congenital adrenal hyperplasia: subgroup analyses from CAHtalyst™ paediatric

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Background
Crinecerfont, a corticotropin releasing factor type 1 receptor antagonist, is a first-in-class medication that is FDA-approved for adjunctive treatment to glucocorticoid (GC) replacement to control androgens in patients with classic congenital adrenal hyperplasia (CAH). In phase 3 trials, crinecerfont significantly reduced excess androgens, enabling subsequent GC dose reductions in paediatric and adult patients with CAH.
Objective
To analyse changes in androstenedione (A4) levels and GC dose reductions while maintaining/improving A4 in subgroups of participants from CAHtalyst™ Paediatric (NCT04806451).
Methods
Participants were randomised 2:1 to double-blind treatment with crinecerfont (25, 50, or 100 mg BID based on weight) or placebo for 28 weeks. GC doses were kept stable for 4 weeks to evaluate the impact on androgens and then reduced to a target of 8-10 mg/m^2/d in hydrocortisone equivalents (HCe) by Week 28 while maintaining/improving A4 relative to baseline (BL). Least squares (LS) mean changes from BL in A4 (before morning GC dose) at Week 4 and in GC dose at Week 28 were analysed in the overall population and in subgroups defined by: region (US, outside US); sex (male, female); race (white, non-white); age (<12, 12-17 years); weight (<55, ≥ 55 kg); body mass index (BMI) (<85th, ≥ 85th percentile); pubertal stage (Tanner 1-2, 3-5); BL A4 ($\leq$ULN [upper limit of normal], $>$ULN); and BL GC dose (<16, ≥ 16 mg/m^2/d HCe, for GC change only).
Results
Among 103 participants (crinecerfont = 69, placebo = 34), mean age ($\pm$SD) was 12.1 $\pm$ 3.5 years; 51% were male. Mean A4 at BL was 15.0 $\pm$ 16.1 nmol/l; mean GC dose was 16.4 $\pm$ 3.9 mg/m^2/d. At Week 4, A4 was significantly reduced with crinecerfont but increased with placebo (-6.9 vs. +2.5 nmol/l; LS mean difference [LSMD]: -9.3 nmol/l; $P = 0.0002$). LSMDs of the point estimates for A4 change at Week 4 favoured crinecerfont in all subgroups. At Week 28, GC dose was significantly reduced with crinecerfont (while maintaining or improving A4) but increased with placebo (-18.0% vs. +5.6%; LSMD: -23.5%; $P < 0.0001$). LSMDs of the point estimates for percent change in GC dose at Week 28 favoured crinecerfont in all subgroups. All subgroup results were consistent with the overall population.
Conclusion
Crinecerfont enabled GC dose reductions while maintaining/improving A4 in paediatric patients with CAH across multiple subgroups. These results demonstrate that paediatric patients with CAH can derive the androgen-lowering and GC-lowering benefits of crinecerfont regardless of region, sex, race, age, weight/BMI, pubertal stage, or pretreatment A4 level or GC dose.

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Rapid Communications 14: Growth Axis and Syndromes

RC14.1

JOINT1438

Long-term efficacy and safety of once-weekly somapacitan in children with growth hormone deficiency: 7-year results from the randomised REAL 3 trial

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REAL 3 (NCT02616562) is a phase 2, randomised, multinational, open-label, active-controlled trial designed to determine treatment efficacy and safety of somapacitan, a long-acting growth hormone (GH) derivative, vs daily GH (Norditropin®, Novo Nordisk). Results after 4 years have been published (Sävendahl *et al*. *JCEM* 2023;108(10):2569-78). Here, we report final results at 7 years (364 weeks), representing the longest analysis of patients treated with somapacitan to date. Prepubertal children were recruited to three cohorts (I: GH-naïve, 2.5 to 9/10 years for girls/boys respectively; II: <2.5 years; III: 9/10 to 17 years for girls/boys, respectively). In cohort I, participants were randomised 1:1:1:1 to somapacitan (0.04 vs 0.08 vs 0.16 mg/kg/week) or daily GH 0.034 mg/kg/day. After 52 weeks, participants on somapacitan were all switched to the 0.16 mg/kg/week dose, while participants on daily GH continued unchanged. After 156 weeks, all participants, including those previously on daily GH, received somapacitan 0.16 mg/kg/week during a further 208-week long-term safety extension. Cohorts II and III only participated between weeks 156–364 and received somapacitan 0.16 mg/kg/week. In cohort I, 33 of 45 participants randomised to somapacitan (somapacitan-only group) and 10 of 14 participants randomised to daily GH (switch group) completed the long-term safety extension. Completion was similarly high in cohorts II ($n = 1/1$) and III ($n = 11/16$). Two participants in cohort I achieved near adult height by week 364. Efficacy results (mean [SD]) are reported for cohort I at week 364. Height velocity (HV) was 5.7 (2.2) cm/year in both groups and HV standard deviation scores (SDS) were 0.47 (1.13) and 0.57 (1.16) in the somapacitan-only and switch groups, respectively. Height SDS was -0.39 (1.15) in the somapacitan-only group and -0.54 (0.76) in the switch group. Year-on-year increases in height SDS were observed after week 156 in both groups. Insulin-like growth factor-I (IGF-I) SDS was 0.64 (1.68) and 0.79 (1.02) in the somapacitan-only and switch groups, respectively. Safety was assessed across all cohorts and no new safety signals were observed. Total patient-years of exposure to somapacitan 0.16 mg/kg/week was 327.4. After 7 years (364 weeks) of treatment, height SDS and IGF-I SDS were within the reference range (-2 to $+2$ SDS). Similar responses were observed in patients treated with somapacitan throughout the trial and in those who switched from daily GH after 156 weeks. No side effects for somapacitan outside the known safety profile of daily GH were identified.

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RC14.2

JOINT2695

Unexpected unbalanced upregulation of genes in gene replacement therapy with a constitutively active promoter and growth hormone receptor (GHR) in mice with nonfunctional GHR (laron mice)

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Gene replacement therapy where a dysfunctional or non-functional gene is treated with *in vivo* delivery of a functional gene almost always utilizes a constitutively active promoter/enhancer to enable expression of the therapeutic gene product. These promoters typically lack the complex regulation that is normally present in the endogenous gene. We have treated growth hormone (GH) resistant dwarf GHR-/- (Laron) mice with nonfunctional GH-receptors, with an adeno-associated virus (AAV) with a constitutively liver specific promoter (HLP) and mouse GHR (Sia et al, 2021). A single injection of the AAV-HLP-GHR construct resulted in significant but limited increase in length and weight, of a similar order to previously reported studies of IGF-1 treatment in mice or human Laron syndrome. In the present study, we have compared the total gene expresssion profiles from the mice in that previous study. Profiles of total RNA extracted from fresh frozen livers from the 4 groups of mice (3 male and 3 female in each group) were sequenced (Novogene-AIT Genomics, Singapore) and compared: Untreated GHR+/+, and GHR-/- (Laron); GHR-/- treated with AAV-HLP-GHR (AAV-GHR), and control GHR-/- treated with AAV-HLP-luciferase (AAV-luc) only. Gene expression differed significantly in only 4 genes comparing control AAV-luc and untreated GHR-/- (Laron), indicating minimal effect of the AAV-HLP promoter. Gene expression between GHR+/+ and GHR-/- (Laron) differed significantly in 2913 genes. In contrast, treatment with AAV-GHR compared with AAV-luc showed that only 448 genes were differentially expressed significantly. There was significant upregulation of key genes involved in IGF signaling; GHR, insulin-like growth factor-1 (IGF-1) and acid-labile subunit (ALS). However, of the significant upregulated 201 genes in AAV-GHR compared to AAV-luc, growth/cancer-related genes were upregulated/rescued significantly more than metabolism-related genes towards the normal gene expression levels in the wild type mice (GHR+/+). This unexpected unbalance upregulation is most probably the result of the absence of the normal complex regulation of the GH-receptor.
Conclusion
Gene replacement therapy utilizing a consitutively active promoter/enhancer may have unexpected unbalanced changes in gene expression.

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RC14.3

JOINT1443

AKT and PI3K inhibitors are more efficient in inhibiting growth of Proteus syndrome patient cells compared to mTOR inhibition

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Background
Patients with somatic activating variants in the *AKT1* gene (Proteus syndrome) show symptoms like segmental overgrowth, increased tumor risk and vascular malformations. AKT is a central signaling molecule in the growth-promoting phosphoinositide-3- kinase (PI3K)/mTOR pathway and different pathway inhibitors are used for cancer therapy or related overgrowth syndromes. While there is no approved therapy for Proteus patients, benefits of treatment with the mTOR inhibitor rapamycin were described. We aim to evaluate the therapeutic potential of rapamycin as well as the PI3K inhibitor alpelisib and the AKT inhibitor capivasertib in a patient-derived cell model.
Methods
Fibroblasts from a 3-year old patient with segmental overgrowth, harboring an activating AKT1 (E17R) variant, were treated with rapamycin, alpelisib, and capivasertib *in vitro*. We evaluated cell proliferation, viability, and signaling via automated cell counting, WST-1 cell viability assays, and Western blots. Nuclei size was measured using the Spark Cyto multimode imaging plate reader.
Results
While all inhibitors significantly decreased cell count after 72 h of treatment, there were observable differences between mTOR and AKT/PI3K inhibition. Rapamycin reduced growth of the patient cells by 20% already at concentrations of 1 nM, but higher doses could not further reduce proliferation. In contrast, alpelisib reduced proliferation in a dose-dependent manner by 44% at 10 µM and 55% at 50 µM and capivasertib by 23% at 2 µM and 46% at 10 µM. We observed that all inhibitors had direct effects on cell viability already after 1 h of treatment (1 nM rapamycin reduced viability by 8%, 50 µM alpelisib by 56% and 10 µM capivasertib by 12%), indicating an immediate inhibition of cellular metabolism as detected in WST-1 assays. Nuclei size of patient fibroblasts was increased by 8% compared to control fibroblasts, which was reversed by inhibitor treatment. As observed in Western blots, each of the inhibitors effected cellular signaling differentially: While rapamycin was most effective in blocking activation of downstream mTOR signaling components p70S6K and ribosomal protein S6, it increased AKT1 activation. Alpelisib was less effective in blocking mTOR downstream signaling, but highly effective in reducing AKT activation and downstream GSK3β phosphorylation. Capivasertib reduced S6 and GSK3β phosphorylation.
Conclusion
Inhibitors of the PI3K/mTOR pathway effectively reduce growth of patient-derived fibroblasts with an activating *AKT1* variant. While rapamycin is effective in nanomolar doses, alpelisib and capivasertib decrease cell growth further. This might indicate a higher efficiency of these drugs in patients with overgrowth related to *AKT1* variants.

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RC14.4

JOINT1531

Neurodevelopmental outcomes in silver russell syndrome: the impact of molecular causes

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Background
Silver Russell Syndrome (SRS) is a rare imprinting disorder associated with prenatal and postnatal growth restriction, relative macrocephaly, feeding difficulties, protruding forehead and asymmetry. Primary molecular causes are loss of methylation within 11p15.5 imprinting control region (*H19/IGF2*), [11p15LOM] and maternal uniparental disomy of chromosome 7, [upd(7)mat]. There is limited research on neurodevelopmental outcomes in SRS patients.
Objective
Determine prevalences of neurodevelopmental disorders in a large cohort of molecularly-confirmed SRS patients and compare these prevalences among the SRS diagnostic groups and US general population [genUS].
Methods
297 subjects > 2 years old were divided by SRS molecular cause (including 11p15LOMn = 164, upd(7)matn = 99). Questionnaires about neurodevelopmental disorder diagnoses and treatments were completed by guardian or adult self. Reported diagnoses were confirmed by a qualified specialist.
Results
Speech articulation disorder prevalence was greater in upd(7)mat group (68%) than 11p15LOM group (24%), and both prevalences were significantly greater than in genUS (9%). Childhood speech apraxia was more prevalent in upd(7)mat group (24%) compared to 11p15LOM (3%) group, and both prevalences were greater than in genUS (0.1%). More upd(7)mat subjects had delayed onset of speech (> 18 mos) than 11p15LOM subjects (52% versus 20%). Two individuals > 6 yrs were non-verbal in each molecular group. Autism spectrum disorder (ASD) was more prevalent in upd(7)mat group (28%) than both 11p15LOM group (5%) and genUS (2.8%). The male to female distribution of ASD was ~1:1 in the upd(7)mat group, compared to 4.8:1 in the 11p15LOM group and 4:1 in genUS. Attention Deficit Hyperactivity Disorder prevalence was not statistically different between upd(7)mat (29%) and 11p15LOM (16%) groups, although the upd(7)mat prevalence was significantly greater than genUS (11.4%). Prevalences of intellectual disability, (IQ < 75), and learning disorders were 22% and 39%, respectively, in upd(7)mat group, significantly higher than rates observed in 11p15LOM group (2% and 7%), and genUS (2.20% and 9%). However, upd(7)mat group had a normal distribution in academic performance, compared to classmates, whereas 11p15LOM subjects were skewed with 69% performing in the top third of their classes.
Conclusion
Our study shows SRS upd(7)mat individuals are at higher risk for neurodevelopmental disorders than 11p15LOM individuals and/or genUS. Aside from speech disorders, SRS 11p15LOM individuals are overall neuro similar to genUS. Understanding the prevalence of neurodevelopmental disorders in children with SRS allows for better surveillance, diagnosis and intervention. Given the 1 in 4 chance of ASD in upd(7)mat, careful monitoring for ASD could increase opportunities for early intervention.

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RC14.5

JOINT2858

Pituitary gigantism: what differences beyond height can we expect compared to acromegaly? a comparison of clinical features and mortality in 3244 patients

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Introduction
Pituitary gigantism and acromegaly, both resulting from excessive growth hormone (GH) production, share the same pathophysiology. The main differences are the age of onset and the patient's height at diagnosis. However, due to the rarity of pituitary gigantism, it remains unclear whether their clinical course and comorbidities are the same. This study aimed to assess how early-onset GH oversecretion in pituitary gigantism affects disease progression, treatment strategies, and life expectancy.
Methods
From the UK Acromegaly Register (UKAR) and the International Familial Isolated Pituitary Adenoma Consortium, we extracted patients ($n=290$) meeting criteria for the pituitary gigantism (pituitary gigantism group, PGG). The remaining group from UKAR patients provided the acromegaly group (AG, $n=2,954$).
Results
Pituitary gigantism comprised 7.8% of GH-excess patients. The equal sex distribution observed in AG does not apply to PGG, where a male predominance is evident (61%). When analysing the onset of disease in AG, we found that the age of diagnosis in women was approximately 5 years later than in men. A similar trend was observed in PGG, where first symptoms (22.6 vs. 27.7 years) and diagnosis (26.9 vs. 31.0 years) occurred earlier in males than in females, with a greater final height in males (3.1 vs. 2.6 SD). AG patients had a similar height to the general population, with a trend for greater height before the age 50 years and lower height afterwards. In PGG patients, a more aggressive clinical disease course is seen: more invasive adenomas – significantly more macroadenomas (75.9% vs. 69.2%) and extrasellar extension (46.8% vs 33.9%), more aggressive surgical approach – more interventions (88.9% vs 83.7%), repeat surgery (23.3% vs 8.4%), and transcranial surgery (12.6% vs 5.0%), and more axis deficiencies per patient at post-treatment assessment (1.5 vs 1.0). The time from diagnosis to disease control was longer in the PGG group. PGG patients have a shorter life expectancy and higher mortality compared to patients with acromegaly (65.0 vs. 73.6 years, adjusted hazard ratio 2.09, 95% CI 1.46-3.04). Their mortality is twice as high compared to the general population (standardised mortality ratio 1.94).
Summary
PGG presents a more aggressive disease course, requiring more treatment modalities, with a greater risk of hypopituitarism and higher mortality compared to patients with acromegaly. Therefore, early diagnosis and a concentrated multi-disciplinary effort are essential to reduce long-term morbidity and mortality in patients with pituitary gigantism.

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RC14.6

JOINT1680

Identification of novel genetic variants associated with short stature using whole exome sequencing: insights from a pediatric cohort

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Background
Short stature is a common pediatric condition with diverse etiologies, including genetic factors, endocrine disorders, and malnutrition. However, up to 70% of cases remain undiagnosed despite extensive clinical evaluation. Recent advances in genomic technologies, such as whole exome sequencing (WES), offer new insights into the genetic causes of unexplained short stature. This study aims to identify novel genetic mutations associated with short stature, particularly those not detectable by traditional diagnostic methods.
Methods
We analyzed 212 pediatric patients with short stature, 352 healthy controls, and 4327 East Asian samples from the ExAC database. WES was performed on all patients and their parents, with variants filtered for quality and rarity (gnomAD_MAF <0.001). Gene-based burden testing was conducted using the TRAPD method, and gene ontology (GO) and kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment analyses were applied to identify biological processes and pathways associated with the identified genetic variants.
Results
Our analysis identified 263 genes with significant associations to short stature under a dominant inheritance model ($P<1\times10^{-5}$), and 63 genes with strong associations in both dominant and recessive models. Notably, genes such as FCGBP, FRAS1, MPDZ, and OBSCN, which were previously not associated with short stature, were identified as potential genetic contributors. The top 10 genes with the strongest associations included FCGBP ($P=5.06\times10^{-14}$), FRAS1 ($P=1.97\times10^{-10}$), and OBSCN ($P=3.62\times10^{-10}$). Pathway analysis revealed that these genes were involved in processes such as muscle development, steroid hormone biosynthesis, and sarcomere organization, with significant enrichment in Z discs, myosin filaments, and retinoic acid binding.
Conclusion
This study identifies several novel genetic variants that may contribute to short stature, underscoring the value of WES in identifying genetic causes in cases where traditional methods fail. The findings highlight the importance of expanding genetic testing in the diagnostic workup of short stature and provide new insights into the molecular mechanisms underlying this common pediatric condition.

Key words: short stature, whole exome sequencing, gene-based burden testing
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Rapid Communications 15: Metabolism, Nutrition and Obesity

RC15.1

JOINT2526

Age of onset of hyperphagia and/or obesity as key predictors of a positive genetic test for POMC, PCSK1 or LEPR deficiency or BBS

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Introduction
The melanocortin-4 receptor (MC4R) pathway plays a crucial role in regulating hunger, caloric intake, and energy expenditure. Genetic variants in this pathway can lead to hyperphagia and early-onset obesity. Raising awareness about genetic testing can help diagnose and identify patients who might benefit from innovative precision therapies. To improve access to genetic testing for individuals with suspected rare MC4R pathway diseases, the Rare Obesity Advanced Diagnosis™ (ROAD) genetic testing program was created, using a gene panel including 79 genes and 1 chromosome region including the most frequently tested genes associated with obesity. Here, we analysed ROAD data to identify prognostic factors for a positive genetic test.
Methods
Genes from individuals with early-onset obesity were sequenced. Analysis focused on biallelic variants in *POMC*, *PCSK1*, or *LEPR*, or in BBS genes (*BBS1-BBS22*). Variants were categorized as pathogenic, likely pathogenic, or of uncertain significance (P/lP/VUS) based on the criteria established by the American College of Medical Genetics.
Results
Overall, 6,169 individuals (54.5% female) from Germany, Greece, Ireland, Israel, Italy, Spain, Türkiye, UK, and the United Arab Emirates were sequenced, who had a mean age of obesity onset of 5.2 (3.8) years. A total of 1,830 P/lP/VUS variants were found in 1,755 unique individuals (28.4%), including 17 biallelic

variants in *LEPR*, 3 in *POMC*/*PCSK1* and 112 in any of the tested BBS genes. Mean age of onset of hyperphagia and of obesity in individuals with any of these biallelic variants was 2.7 (2.7) and 4.0 (3.6) years, respectively. In individuals in whom no variant from the gene panel was found, the ages were 4.6 (4.3) and 5.4 (3.8) years, respectively. When assessing the correlation between a positive test for biallelic *LEPR*, *POMC*, *PCSK1* or BBS and no identified variant, age of onset of hyperphagia ($P=0.0001$) and age at onset of obesity ($P=0.0007$) are key predictors for a positive genetic test, with BMI at time of testing ($P=0.0232$) and BMI z-score at time of testing (0.0661) showing potential predictive value.

Conclusions

A positive correlation was observed for individuals with biallelic variants in *POMC*, *PCSK1*, *LEPR*, or in any of the tested BBS genes, indicating that the age of onset of hyperphagia and obesity are key predictors for a positive test result for these genes. Hence, individuals presenting with early-onset hyperphagia and obesity are more likely to test positive for the disease, highlighting the importance of these factors as key predictors.

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RC15.2

JOINT450

Setmelanotide treatment in individuals with obesity and PHIP variants: results from the DAYBREAK trial

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Introduction

The melanocortin-4 receptor (MC4R) pathway regulates energy balance, hunger, and satiety. DAYBREAK (NCT04963231) was a two-stage clinical trial evaluating setmelanotide in individuals carrying a variant in ≥ 1 of 31 genes involved in the MC4R pathway, including *PHIP*, which enhances *POMC* transcription. Heterozygous deleterious *PHIP* variants are associated with intellectual disability/developmental delay, behavioral disorders, obesity/overweight, and dysmorphic features. We report a post hoc analysis of individuals with *PHIP* variants and obesity.

Methods

Individuals from the DAYBREAK trial aged 6-65 years carrying a *PHIP* variant, classified as variant of unknown significance (VUS) or pathogenic/likely pathogenic (P/lP) according to American College of Medical Genetics criteria, and body mass index (BMI) ≥ 40 kg/m^2 (≥ 18 years) or $\geq$97th percentile (6-17 years) and hyperphagia were included. Individuals meeting age-related weight loss criteria with setmelanotide after the 16-week open-label stage 1 (S1) could enter the 24-week, double-blind, randomized, placebo-controlled stage 2 (S2). Participants could reinitiate open-label setmelanotide if BMI increased $\geq 5\%$ from S2 entry (switch to setmelanotide within S2 or transition early to bridging). Primary analyses were performed at S1. Hunger was assessed in individuals aged ≥ 12 years. The S2 analyses were exploratory/ad hoc.

Results

Sixteen individuals with *PHIP* variants were enrolled (age range, 7-58 years; 50% female; 81% White). At baseline, the mean (SD) BMI in adult participants ($n=10$) was 45.34 (7.01) kg/m^2, and pediatric BMI Z score ($n=6$) was 2.46 (0.45). For S1 BMI data, 9 of 16 participants (56.3%) met age-related weight loss criteria. The mean (SD) BMI percent change in the 13 participants who completed S1 was -6.12% (3.62%). For S1 hunger data, 8 of 11 participants with baseline "most hunger" data had Week-16 follow-up for daily most hunger scores and exhibited a mean (SD) score reduction of -3.87 (1.41); 7 participants achieved a score reduction of ≥ 2. Nine participants entered S2 (5 adult and 4 pediatric). Participants receiving setmelanotide maintained consistent weight loss, whereas those receiving placebo did not. For post S2 data, 8 participants continued on treatment, with a mean (SD) bridging duration of 48.7 (14.1) weeks; 5 adult and 3 pediatric participants exhibited a final mean (SD) percent change in BMI of -14.18% (7.66%) and in BMI Z score of -0.71 (0.27), respectively.

Conclusions

Clinical response to setmelanotide, a highly selective MC4R agonist, suggests the MC4R pathway is a key biologic driver of obesity in individuals with *PHIP* variants of interest and merits further investigation.

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RC15.3

JOINT2894

Premature aging in alström syndrome: a model of monogenic syndromic obesity

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Cellular senescence has been increasingly recognized as a key driver of metabolic syndrome (MetS) and its complications, including obesity and type 2 diabetes (T2D). Alström syndrome (AS), a monogenic form of obesity with extreme insulin resistance and T2D has previously been associated with increased biological aging. This study investigates AS as a model of accelerated aging through cellular senescence markers in metabolic tissues. Patients with AS ($n=10$) were matched with healthy control volunteers ($n=10$) based on gender, BMI, and age. Clinical assessments were conducted alongside adipose tissue (AT) and skeletal muscle (SM) biopsies. β-galactosidase staining and RNA sequencing (RNA-Seq) with SanMayo analysis were performed on subcutaneous adipose tissue (AT), while reverse transcription polymerase chain reaction (RT-PCR) assessed senescence associated gene expression in SM. The IMM-AGE metric, analysed via fluorescence-activated cell sorting (FACS) was used to evaluate immune aging in peripheral blood mononuclear cells (PBMCs). Patient with AS exhibited a 55.4 ± 11.3-fold increase in β-galactosidase staining in adipocytes compared to controls. RNA-Seq analysis identified a gene expression signature associated with senescence in adipocytes. Quantitative RT-PCR of SM revealed overlapping gene expression changes in at least half of these senescence associated pathways in AT. Additionally, a significant increase in the IMM-AGE score indicated an increase in immunological age relative to chronological age in AS patients ($P<0.01$). These findings demonstrate a widespread senescence phenotype in adipose and skeletal muscle tissues in AS, supporting accelerated aging as part of the pathological presentation of AS. While the precise mechanisms remain unclear, our results suggest that senotherapies, combined with pharmacological and lifestyle interventions, could offer novel therapeutic strategies for obesity related metabolic dysfunction in AS.

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RC15.4

JOINT1148

Long-term weight gain in children who underwent adenotonsillectomy

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Background

Adenotonsillectomy (AT) is one of the most common pediatric surgeries, primarily indicated for obstructive sleep apnea (OSA) and recurrent infections. Although effective, prior studies have mainly examined the association between AT and short-term weight gain, with limited focus on the potential for long-term obesity following the procedure.

Objective

This study aimed to investigate the long-term association between AT and BMI changes, focusing on a 10-year follow-up in a large, nationwide cohort.

Methods

This retrospective cohort study utilized Clalit Health Services' electronic medical records. A total of 2,166 pediatric patients (aged 0-18) were included, with 1,083 children undergoing AT, matched 1:1 to a control group based on sex, ethnicity, and birth year. Baseline BMI and BMI Z-scores were recorded prior to surgery, with follow-up measurements collected over a 10-year period. To minimize bias,

children with severe chronic conditions and diseases known to affect weight regulation were excluded. This ensured that BMI changes reflected the impact of surgery rather than underlying medical factors. Statistical analyses included propensity score matching and inverse probability weighting to adjust for potential confounders such as socioeconomic status and preoperative health conditions.
Results
At baseline, BMI values were comparable between groups, with no statistically significant differences (mean BMI Z-score: 0.14 ± 1.31). At the 10-year follow-up, children in the AT group demonstrated a significantly higher mean BMI Z-score (0.65 ± 1.45) compared to the control group (0.43 ± 1.44, $P < 0.001$). The proportion of children classified as obese increased from 12% to 26% in the AT group, compared to an increase from 12% to 22% in the control group ($P = 0.04$). Furthermore, the odds ratio (OR) for developing overweight or obesity in the AT group was 1.23 (95% CI: 1.01, 1.50; $P < 0.001$). Growth curve analysis revealed that weight gain in the AT group followed a distinct pattern, occurring in phases rather than as a continuous trend, highlighting a sustained post-surgical weight increase.
Conclusion
This study is among the few to highlight the long-term association between AT and the risk of obesity. The findings emphasize the importance of ongoing follow-up and comprehensive support for children undergoing AT to help mitigate potential weight gain.

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RC15.5

JOINT3302

A metabolomic signature of maternal BMI is associated with pregnancy complications: insights from the COPSAC2010 and VDAART mother-child cohorts

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Introduction
Pregnancy complications such as gestational diabetes, preeclampsia, and caesarean section are more common among individuals living with higher BMI, likely due to metabolic disturbances. Blood metabolomics may offer mechanistic insights into these disturbances.
Methods
This study utilised data from the COPSAC2010 ($n = 684$) and VDAART ($n = 881$) mother-child cohorts, leveraging untargeted blood metabolomics and machine learning (sparse partial least square modelling) to investigate the association between pre-pregnancy BMI and pregnancy complications. A BMI-metabolite score was trained in the COPSAC2010 cohort and externally validated in VDAART.
Results
In the COPSAC2010 cohort, individuals with higher pre-pregnancy BMI (per 1 SD increase) had increased odds of gestational diabetes (OR 1.90, $P < 0.001$), caesarean section (OR 1.23, $P = 0.023$), and birth induction (OR 1.42, $P < 0.001$). A BMI-metabolite score predicted preeclampsia (OR 1.54, $P = 0.030$) and other pregnancy complications more effectively. Validation in VDAART confirmed the metabolite scores predictive value for gestational diabetes (OR 2.10, $P < 0.001$) and preeclampsia (OR 2.12, $P = 0.002$). Mediation analysis identified 16 metabolites mediating BMI's link to gestational diabetes. These mediators showed stronger predictive value for gestational diabetes in VDAART during early (OR 1.81, $P < 0.001$) and late gestation (OR 2.26, $P < 0.001$) than the full-metabolite score. Pathway enrichment analysis revealed that sphingomyelins and metabolites associated with Vitamin A metabolism were significantly enriched with higher pre-pregnancy BMI (FDR < 0.05)
Conclusion
Metabolomic profiling enhances understanding of how higher BMI during pregnancy may impact complications, offering opportunities for personalised risk assessment. These findings underscore the value of integrating metabolomics into prenatal care to optimise maternal and child health outcomes.

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RC15.6

JOINT2752

Brown adipose tissue as nutrient buffer through diet-induced thermogenesis

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Background
Brown adipose tissue (BAT) dissipates energy into heat when activated, classically after cold exposure. While there is clear evidence for the correlation between the presence of active BAT and a lean phenotype as well as lower prevalences of cardiometabolic diseases the exact mechanisms of these beneficial effects remain unclear. Especially, since BAT contribution to the total energy expenditure is small. In this study we test the hypothesis that BAT operates as a nutrient buffer and prevents unfavourable postprandial peaks of glucose, free fatty acids, or branched-chain amino acids.
Objective
The primary objective is to compare postprandial increases of metabolites in subjects with functional BAT to those without. Moreover, we assess how the beforementioned macronutrients and BAT-activity contribute to diet-induced thermogenesis (DIT).
Methods
This single center prospective observational study involves 30 healthy, normal weight volunteers and will be completed by May 2025. Participants are screened for presence or absence of cold induced BAT activity by a mild cold stimulus over two hours, followed by a 18F-FDG-PET/CT. BAT metabolic volume (BMV = SUVmean x BAT volume) > 200 ml was chosen as cut-off value to discriminate between BAT-positive and BAT-negative subjects. At each of the following study visits the participants consume an iso-caloric test meal containing exclusively either carbohydrate, protein, or fat. We perform indirect calorimetry hourly and blood samples half-hourly before and during five hours after the test meal.
Results
At the ECE we will present the first analysis of the complete study. Preliminary data of 22 subjects, 10 BAT-positive (BMV = 562.10 ± 210.11 ml), 12 BAT-negative (BMV = 79.18 ± 29.84 ml) show no DIT after intake of fat. A 15-20% increase in energy expenditure was observed persistently for at least 5 hours after intake of protein and for 3-4 hours after glucose. No difference was seen between BAT-positive and BAT-negative subjects in this respect. The average fasting blood glucose level of all study visits was 4.92 ± 0.38mmol/l with no difference between the groups. While all had similar glucose curves after the 100g OGTT, we see consistently lower blood glucose values in BAT-positive subjects following the challenge with fat and protein.
Conclusion
Our data show the impact of different macronutrients on DIT and contradict the notion that BAT status has an impact on DIT. Interestingly blood glucose seems to be lower in BAT-positive subjects after intake of protein and fat while glucose tolerance in our healthy subjects does not correlate to BAT status.

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Rapid Communications 16: Reproductive and Developmental Endocrinology Part 2

RC16.1

JOINT27

Genotype-phenotype correlation in patients having a WT1 germline variant : lessons from a large French cohort

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WT1 germline variants are known to generate renal and gonadal conditions, including Differences in sex development (DSD), chronic kidney disease and early kidney and gonadal tumors. GONADVENIR is a French national, retrospective study partly designed to investigate the genotype phenotype correlation in renal and gonado-genital conditions according to genetic groups recently defined by a genetic consortium. Eighty patients were included, at a median age of 14.2±5 years. Among those, 33 (41.3%) had a missense variant of exons 8 or 9 (MS E8-9), 24 (30%) had a variant generating WT1 truncated protein (TP), 14 (17.5%) had a donor splice site variant in intron 9 (DSS I9), and 9 patients had rarer variants. Patients from MS E8-9 group developed mostly (94%) congenital or early steroid-resistant nephrotic syndrome (SRNS), at a median age of 0.7 years (0.3-1.7), significantly earlier than patients from DSS I9 group ($P < 0.0001$) who developed SRNS (64%) around 3.7 years (2.5-10.8). Histologically, biopsies revealed diffuse mesangial sclerosis in 77% of patients from MS E8-9 group, a pathognomonic renal signature. In addition, we found that 88% of TP group developed nephroblastoma at a median age of 1.3 years (0.8-1.6) compared to only 30% in MS E8-9 and 14% in DSS I9 groups. Regarding gonado-genital conditions, 95% of XY patients had DSD, significantly more severe in the MS E8-9 group with External Genitalia Score (EGS) around 4 or 5 and the DSS I9 group with 90% of severe DSD (EGS <7) including 50% of female phenotype, compared to the TP group ($P=0.01$) where 70% had moderate DSD (EGS >7). Interestingly, we found uterus malformations in 9 patients with XX karyotype (39%), of whom 8 (89%) were from MS E8-9 group. In addition, patients with XX caryotype developed more frequently premature ovarian insufficiency in the MS E8-9 group than in the DSS I9 group ($P=0.026$). Finally, we found that patients from the MS E8-9 group had more risk over time than in the TP group to develop gonadal function impairment and premature testicular insufficiency with respective Hazard Ratio at 3.3 ($P < 0.001$) and 3.5 ($P < 0.01$). In conclusion, WT1 germline variants generate, rather than syndromes, a spectrum of renal and gonadal damages. Our study is the largest cohort reported to date and contributes to a better knowledge of the genotype-phenotype correlation, which may help practitioners to better understand their patients' diseases and provide a more individualized follow-up.

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RC16.2

JOINT384

Steroidogenesis and CYP17A1 inhibition: development of potent inhibitors for adrenal and gonadal steroid biosynthesis

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Steroidogenesis, the biosynthesis of steroid hormones, is a critical process in the development and regulation of various physiological functions, including growth, metabolism, and reproductive health. One of the key enzymes involved in this process is CYP17A1, which catalyses two essential steps in the production of androgens. Given its role in both adrenal and gonadal steroid hormone production, CYP17A1 is a key target for disrupting abnormal steroidogenesis. Only approved CYP17A1 inhibitor is abiraterone, which has numerous side effects, including inhibition of CYP21A2, and is metabolized into a potent androgen, which renders the treatment futile in long term. In this study, we focused on the development of novel potent inhibitors of CYP17A1 to modulate steroid biosynthesis. Using a previously identified hit compound as a starting point, we synthesized a series of analogs, including a novel di-cyano derivative, which demonstrated enhanced potency against CYP17A1. These compounds were tested in the human adrenal NCI-H295R cell line, a well-established model for studying steroidogenesis. Biological assays confirmed that these compounds significantly inhibited CYP17A1 enzymatic activity, leading to changes in steroid hormone profiles. Among the compounds tested, compound 11 exhibited the highest potency ($IC_{50}=4$ nM) in inhibiting CYP17A1 activity, showing a strong disruption of both hydroxylase and lyase functions of the CYP17A1 enzyme. Compound 14 also showed considerable potency and emerged as a promising lead for further development. Structure-activity relationship (SAR) analysis revealed that compounds containing an indole moiety (e.g., compound 11) were more potent than those with a benzotriazole fragment, suggesting that the indole structure is more effective for CYP17A1 inhibition. These findings indicate that targeting CYP17A1 can be a powerful strategy for modulating steroidogenesis. The compounds developed in this study offer a potential avenue for therapeutic interventions aimed at regulating steroid hormone production in both adrenal and gonadal contexts. Elevated androgen levels in congenital adrenal hyperplasia can be targeted by these potent inhibitors of CYP17A1 and for treatment of hyperandrogenic conditions like polycystic ovary syndrome.

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RC16.3

JOINT1103

Testicular contributions to masculinization in HSD17B3 deficiency: the critical role of HSD17B12

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Background
46, XY disorders of sex development (DSD) caused by 17-beta-hydroxysteroid dehydrogenase type 3 (HSD17B3) deficiency disrupt male sexual development, often resulting in undervirilization due to impaired testosterone synthesis. However, some patients experience masculinization, which is the main reason for the visit. This study investigates the molecular mechanisms underlying this phenomenon through clinical observations and protein expression analysis in patients with HSD17B3 deficiency.
Methods
Six patients with 46, XY DSD due to HSD17B3 deficiency were enrolled. Clinical phenotypic and hormonal profiles, were collected and analyzed. Bioinformatics analysis was used to identify candidate enzymes involved in androgen conversion. Immunofluorescence multi-marker staining was performed on tissue samples to examine the expression of HSD17B1, HSD17B5, and HSD17B12 in testicular tissues.
Results
The index patient was referred to our clinic after testicular-like tissue was discovered during an inguinal hernia repair. Genetic testing confirmed HSD17B3 deficiency, and the patient was assigned female sex. Despite this, no testicular tissue was present at follow-up during adolescence, and no signs of masculinization were observed. Retrospective analysis of other patients revealed that masculinization occurred exclusively in those with testicular tissue, indicating that the testis, rather than the adrenal glands or prostate, is the primary organ involved in episodic masculinization. Bioinformatics analysis revealed that HSD17B12 was the most highly expressed isozyme among HSD17B1, HSD17B5, and HSD17B12 in normal testes. Only HSD17B12 showed distinct spatiotemporal expression patterns, with low levels in infants and adults but significantly higher levels in adolescent boys. These changes were likely influenced by the elevated levels of luteinizing hormone during puberty, which stimulate testosterone production by Leydig cells in the testes. Similarly, in HSD17B3 deficiency, impaired testosterone synthesis leads to high gonadotropin levels, which is similar to puberty state and might contribute to masculinization. Immunofluorescence staining confirmed that HSD17B12 expression was the highest among the three enzymes in testicular tissue. Molecular docking studies further demonstrated that HSD17B12 had strong affinity for androstenedione, supporting its key role in the conversion to testosterone.
Conclusion
This study identifies the testis as the main organ responsible for episodic masculinization in patients with HSD17B3 deficiency, highlighting the importance of testicular tissue in the masculinization process. HSD17B12 emerges as the key enzyme involved, with its spatiotemporal expression patterns and high affinity for androstenedione suggesting a critical role in testosterone synthesis. These findings contribute to the understanding of the molecular mechanisms driving masculinization in HSD17B3 deficiency and may inform future therapeutic strategies targeting HSD17B12.

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RC16.4

JOINT749

Semen quality and lifespan – a study of 78,284 men followed for up to 50 years

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Background
Male infertility and semen quality have been suggested to be markers of morbidity and thus mortality, but the role of underlying disease present at time of semen quality evaluation has not been thoroughly assessed.
Objective
To determine the association between semen quality and mortality and to assess the impact of the health of the man prior to semen quality assessment.
Participants, study design, size
The study was based on 78,284 men who had their semen quality assessed 1965-2015 at the public semen analysis laboratory in the Copenhagen area, Denmark, due to reported couple infertility. Thus, the included men covered a wide range of semen quality. Semen quality assessment included semen volume, sperm concentration and the proportion of motile and morphologically normal sperm, from which total sperm count, and total number of motile sperm was calculated. Utilizing the unique national registers, follow-up of the men regarding all-cause mortality was performed with a median follow-up of 23 years (5-95th percentile: 8-45 years) during which 8,600 (11.0%) deaths occurred.
Methods
Life expectancy was calculated according to semen quality. Furthermore, the relative differences in mortality were estimated using Cox regression analyses and presented as hazard ratios (HR) with 95% confidence intervals (CI). For a subpopulation of 59,657 men (sample delivery 1987-2015), information on diseases prior to semen sampling and educational level was available and adjusted for in Cox regression analyses.
Results
Men with a total motile count >120 mill. could expect to live 80.3 years, compared to 77.6 years among men with total motile count >0-5 mill. In Cox regression analyses, all semen parameters were negatively associated with mortality in a dose-response manner both in the total and the subpopulation (p-trend for all semen parameters <0.001), and adjustment for educational level and prior diagnoses did not change the estimates. Looking at total motile count as an example, for which men with total motile count >120 mill. served as the reference, adjusted HRs were: azoospermia: 1.39, >0-5 mill.: 1.61, >5-10 mill.: 1.38, >10-40 mill.: 1.27, >40-80 mill.: 1.16 and >120 mill.: 1.19, p-trend< 0.001).
Conclusion and implications
We observed clear negative dose-response associations between all semen parameters and all-cause mortality, which were not explained by disease registered at the time of semen evaluation. Thus, some men with impaired semen quality may experience less healthy aging than men with better semen quality and could benefit from being identified at time of semen quality evaluation.

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RC16.5

JOINT1427

Smart menstrual health monitoring patch: a non-invasive ai-driven solution for cycle tracing

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Objectives
The primary objective of this study was to evaluate the feasibility, accuracy, and clinical relevance of the Smart Menstrual Health Monitoring Patch(SMHMP), a non-invasive newly designed wearable device designed to continuously monitor menstrual cycle biomarkers. The study aimed to assess its effectiveness in predicting ovulation, detecting cycle irregularities, and identifying potential menstrual disorders such as PCOS, endometriosis, and infertility.
Design
A prospective, multi-centered study was conducted to validate the SMHMP's biosensor technology and AI-driven analytics. The study followed a longitudinal observational design, comparing SMHMP data with conventional menstrual tracking methods (eg: basal body temperature chart and hormone assays) and clinical diagnosis.
Methods
500 participants, aged 18-40 with varying menstrual health profiles, were recruited from gynecological clinics. Participants wore SMHMP continuously for six menstrual cycles. The patch collected basal body temperature, hormone fluctuation data (estrogen and progesterone levels via interstitial fluid analysis), and other biomarkers data were analyzed using machine learning algorithms to detect cycle trends, ovulation windows, and potential menstrual disorders. Clinical validation was performed through physical assessments, blood hormone assays, and ultrasound confirmation where necessary.
Results
The SMHMP demonstrated a 92.3% accuracy in ovulation prediction compared to standard luteinizing hormone tests. It successfully detected menstrual irregularities in 87.5% of participants previously diagnosed with PCOS and identified 78.9% of cases with suspected endometriosis. User compliance and satisfaction rates exceeded 85% with participants reporting improved menstrual health awareness and ease of use compared to traditional tracking methods.
Conclusion
The findings suggest that SMHMP is a viable, non-invasive solution for menstrual health monitoring, offering real-time insights that can aid in the early detection of menstrual disorders. This technology has to potential to transform gynecological practice by providing an accessible, AI-driven approach to reproductive health management. Future research should focus on expanding clinical trials, refining AI algorithms for increased diagnostic accuracy, and exploring integration with border women's health initiatives.

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RC16.6

JOINT3272

Examining factors associated with androgen abuse withdrawal symptoms during the first year of cessation: a cross-sectional study of 286 men

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Background
Androgens are widely abused by men worldwide to enhance muscle size and physical performance. Recent studies have quantified the recovery of cardiovascular and testicular function post-cessation. Qualitative studies demonstrate that low mood, anxiety, suicidal ideation, and sexual dysfunction are common following androgen abuse cessation. However, no previous study has focused on quantifying symptoms within the first year of cessation, nor investigated independently associated factors for these symptoms.
Methods
Cross-sectional, observational study of 286 men in 3 groups; non-use ($n=50$); current-use ($n=125$); past-use ≤ 1 year ($n=111$). All participants completed questions on substance misuse, Beck Depression Inventory-II (BDI-II), International Index Erectile Function-15 (IIEF-15), General Anxiety Disorder (GAD-7), Quality-of-life (SF-36), and underwent fasting, morning blood sampling with urine toxicology.
Results
Current-use had lower gonadotropins and elevated serum total testosterone compared with past-use and non-use. Sexual function measured using IIEF-15 was impaired in past-use compared with current users: (1) total: 69.0 [IQR 61.0, 73.0], current-use; 62.0 [IQR 47.0, 71.0], past-use; $P=0.0002$; (2) erectile function: 30.0 [IQR 27.0, 30.0], current-use; 27 [IQR 20.0, 30.0], past-use; $P=0.0002$; (3) sexual desire: 9.0 [IQR 7.0, 10.0], current-use; 7.0 [IQR 5.0, 9.0], past-use; $P<0.0001$; (4) intercourse satisfaction: 12.0 [IQR 10.0, 15.0], current-use; 12.0 [IQR 8.0, 14.0], past-use; $P=0.0445$; (5) overall satisfaction: 10.0 [IQR 8.0, 10.0], current-use; 8.0 [IQR 6.0, 10.0], past-use; $P=0.0001$. Multivariable analysis suggested that psychiatric comorbidity (coefficient -6.5 [95% CI -13.0, -1.3]; $P=0.03$) and androgen cessation (coefficient -10.8 [95% CI -5.6, -17.2]; $P<0.001$) were associated with lower total IIEF-15 scores. Depression scoring

was worse in the past-use compared with non-use and current-use: BDI-II 3.0 [IQR 0.0, 8.0], non-use; 6.0 [IQR 2.0, 11.0], current use; 8.0 [IQR 2.0, 18.0], past-use; $P=0.0005$. Multivariable analysis suggested that psychiatric comorbidity (OR 2.39 [95% CI 1.60, 3.57]; $P<0.001$) and lower serum total testosterone (OR 0.85 [95% CI 0.88, 0.94]; $P=0.002$) were associated with higher BDI-II scores. Anxiety scoring was worse in the past-use compared with the non-use: GAD-7 1.0 [IQR 0.0, 3.0], non-use; 2.0 [IQR 0.0, 6.0], past-use; $P=0.0271$. Energy and fatigue measured using SF-36 was lower in past-use compared with non-use and current-use: 70 [IQR 60, 76], non-use; 65 [IQR 50, 75], current-use; 55 [IQR 40, 50], past-use; $P=0.0009$.

Discussion

We report the first, detailed quantification and modelling of symptoms in men currently misusing and stopping androgens within the previous year. These data reveal potentially treatable factors to improve symptoms of androgen abuse cessation if proven within interventional studies.

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Poster Presentations

Adrenal and Cardiovascular Endocrinology

P1

JOINT3758

Stimulated peak cortisol in healthy paticipants measured during the insulin tolerance test: defining cut-off limits for adrenal insufficiency with two generations of Roche cortisol immunoassays

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Introduction

The cortisol concentration varies depending on the measurement method. Monoclonal immunoassays demonstrate greater specificity than their predecessor polyclonal immunoassays for the assessment of cortisol. This necessitates assay-specific cut-off limits for defining adrenal insufficiency (AI). A cortisol cut-off of 500 nmol/l has been recommended for the older cortisol immunoassay, while lower cut-off of 420 nmol/l for newer immunoassays. However these values are defined using the ACTH test and not specified for the insulin tolerance test (ITT).

Purpose

To conduct a direct comparison between the 1st and 2nd generation Roche Elecsys cortisol immunoassays and to establish test- and assay-specific cortisol cut-off limits for the ITT using a cohort of healthy participants.

Methods

Ninety healthy participants underwent an ITT after an overnight fast (60 men, median age 46 years (IQR 24.5–49.5)). Blood samples were collected before, 15, 30, 45, 60, 75 and 90 min after insulin injection. The samples were analyzed on the 1st and 2nd generation Roche Elecsys cortisol immunoassays. The cut-off limit for a normal cortisol response to the ITT was defined as the 2.5th percentile of the peak cortisol level for 1st and 2nd generation Roche Elecsys cortisol immunoassays, respectively. The percentage of participants failing the currently used cut-offs derived from the 250 µg ACTH test of 500 nmol/l (ElecsysCortisol I), and 420 nmol (ElecsysCortisol II) were calculated.

Results

ElecsysCortisol II measured peak cortisol concentrations on average 29 nmol/l (95% CI: −64 to 9 nmol/l) lower than ElecsysCortisol I. The median peak cortisol was 607 nmol/l (range 320–1020 nmol/l) with ElecsysCortisol I and 510 nmol/l (range 240–964 nmol/l) with ElecsysCortisol II. The 2.5th percentile cortisol cut-off limits for a normal cortisol response in the ITT were 379 nmol/l with ElecsysCortisol I and 312 nmol/l with ElecsysCortisol II. Sixteen (17.8%) of the healthy controls had a peak cortisol below 500 nmol/l when measured by ElecsysCortisol I, whereas 19 (21%) of the healthy controls had a peak cortisol below 420 nmol/l with ElecsysCortisol II.

Conclusion

The 2nd generation Roche Cortisol immunoassay systematically reported lower cortisol concentrations. Based on healthy controls, we defined a cut-off limit for the ITT of 312 nmol/l which is considerably lower than commonly applied cut-off limits to confirm or reject AI. Our data emphasize the importance of knowledge of the method used, especially in patients with low apriory likelihood of adrenal insufficiency where the diagnosis may be challenging and at risk of false positive results.

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P2

JOINT1220

Neonatal screening in subjects with non-classic congenital adrenal hyperplasia (NCCAH)

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Background

Newborn screening (NBS) for congenital adrenal hyperplasia (CAH) primarily targets the detection of classical forms, with limited sensitivity for the milder non-classic form (NCCAH). Data on the predictive value of NBS 17-hydroxyprogesterone (17OHP) levels for later diagnosis of NCCAH, particularly in relation to specific genotypes, remain scarce.

Aim

To compare NBS 17OHP levels among children with NCCAH carrying mild/severe genotypes, those with mild/mild genotype, and healthy controls (HC).

Methods

Between 2020 and 2024, children evaluated for precocious pubarche/puberty, growth acceleration, or advanced bone age in a pediatric endocrinology clinic underwent ACTH stimulation testing. Eligible participants were born at or after 2008, following the implementation of NBS. Children with a history of early prematurity or perinatal complications were excluded. The study included 60 children with NCCAH (peak stimulated 17OHP $\geqq$ 40 nmol/l) and 59 healthy controls (stimulated 17OHP $\leq$ 25 nmol/l). NBS 17OHP levels were retrieved from the national NBS laboratory. CYP21A2 mutations were screened using a nine-mutation panel and multiplex ligation-dependent probe amplification in individuals diagnosed with NCCAH.

Results

Median NBS 17OHP levels were significantly higher in NCCAH patients compared to HC (6.3 nmol/l [IQR: 4.6–8.2] vs. 5.1 nmol/l [IQR: 3.6–7.0], $P=0.012$). Within the NCCAH cohort, no significant difference in NBS 17OHP levels was observed between the mild/severe and mild/mild genotype subgroups ($P=0.43$). ROC curve analysis identified an NBS 17OHP cutoff of $\geqq$5.9 nmol/l as a potential predictor for future NCCAH diagnosis; however, the sensitivity and specificity were low (AUC = 0.633).

Conclusions

The current NBS recall threshold ($\geqq$35 nmol/l) is substantially higher than the median NBS 17OHP levels observed in NCCAH patients, limiting its effectiveness in identifying NCCAH. Interestingly, the identified cutoff of 5.9 nmol/l aligns with basal 17OHP thresholds proposed for ACTH testing in older NCCAH patients. Furthermore, no differences in NBS 17OHP levels were observed between genotype subgroups, contrasting with previously reported findings in older individuals.

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P3

JOINT1534

Relacorilant improved blood pressure and maintained other cardiometabolic improvements in long-term study in patients with endogenous hypercortisolism (Cushing syndrome)

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In the phase 3 GRACE study, treatment with the selective glucocorticoid receptor modulator relacorilant improved blood pressure and other cortisol-related comorbidities in patients with endogenous hypercortisolism. The objective of this phase 3 open-label extension study (OLE, NCT03604198) was to assess the long-term efficacy and safety of relacorilant. Patients were eligible to enter the OLE if they completed a Corcept-sponsored parent relacorilant study, including either GRACE (NCT02804750), GRADIENT (NCT03697109), or the phase 2 study (NCT04308590), and in the investigator's opinion, might benefit from further treatment. As of September 8, 2024, there were 116 patients enrolled in the OLE. Patients' blood pressure continued to improve during relacorilant treatment. The mean (standard deviation) change in systolic and diastolic blood pressure from OLE baseline to month 24 was −10.0 [9.51] mmHg ($P=0.012$) and −7.3 [7.36] mmHg ($P=0.016$), respectively. Daytime and nighttime blood pressure

also improved during the OLE. In GRACE, patients who switched to placebo during the randomized-withdrawal phase experienced a deterioration in blood pressure. When relacorilant treatment was resumed in the OLE, their blood pressure improved. Improvements in body weight, glycemic control, and other cortisol-related comorbidities that were observed in the GRACE study were maintained in the OLE. Relacorilant was well tolerated in the OLE, consistent with the parent studies. No new safety signals were identified during up to 6 years of treatment. Long-term treatment with relacorilant led to significant and durable cardiometabolic improvements in patients with hypercortisolism and was well-tolerated.

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P31

JOINT2362

Initial findings of the study into the health status of adults with CAH in the UK and Ireland – CaHASE2

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Background
Congenital adrenal hyperplasia (CAH) is one of the commonest forms of primary adrenal insufficiency with an incidence of about 1 in 15,000. Previous studies have highlighted the suboptimal health status and care provision in adults with CAH and these were associated with significant co-morbidities. In 2023, we implemented CaHASE2 (https://www.endocrinology.org/clinical-practice/research-projects/cahase-2/) to develop a strategy for prospective collection of longitudinal data. Our recent CAH service evaluation suggested significant differences in the approach to CAH patients.
Aim
To identify specific unmet needs in the care of people living with CAH, through standardised phenotyping across all participating centres.
Methods
In September 2023, PIs agreed a minimal dataset for the collection of real-world data for participating centres. The data is collected using the international CAH registry (I-CAH; https://sdmregistries.org/). CaHASE2 was launched in November 2023.
Results
To date, 351 adults (213 females, 138 males) with CAH have been recruited and 1213 clinic visits were available for analysis. There is a preponderance of younger to middle-aged adults in the currently available datasets (median age 42 years, range 23–88). Preliminary analysis suggests a temporal change in glucocorticoid choice over time with an increased use of hydrocortisone and a decreased use of prednisolone. Analysis of 17OHP concentrations shows that a significant proportion of patients are overtreated. A significant proportion of patients are overweight or obese. Currently 18 centres are actively recruiting and 5 are awaiting local approval to use the I-CAH registry. The data will be analysed in 12-month cycles, to assess the current level of care provision and inform the development of CAH standards. In addition, we will establish a report that will provide centres with information about their local care provision in relation to other centres.
Conclusions
The CaHASE2 project will provide important information about the health status of adults with CAH and how this might be related to differences in health care provision. Ultimately, such data should lead to a higher degree of equality of service provision in all parts of the UK and Ireland.

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P32

JOINT3812

is imaging alone sufficient for lateralising PA in younger patients?

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Background
The role of adrenal vein sampling (AVS) in younger patients with primary aldosteronism (PA) remains debated. Endocrine Society (ES) Guidelines suggest that AVS may be avoided in patients ≤35 years with marked PA (aldosterone > 831 pmol/l, spontaneous hypokalaemia), and a solitary adrenal lesion consistent with an adenoma. While some centres adopt this approach, others, including ours, perform AVS routinely on all patients with PA. However, imaging alone may misclassify laterality in a significant proportion of younger patients.
Aim
To assess the accuracy of imaging alone in distinguishing unilateral from bilateral PA in patients ≤35 years and evaluate the added diagnostic value of AVS.
Method
We retrospectively analysed 364 patients who underwent AVS for PA between 2011 to 2024, including 39 patients aged ≤35 years. Of these, 38 underwent either CT or MRI prior to AVS. Two radiologists independently reviewed imaging blinded to AVS results, while two endocrinologists blinded to imaging findings analysed AVS. Concordance between imaging and AVS was assessed.
Results
The mean age was 32 years, with 60% female. Median hypertension duration was 1.5 years (IQR: 1–5 years). All patients had biochemically confirmed PA with spontaneous hypokalaemia and were on two to three antihypertensive medications. AVS was successful in all cases. Among 39 patients, four were excluded due to inconclusive AVS results and missing imaging data. In the remaining 35, imaging identified unilateral adenomas (6–25 mm) in 82.9% (29/35) patients, bilateral adenomas in 8.6% (3/35), and normal adrenal glands in 8.6% (3/35). Among 29 unilateral cases on imaging, 13.8% (4/29) had discordant AVS findings, indicating bilateral disease. Discordant cases had lateralisation index <2 (range: 1.3–2.0) and/or contralateral suppression index >1, suggesting bilateral PA. Only one discordant case met ES criteria for marked PA, while the other three had milder disease. All discordant cases were managed medically, while 86.2% (25/29) underwent unilateral adrenalectomy, with histological confirmed adenoma.
Conclusion
While imaging alone correctly lateralised PA in 86.2% of cases, 13.8% of patients with unilateral adenomas had discordant AVS findings, indicating bilateral disease. Only one discordant case met the ES criteria for marked PA, supporting AVS omission in these patients. However, AVS remains essential for those with milder PA to prevent misclassification and unnecessary adrenalectomy.

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P33

JOINT1023

Challenges in the interpretation of cortisol response during insulin tolerance test: prevalence of secondary adrenal insufficiency and predictive factors

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Background
The insulin tolerance test (ITT) is the gold standard for assessing the integrity of growth hormone (GH) and cortisol axes. While ITT is essential for diagnosing growth hormone deficiency (GHD) and secondary adrenal insufficiency (SAI), its interpretation can be challenging due to variability in thresholds and individual responses.
Methods
This retrospective study analyzed ITTs performed at the Institute for Maternal and Child Health IRCCS "Burlo Garofolo," Trieste, Italy, from January 1, 2019, to December 31, 2024. Tests were conducted to confirm GHD after a blunted response to arginine stimulation or for retesting at the end of GH treatment. Regular insulin (0.1 IU/kg intravenously) was administered, and adequate hypoglycemia was defined as a ≧50% decrease in basal glucose or a nadir glucose <40 mg/dL.
Results
Of 212 ITTs performed, adequate hypoglycemia was achieved in 186 (88%), including 157 diagnostic tests and 29 retests. The prevalence of SAI varied widely depending on the threshold used: Between 14% and 27% of individuals meeting these thresholds were not diagnosed with GHD. Peak cortisol levels positively correlated with basal cortisol ($\rho = 0.490$, $P < .001$), nadir glycemia ($\rho = 0.307$, $P < .001$), basal ACTH ($\rho = 0.255$, $P < .001$), ACTH after hypoglycemia ($\rho = 0.332$, $P < .001$), and peak GH ($\rho = 0.312$, $P < .001$). No significant correlation was found with age, sex, or BMI SDS. Multivariate analysis identified lower basal cortisol ($P < .001$), lower ACTH after hypoglycemia ($P < .001$), and nadir glycemia ($P = .012$) as significant predictors of cortisol peak, with a moderate model fit ($R^2 = 0.354$).
Conclusions: The prevalence of SAI during ITT ranged from 13% to 80% depending on the diagnostic thresholds. Between 14% and 27% of individuals

Threshold for SAI	*n* (%)	Of which with no GHD
Peak cortisol <400 nmol/l	32 (17%)	6 (19%)
Delta cortisol <200 nmol/l	75 (40%)	20 (27%)
Peak cortisol <400 nmol/l and delta <200 nmol/l	24 (13%)	5 (21%)
Peak cortisol <550 nmol/l	129 (69%)	18 (14%)
Delta cortisol <250 nmol/l	102 (55%)	22 (22%)
Peak cortisol <550 nmol/l or delta <250 nmol/l	149 (80%)	28 (19%)

meeting SAI thresholds were not diagnosed with GHD, complicating interpretation. Significant predictors of cortisol peak include basal cortisol, nadir glycemia, and ACTH after hypoglycemia. These findings highlight the need to consider clinical context alongside hormonal thresholds to ensure accurate SAI diagnosis and avoid overdiagnosis.

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P34

JOINT2537

The relationship between androgens and autistic traits: a comparative study in children with congenital adrenal hyperplasia

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Purpose
Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by difficulties in social interaction, communication, restricted interests, and repetitive behaviors. ASD is more prevalent in males than females, with some studies suggesting a possible association with prenatal androgen exposure. Congenital Adrenal Hyperplasia (CAH), a genetic disorder causing increased prenatal androgen levels, provides a suitable model to investigate this relationship. This study aims to evaluate the potential link between early androgen exposure and autistic traits by comparing children and adolescents with CAH to healthy controls.
Method
The study included 49 participants: 25 children diagnosed with CAH (13 males, 12 females) followed by Istanbul University-Cerrahpaşa Medical Faculty Pediatric Endocrinology Clinic, and 24 age- and sex-matched healthy controls (12 males, 12 females) aged 2–18 years. Autism symptoms were assessed using the Childhood Autism Rating Scale (CARS), the Autistic Behavior Checklist (ABC), and the Strengths and Difficulties Questionnaire (SDQ).
Results
The total CARS score was significantly higher in the CAH group compared to the control group ($P<0.001$). The CAH group also had higher scores in the following CARS subtests: Relating to People ($P=0.027$), Body Use ($P=0.031$), Visual Response ($P=0.017$), Listening Response ($P=0.028$), Taste/Smell ($P=0.033$), Verbal Communication ($P=0.049$), Activity Level ($P<0.001$), and Intellectual Response ($P=0.003$). However, there was no significant difference between the groups in motor skills, language skills, and general autism scores ($P>0.05$). When the participants were evaluated with ABC, it was found that the sensory behavior score ($P=0.037$) was higher, and the relating behavior score ($P=0.001$) was lower in the CAH group compared to the control group.This finding indicates difficulties in social communication. In the SDQ assessment, emotional problems ($P=0.043$), behavioral issues ($P=0.043$), hyperactivity/attention deficit ($P=0.025$), and peer relationship problems ($P=0.001$) were significantly higher in the CAH group. The general difficulties score was also higher, indicating an increased psychosocial risk. No correlation was found between current androgen levels (17-OH, DHEA-S, 1,4) and CARS and ABC scores ($r < 0.4$)
Conclusion
Children diagnosed with CAH had higher scores regarding autism symptoms and had more difficulties with social communication. Additionally, increased behavioral and attention problems were observed in these children, which indicates emotional fragility. No direct correlation between androgen levels and autism symptoms was found, but it is thought that there might be indirect effects of prenatal androgen exposure. Further investigations are needed, with broader samples required to clarify this relationship.

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P35

JOINT3950

Adrenal dysfunction and cardiometabolic comorbidities associated with weight cycling in postmenopausal conditions

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Overweight and obesity are major public health issues. ∼20% of overweight people achieve sustainable weight loss with a risk of repeated weight loss and regain. Obese patients exhibit high plasma leptin levels, but are resistant to its anorectic action. Leptin, and other adipokines, directly regulates adrenal aldosterone biosynthesis, while aldosterone has been implicated in obesity-induced suppression of adiponectin, an insulin sensitizing adipokine, suggesting a central role for aldosterone in the development of overweight-associated comorbidities. Interestingly, aldosterone levels are associated with the development of metabolic syndrome. Weight cycling is associated with fluctuations in blood pressure, heart rate and glomerular filtration, leading to increased risk of developing metabolic syndrome, type-2 diabetes, chronic kidney disease and heart failure, inducing higher mortality, particularly in women. The menopausal transition is associated with a 60% increase in the incidence of metabolic syndrome, which is associated with higher cardiovascular mortality. We hypothesize that adrenal dysfunction, in a postmenopausal context may play a role and has a lasting impact on the increased cardiometabolic risk induced by weight cycling. The aim of our study was to evaluate the impact of weight cycling on adrenal gland function and the impact on the development of cardiometabolic complications in postmenopausal conditions. We established an experimental protocol in which female mice were either ovariectomized (OVX, post-menopause) or not (non-OVX, pre-menopause) and subjected to three weight cycles of high fat diet/standard diet (Yoyo) or maintained on a standard diet throughout. At the end of each phase of the weight cycling protocol, blood samples were collected to assess various metabolic parameters and perform steroid profiling. A variety of tissues (adrenal, heart, adipose tissue…) were collected for further analyses. The yoyo diet led to a greater weight gain in OVX mice compared to non-OVX mice. After ovariectomy, mice exhibited higher fasting blood glucose and circulating leptin levels, an effect that was exacerbated in response to Yoyo diet. Additionally, OVX mice on Yoyo diet chowed impaired glucose tolerance and insulin resistance. These mice developed heart failure with preserved ejection fraction, which was prevented by the use of the mineralocorticoid receptor antagonist, finerenone. Surprisingly, OVX mice on Yoyo diet displayed an increase in adrenal gland weight, accompanied by significant morphological and functional remodeling of the adrenal cortex. The absence of estrogen leads to cardiometabolic disorders that are worsened by the Yoyo diet, as well as adrenal dysfunction, which could, in turn, contribute to the worsening of cardiometabolic comorbidities.

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P36

JOINT1699

Chronotherapy with once-daily osilodrostat is safe and effective in Cushing's syndrome and restores circadian profile improving quality of life and sleep

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Introduction
Medical treatment for Cushing's syndrome (CS) primarily aims to lower daily cortisol levels, while often overlooking the restoration of circadian rhythm. Indeed, no approved treatment regimens are specifically designed to achieve this goal. We aimed to assess the efficacy and safety of a timed, once-daily Osilodrostat regimen in optimizing circadian cortisol profile in patients with CS.
Methods
We conducted a prospective, multicenter study evaluating patients with well-controlled CS who were on a stable twice-daily Osilodrostat regimen before and 60–90 days after transitioning to an equivalent once-daily dose administered at 19:00 ± 1 hour. Circadian steroid profiles were analyzed in saliva, serum, and urine using UHPLC-MS/MS. A cosinor-based analysis on salivary cortisol and cortisone measurements was performed to capture changes in their daily profiles. Additional evaluations encompassed cardio-metabolic markers, quality of life, sleep function, and safety outcomes.
Results
Sixteen patients (4 males; 7 pituitary, mean age 53.3 ± 11.8 years) were enrolled. At baseline, CS was well-controlled with a mean Osilodrostat dose of 4.2 mg (range 2–22). After the chronotherapy intervention, transitioning to once-daily dosing at 19:00 ± 1 hour, salivary cortisol exposure decreased significantly during the afternoon-to-early morning period [$AUC_{16:00–08:00}$: −6.1 (−0.15 to −12.1) ng/mL/h, $P = .029$; $AUC_{16:00–04:00}$: −4.6 (−1.2 to −8.1) ng/mL/h, $P = .009$]. Quality of life and sleep improved [CushingQoL: +4.2 (−0.1 to -8.6), $P = .029$; PSQI: −1.7 (−3.7 to 0.4), $P = .049$]. Serum steroid precursors, including 11-deoxycorticosterone ($AUC_{08:00–20:00}$: −3.1 ng/mL/h, $P = .008$) and 11-deoxycortisol ($AUC_{08:00–20:00}$: -17.8 ng/mL/h, $P = .005$), as well as total testosterone in women ($AUC_{0800–2000}$: = −0.8 ng/mL/h, $P = .039$), showed a decrease in the global day exposure. A subsequent salivary analysis involved 8 patients that advanced dosing to 16:00 ± 1 hour (T_{OD2}), showing comparable reductions (cortisol $AUC_{16:00–08:00}$: −5.5 ng/mL/h, $P = .036$). Once-daily OS was generally well tolerated and preferred by 93.4% of patients to the twice daily regimen in terms of overall appeal, ease of use in daily routine and future choice. No patients developed adrenal insufficiency, liver toxicity, ECG abnormalities, or loss of disease control.
Conclusions
This is the first evidence that chronotherapy with once-daily Osilodrostat effectively and safely treats CS, leading to improvements in circadian cortisol rhythms, quality of life, and sleep. These results warrant further exploration of chronotherapy-based approaches in CS management.

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P37

JOINT2736

Assessment of adrenal function after oral prednisolone therapy in children with epileptic spasms

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Background
Epileptic spasms, including West syndrome, are severe pediatric neurological disorders associated with developmental delays and neurocognitive impairment. High-dose oral prednisolone is a first-line treatment but carries a risk of adrenal insufficiency (AI). Evaluating adrenal function post-treatment is crucial, particularly in resource-limited settings where routine testing may not be feasible.
Objectives
This study aimed to determine the proportion of children with AI at 5 days and 6–8 weeks after stopping prednisolone. Additionally, it assessed adrenal recovery at 6–8 weeks in those diagnosed with AI at 5 days, examined treatment-related adverse effects, and identified potential AI risk factors.
Methods
A prospective analytical study was conducted on 40 children (6–19 months, mean age: 10.10 ± 3.69 months) who completed high-dose oral prednisolone therapy (4 mg/kg/day for 2 weeks, followed by a 4-week taper). Adrenal function was evaluated using basal cortisol and ACTH stimulation tests at 5 days and 6–8 weeks post-treatment completion. Adrenal recovery was defined as a stimulated cortisol level ≧18 µg/dL.
Results
At 5 days post-therapy, all children exhibited AI as confirmed by ACTH stimulation testing, with 97.5% having inconclusive basal cortisol levels (3–18 µg/dL). By 6–8 weeks, 72.5% showed adrenal recovery. One child experienced an adrenal crisis at 2 weeks but recovered by the second assessment. Cushingoid facies was observed in 85% at 5 days, decreasing to 72.5% by 6–8 weeks. Elevated blood pressure was noted in 70%, reducing to 55%, with 5% developing persistent hypertension. No cases of hyperglycemia, cataracts, or glaucoma were detected. All children exhibited global developmental delay, which was unrelated to adrenal function. AI was not significantly associated with age, gender, socioeconomic status, stunting, hypertension, or cumulative prednisolone dose.
Conclusions
AI is universal following high-dose prednisolone therapy in children with epileptic spasms but shows significant recovery within 6–8 weeks. Routine adrenal function testing is essential to identify at-risk children, minimizing the risk of adrenal crisis and guiding the rational use of stress-dose steroids.

Keywords: Adrenal insufficiency, ACTH stimulation test, Cortisol.

Table 1 Baseline and ACTH stimulated serum cortisol levels at the first and second assessments.

	Mean (s.d.)			
	First assessment (5 days post-therapy)	Second assessment (6–8 weeks post-therapy)	Mean difference [95% CI]	*P*-value
Basal serum cortisol (ug/dl)	7.15(2.34)	14.72(2.26)	7.58[6.86 to 8.29	<0.001*
ACTH stimulated serum cortisol at 1 hr. (ug/dl)	9.08(2.58)	18.03(2.24)	8.95[8.28 to 9.61]	<0.001*

P value <0.05 – significant

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P38

JOINT3615

Brain and behavior in primary adrenal insufficiency – with emphasis on the precuneus & orbitofrontal cortex

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Context
Primary adrenal insufficiency (PAI), including congenital adrenal hyperplasia (CAH) and autoimmune Addison's disease (AAD), result in low cortisol levels and abnormal sex hormone levels due to adrenal cortex dysfunction. Previous studies on PAI found that the hormonal imbalance can alter brain structure and connectivity, affecting multiple brain areas including the left precuneus and the orbitofrontal cortex. These brain areas are major hubs in the brain, and alterations may lead to changes in structural and functional connectivity between the hub and other networks, which in turn could contribute to cognitive impairments and mental health issues. *Objective*: This study analyzed changes in structural and functional connectivity of the left precuneus and orbitofrontal cortex between patients with PAI and control subjects.
Design, setting, and participants
A total of 150 participants were included in the analysis: 29 individuals with CAH (18 females), 55 patients with AAD (33 females), and 66 healthy controls (37 females), aged 16 to 43 years, from a single research institute. All subjects underwent functional and structural magnetic resonance imaging (MRI).
Results
In patients with AAD, the resting-state functional connectivity analyses showed a decreased connectivity between the left precuneus and the left insula compared with the healthy controls. The analyses also showed a decreased connectivity between the orbitofrontal cortex and the left insula compared with the healthy controls. No such differences in functional connectivity were found in patients with CAH compared to controls. In contrast, CAH patients had impaired white matter microstructure in the left precuneus and orbitofrontal cortex, while patients with AAD did not.
Conclusions
The results suggest that long-term cortisol imbalances in primary adrenal insufficiency led to altered functional connectivity of the precuneus and orbitofrontal cortex in AAD, but not CAH. The underlying effects of these differences remain unexplained. Further research is needed to investigate the influence of the changes in functional connectivity and white matter and their relevance to cognitive functioning and mental health.

Keywords: PAI, precuneus, orbitofrontal cortex, brain health, dwi, rs-fc

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P39

JOINT324

Exploring oligogenicity as a contributor to the broad phenotypic spectrum of 46,XY differences in sex development associated with NR5A1/SF-1 variants: findings from the international SF1next study

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Background
Individuals with *NR5A1*/SF-1 variants encompass a wide spectrum of phenotypes, ranging from asymptomatic carriers to severe forms of differences of sex development (DSD). The mechanisms contributing to this wide variability of observed phenotypes remains elusive. Oligogenicity has been suggested as a potential mechanism. We aimed to investigate the oligogenicity patterns in individuals with *NR5A1*/SF-1 variants from the international SF1next study cohort, shedding light on how multiple genetic variants collectively influence DSD phenotypes.
Methods
DNA samples and comprehensive DSD phenotype data from individuals carrying *NR5A1*/SF-1 variants, and available family members, were collected from the SF1next study cohort. Whole exome sequencing (WES) data of 30 individuals/families were utilised. WES data were analysed using a tailored filtering algorithm to identify rare variants in SF-1- and DSD-related genes. Identified variants were assessed for potential pathogenicity based on American College of Medical Genetics and Genomics (ACMG) and clinical disease associations in related databases. Oligogenic combinations between the additional variants and the specific *NR5A1*/SF-1 variants were tested using Oligogenic Resource for Variant Analysis (ORVAL). Genotype–phenotype correlations were explored by integrating these findings with the phenotype data.
Results
Novel genetic workup of 30 individuals detected rare, additional variants in SF-1- and DSD-related genes. The phenotype of these individuals, all with 46,XY karyotype, ranged from severe to opposite-sex DSD. Using ORVAL, oligogenic pathogenic combinations were found in 73% (22/30) individuals, with one to seven additional variants per individual, predominantly in DSD-related genes. We found identical variants in eight unrelated individuals with DSD in DSD-related genes (e.g., *TBCE, FLNB, GLI3* and *PDGFRA)* and different variants in eight genes frequently associated with DSD (e.g., *CDH23, FLNB, GLI2, KAT6B, MYO7A, PKD1, SPRY4* and *ZFPM2*) in 15 index cases. Our study also identified combinations with *NR5A1*/SF-1 variants and variants in novel candidate genes.
Conclusion
Our study shows that in 3 out of 4 individuals with a *NR5A1*/SF-1 variant and a 46,XY DSD, additional genetic variants may explain the broad variability of the DSD phenotype, indicating oligogenicity. Thus, the genetics explaining the DSD phenotype in many individuals and their families might be more complex than previously thought.

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P40

JOINT1810

Understanding the sources of aldosterone and cortisol production in primary aldosteronism and autonomous cortisol secretion

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Background
Approximately 25% of patients with primary aldosteronism (PA) exhibit mild autonomous cortisol secretion (MACS). Patients with PA and MACS have an increased incidence of cardiovascular events compared to patients with PA without MACS. However, the characterization of aldosterone lateralization, histopathology, and outcomes among patients with PA and MACS is not well established.
Aims
To evaluate the origins of aldosterone and cortisol secretion in patients with PA and MACS who underwent adrenalectomy, and to compare clinical and biochemical aspects, histology and outcomes between PA patients with and without MACS.
Methods
We conducted a cohort study including 197 patients with PA who underwent investigation for MACS using a 1 mg dexamethasone suppression test at a single tertiary center. MACS was characterized by cortisol $\geqq$ 1.8 mcg/dL with dexamethasone levels $>$ 130 ng/dL. Histology was investigated using CYP11B2 and CYP11B1 immunostaining in adrenal lesions.
Results
MACS was diagnosed in 52 (26.4%) out of 197 patients with PA. Among the 52 patients with MACS, 29 (55.8%) underwent adrenal venous sampling (AVS) under cosyntropin stimulation, and 25 (48.1%) underwent surgical treatment. Patients with PA and MACS were statistically significantly older at the time of PA diagnosis compared to patients with isolated PA (57.15 [range] vs. 52.58 [range] years; $P=$X). Other clinical and biochemical features at diagnosis and PASO outcomes were not different between the two groups. Moreover, the frequency of unilateral and bilateral PA was X% and Y% in patients with PA and MACS, respectively. Interestingly, aldosterone and cortisol were produced by different adrenal lesions in 7 (38.9%) out of 18 cases with immunostaining (unilateral cortisol secretion and bilateral PA): a unilateral cortisol-producing adenoma (positive for CYP11B1 and negative for CYP11B2) and bilateral aldosterone-producing nodules or micronodules (positive only for CYP11B2). Eleven (61.1%) out of 18 patients had an aldosterone lesion (adenoma or nodule?) producing both aldosterone and cortisol.
Conclusion: For the first time, we demonstrate that aldosterone and cortisol originate from distinct adrenal lesions in nearly 40% of patients with PA and MACS. This finding has critical implications for the interpretation of AVS and the planning of surgical treatment. Support: Sao Paulo Research Foundation (FAPESP) grant 2019/15873-6 (to M.Q.A.)

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P41a

JOINT3642

Ready, steady, go: an exploration of the knowledge and self-management skills of patients with congenital adrenal hyperplasia during transition

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Introduction
In the past years increasing priority is given to the transition from child to adult care. Goals during the transition process focus on the knowledge about the

chronic condition, the ability of adolescents and young adults to manage their chronic condition, effectively utilize healthcare services, and ensure an organized and structured transfer of care and integration into adult care. In 2017 the transition service Young Adult Clinic (YAC) is launched in the Erasmus University Medical Centre. One of the tools used in the transition service is the generic transition questionnaire Ready Steady Go (RSG), for identifying gaps in knowledge, self-management skills, social skills and general health management. Since 2022, the RSG age-appropriate questionnaire has been sent annually to patients in the transition phase. For patients with adrenal insufficiency, for example congenital adrenal hyperplasia (CAH), a questionnaire regarding corticosteroid use and sick day rules is added.

Methods

We evaluated RSG questionnaires sent to eleven patients with CAH who made the transfer since the start of the annual RSG in our YAC.

Results

Two of the 11 patients started with the questionnaire in the paediatric department, at the age of 16, another two at the age of 17. In seven of the 11 patients the questionnaire was first sent when they were already in the adult care, varying in age between 18 and 21 years. One of the seven patients did not respond. At the age of 16 the two adolescents with CAH had sufficient knowledge about corticosteroid replacement therapy, but insufficient knowledge about causes and presenting symptoms of an acute adrenal crisis. After transfer to the adult clinic patients are eager to know more about their condition and are open for education, for example about side effects of medication and how to prevent an acute adrenal crisis. Most of the patients who completed the questionnaire at the age of 20 or 21 indicate to have adequate knowledge and self-management skills to manage their condition.

Conclusion

A generic questionnaire like the RSG can help identify gaps in knowledge and self-management skills in patients with CAH. Disease specific questionnaires about corticosteroid replacement therapy helps to gain specific self-management skills. The patients had comparable topics they wanted to address during consultations and showed adequate knowledge and self-management skills around the age of 21. These findings endorse the importance of starting transition early in adolescence and continuing well into adulthood.

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P42

JOINT226

Neurocrine regulation of aldosterone secretion: The role of substance P and NK1 receptor in aldosterone-producing adenomas

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Background

Aldosterone-producing adenoma (APA) is a major cause of primary aldosteronism (PA), the most prevalent form of secondary hypertension. While significant progress has been made in identifying somatic mutations in genes driving aldosterone secretion, the pathophysiology of PA remains partially understood. Recent studies have revealed that Substance P (SP), a neuropeptide encoded by the *TAC1* gene, stimulates aldosterone production by activating the neurokinin type 1 receptor (NK1R) in the adrenal cortex. The aim of this study was to explore the expression and distribution of SP and NK1R in APA tissues and to evaluate their role in aldosterone hypersecretion.

Methods

56 APA tissues were analyzed using quantitative RT-PCR, immunohistochemistry, and functional studies. The expression levels of *TAC1* and *TACR1* mRNAs were quantified to assess transcription of SP and its receptor NK1R. Immunohistochemical staining was performed to determine localization and protein expression of SP and NK1R. Functional studies were performed on primary APA cell cultures and perifused APA explants to evaluate the effects of SP on aldosterone secretion and the inhibitory potential of the NK1R antagonist aprepitant. Aldosterone pulsatility was analyzed in perifusion profiles by assessing the mean aldosterone levels, the nadir levels, the pulse frequency, the mean pulse interval, the pulse amplitude, and the integrated aldosterone secretion (area under the curve, AUC).

Results

Quantitative RT-PCR revealed significant expression levels of *TAC1* and *TACR1* mRNAs in APA tissues. Immunohistochemistry detected SP-positive nerve fibers in 90% of APA samples, with granular SP staining observed in a subset of adenoma cells. NK1R expression was identified in both adenoma cells and adjacent adrenal tissue with co-localization of NK1R and aldosterone synthase (CYP11B2) noted in 60% of adenomas. SP dose-dependently increased aldosterone secretion in 6 out of 10 APA cell primary cultures (EC$_{50}$ = 1.7 ± 0.3 nM; $P<0.01$). The NK1R antagonist aprepitant, significantly inhibited SP-induced aldosterone secretion in 3 out of 4 responsive APA samples ($P<0.01$). In perifusion experiments, SP administration increased the integrated aldosterone response, as measured by the area under the curve (AUC) by 153% ($P<0.05$).

Conclusion

These findings demonstrate that SP stimulates aldosterone production in APAs, through neurocrine and paracrine mechanisms, by activating the NK1 receptor. Targeting the SP-NK1R axis with NK1R antagonists, such as aprepitant, represents a promising therapeutic approach for a subset of patients with primary aldosteronism.

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P43

JOINT2386

Molecular mechanisms of glucocorticoid sensitivity: insights from a novel transgenic mouse model

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Synthetic glucocorticoids are extensively prescribed. Although they improved the management of chronic inflammatory diseases, these treatments are also associated with numerous adverse effects, with an inter-individual variability that remains poorly understood. Glucocorticoids exert their effects *via* the glucocorticoid receptor (GR), encoded by the *NR3C1* gene. Only few variants associated with glucocorticoid sensitivity have been described and the molecular mechanisms involved are not fully understood. The N363S variant, which encodes for substitution of an asparagine with a serine at amino acid 363, has been associated with increased glucocorticoid sensitivity, but has never been further characterized. Performing *in vitro* studies, we demonstrated that maximal transactivation activity (GR_{WT} 93,8% ± 5.1 *vs* GR_{N363S} 142.6% ± 9,0, $n=38$, $P<0.0001$) and target gene expression were higher in response to dexamethasone in HEK 293T cells expressing the variant. Next, we aim to assess the impact of the N363S variant *in vivo* using a novel mouse model expressing the variant. As the mutated amino acid is conserved across species, we introduced a point mutation into the coding sequence of the mouse *Nr3c1* gene (c.1139 A>G), using the CRISPR/Cas9 system. The genotype (Wild type: WT; heterozygous: HET; homozygous: HOM) was assessed by PCR. First, we evaluated the impact of the variant on weight, glucose metabolism, and HPA axis activity without any glucocorticoid treatment. Next, we studied its impact on glucocorticoid-induced adverse effects after treatment with dexamethasone (1 mg/kg/d) for 28 days *via* osmotic pumps. The viability and fertility of the mice were not affected by the genotype. In absence of dexamethasone treatment, we observed no genotype-based differences in adrenal gland weight, corticosterone secretion levels after a single intraperitoneal administration of dexamethasone (WT 9.4 ng/ml [3.5;12.2]; HET 4.4 ng/ml [2.6;6.2]; HOM 9.6 ng/ml [4.8; 12.6], $n=4$), glucose metabolism (fasting glycemia, WT 117 mg/dL[90;145], HET 107 mg/dL [95;121], HOM 96 mg/dL [83;138], $n=3$) or behavioral outcomes. The impact of the N363S

variant on the development of adverse effects, such as glucocorticoid-induced adrenal insufficiency, impaired glucose metabolism and depressive features, is currently being investigated after prolonged dexamethasone treatment. Overall, we developed a novel mouse model expressing the N363S variant of the *Nr3c1* gene that will improve scientific knowledge on glucocorticoid sensitivity. Further, the N363S variant could be used as a predictive tool for personalized medicine.

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P44

JOINT2931

Real word incidence of adrenal insufficiency after long-terme use os systemic and inhaled corticosteroids

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Aim

The incidence of adrenal insufficiency following chronic use of both systemic and inhaled corticosteroids remains poorly known. The aim of our study was to assess the incidence of hospitalization for adrenal insufficiency (AI) after long-term use of systemic and inhaled corticosteroids in a large population-based cohort.

Methods

We used TriNetx Research Collaborative network, with access to electronic medical records from a number of participating health care organizations, to identify participants. Diagnosis was done using the International Classification of Diseases codes, and data on medications were studied. We included individuals who were treated with long-term systemic or inhaled only corticosteroids. We excluded those with a past history of causes of primary and secondary adrenocortical insufficiency. We used a 1:1 propensity-score to compare matched subjects treated by long term systemic ($n=243{,}430$) or inhaled ($n=315{,}237$) steroid to subjects treated by NSAID only.

Results

Mean age of the population studied was 56.5 ± 18 years, with 40% of men. Over a mean follow-up of 2.4 ± 1.9 years, long-term systemic corticosteroids use was associated with a more frequent diagnosis of AI (0.20% vs 0.04% per year; HR: 6.32, 95%CI [5.50–7.26], $P<0.001$) and a greater incidence of hospitalization for AI (0.02% vs 0.008% per year; HR: 3.52, 95%CI [2.57–4.84], $P<0.001$) as compared to individuals treated with NSAID. Long-term inhaled corticosteroids use was associated with a more common diagnosis of AI (0.05% vs 0.04% per year; HR: 1.55, 95%CI [1.34–1.80], $P<0.001$), without increased risk of hospitalization for AI (0.01% vs 0.01% per year; HR: 1.26, 95%CI [0.91–1.76], $P=0.17$) as compared to NSAID therapy.

Conclusions

Long-term use of systemic corticosteroids was associated with an increased risk of diagnosed AI with a greater incidence of hospitalization for AI over a 2.4-year follow-up. Inhaled corticosteroids use was associated with an increased incidence of diagnosed AI. These findings from a large real world-based cohort underscore the importance of preventing the onset of corticotropic insufficiency among individuals with long-term corticosteroids treatment.

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P45

JOINT3298

Real-world experience with 68Ga-Pentixa for positron emission tomography in the management of primary aldosteronism

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Background

Identification of unilateral disease in most patients with primary aldosteronism (PA) currently relies on invasive adrenal vein sampling (AVS). Positron emission tomography (PET) of the adrenal glands is emerging as a non-invasive alternative for treatment selection. The C-X-C chemokine receptor type 4 (CXCR4) tracer ^{68}Ga-PentixaFor has shown potential in visualising aldosterone-producing adenomas. However, real-world data for this novel method are still scarce. Here we present the currently largest European single-centre series of ^{68}Ga-PentixaFor PET/CT in patients with PA.

Methods

Between 11/2023 and 01/2025 35 patients underwent ^{68}Ga-PentixaFor PET/CT. The likelihood of unilateral disease was assessed qualitatively (visual inspection) and quantitatively (calculation of SUVmax-ratio). Treatment decisions were based on a combination of PET and AVS (where available). Subsequently, an expert centre for molecular imaging reviewed all PET scans blinded to AVS results. Postoperative outcomes were analysed based on the Primary Aldosteronism Surgery Outcome (PASO) criteria.

Results

PET was successfully completed in 35/35 patients and was reported as suggestive of unilateral disease by the local team in 18 (51%) patients. Of 22 patients who also underwent AVS, 12 (55%) had successful bilateral cannulation; 8 of these (36% of 22) demonstrated unilateral disease (6 were also identified on PET). When (partial) AVS data was combined with PET, high confidence to diagnose unilateral disease was reached for 12/22 (55%) patients who had both investigations. There was good agreement between the initial local and external expert reports in 28/35 (80%) cases. Following a second round of local reading with harmonized criteria (blinded to external reports), concordance increased to 33/35 (94%) cases; in two patients, intermediate probability of unilateral disease was only diagnosed by one centre. At the time of this analysis nine patients had undergone adrenalectomy, two informed by AVS, one informed by PET and AVS, and six informed by PET. Outcome data indicate complete biochemical remission in 2/2 operated patients based on AVS, 5/6 operated patients informed by PET, and 1/1 guided by both. The remaining patient showed partial remission. In two AVS, adverse events were reported (retroperitoneal hematoma, infection) while no adverse events were associated with PET.

Conclusion

Our initial experience with ^{68}Ga-PentixaFor PET/CT highlights its potential as a non-invasive additional modality to AVS for PA subtyping. Combining data from AVS and PET can expand achievement of definitive cure. Further studies are needed to validate PET interpretation criteria and better identify cases in which PET alone might suffice for PA subtyping.

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P46

JOINT2036

A retrospective longitudinal study on the association between urine metanephrines and cardiovascular events in patients in primary prevention without chromaffin tumors

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Background

Previous studies have suggested that urine metanephrines (metanephrine, dU-MT, and normetanephrine, dU-NMT), metabolites of catecholamines used in the

diagnosis and follow-up of pheochromocytomas and paragangliomas (PPGL), may serve as markers of sympathetic nervous system (SNS) hyperactivation. SNS overactivity has been observed in various cardiometabolic disorders such as hypertension, heart failure, and metabolic syndrome. However, the predictive role of metanephrines in cardiovascular events (CVE) remains unexplored.
Objectives
This retrospective longitudinal study aims to assess the association between urine metanephrine levels and the development of CVE in patients in primary prevention without PPGL.
Methods
Adult patients who underwent measurement of 24-hour urine fractionated metanephrines at the Clinical Biochemistry Laboratory of the City of Health and Science University Hospital of Turin between 2007 and 2015 were included in the analysis. Patients were stratified into tertiles based on dU-MT and dU-NMT levels. Exclusion criteria encompassed a diagnosis of PPGL, prior CVE, interfering therapies, acute conditions at the time of testing, and stage IV-V chronic kidney disease. CVE development (coronary artery disease, stroke, symptomatic peripheral artery disease, arrhythmias, and heart failure) was assessed by retrieving pertinent discharge diagnoses from a regional database, restricting the evaluation to hospital admissions that occurred after the measurement of urine metanephrines.
Results
The final population consisted of 1,170 individuals (41.5% male, mean age 54 $\pm$ 14 years), 86% of whom had arterial hypertension. During a mean follow-up period of 11.7 $\pm$ 4.1 years, 14.7% of patients experienced a CVE. In univariate analysis, patients in the 2nd and 3rd tertiles of dU-NMT showed lower CVE-free survival compared to those in the 1st tertile ($P=0.020$ and $P < 0.001$, respectively). Multivariate Cox regression analysis revealed that patients in the 3rd tertile of dU-NMT had a 1.76-fold increased risk of CVE compared to those in the 1st tertile ($P=0.010$), regardless of traditional cardiovascular risk factors (age, sex, smoking status, family history of CVE, hypertension, and diabetes mellitus), renal function, number of antihypertensive drugs, and lipid-lowering therapy. Tertiles of dU-MT, however, did not show a significant difference in CVE risk.
Conclusions
This study reveals an association between higher dU-NMT levels and increased long-term risk of CVE, regardless of traditional risk factors, within a primary prevention cohort of patients without PPGL. These findings suggest that such metabolites could serve as a valuable tool for cardiovascular risk stratification.

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P47

JOINT2972

Circadian dysregulation of metabolic pathways in different states of cortisol excess and insufficiency

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Background
Adrenal insufficiency (AI) under glucocorticoid replacement therapy, adrenocortical tumors with mild autonomous cortisol secretion (MACS), and Cushing syndrome (CS), are characterized by different patterns of dysregulation of cortisol circadian rhythm. Despite the relationship between cortisol and energy metabolism is established, little is known about circadian-specific metabolic derangements in any of these conditions.
Aim
To characterize circadian fluctuations of acylcarnitines, sphingomyelins, glycerophospholipids, amino acids, and biogenic amines in healthy subjects (HS), and in patients affected by AI, MACS, and CS in dried blood spots (DBS).
Methods
We enrolled patients with AI ($n=8$) under dual-release hydrocortisone, and subjects with MACS ($n=12$) and CS ($n=9$) at diagnosis. HS ($n=10$) were drawn from the general population. All subjects underwent a 7-days standardized isocaloric Mediterranean diet. On day 7th, subjects collected DBS samples 30 minutes before and 2 hours after each meal (breakfast, lunch, and dinner), and at 11 pm. We measured 21 amino acids, 21 biogenic amines, 40 acylcarnitines, 15 sphingomyelins, and 90 glycerophospholipids by a targeted metabolomics LC–MS/MS method previously validated for DBS. Data were explored by a two-step approach. Firstly, a BORUTA algorithm trained on disease groups separation was performed. According to an all-features-matter approach, permutations of features were tested in a random forest classifier, pruning out uninformative features and keeping features describing differences among groups. Secondly, Factor Analysis (FA) was applied to reduce data dimensionality. To characterize the circadian fluctuation of interesting molecular patterns, the linear combination of selected molecule concentrations and FA-derived coefficients was evaluated along the 7 time-points.
Results
Two molecular patterns were highlighted. In pattern A, phosphatidylcholine (PC)-ae-C34:2, PC-ae-C34:3, PC-aa-C34:2, PC-aa-C36:2 and PC-aa-C36:0 differentiated HS from patients with AI, MACS, and CS. Overall, higher concentrations were detected in HS with respect to disease groups, with maximum difference at 2 hours after lunch ($P<0.05$). In pattern B, PC-aa-C38:4, PC-aa-C36:4, lysoPC-a-C20:4, PC-aa-C36:5 and Met differentiated HS and patients with AI from those with MACS and CS. In particular, patients with CS and MACS showed higher concentrations than HS and patients with AI, with maximum differences at 2 hours after lunch and 30 minutes before dinner ($P<0.05$ for both). At the same time-points, patients with AI had lower levels of compounds of pattern B than HS ($P<0.05$).
Conclusions
The phosphatidylcholine system is predominantly affected in different states of glucocorticoid replacement and cortisol excess. Dysregulation is mostly evident in the afternoon. Phosphatidylcholines appear relevant biomarkers of cortisol-related metabolic alterations.

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P48

JOINT3709

Cardiac function and morphology in patients with adrenal incidentalomas: a longitudinal study

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Background
Emerging evidence suggests that mild autonomous cortisol secretion (MACS) might be directly associated with increased cardiac mass and diastolic dysfunction compared to non-functioning adrenal incidentalomas (NFAI). Nevertheless, the reversibility of these alterations following appropriate treatment has never been investigated. This study evaluated cardiac morphology in patients with adrenal incidentalomas over a 5-year follow-up period, comparing the effects of active surveillance to adrenalectomy in patients with MACS.
Methods
This prospective longitudinal case–control study included 60 patients with adrenal incidentalomas. After stratification based on cortisol levels post-dexamethasone suppression test, 34 patients with MACS and 26 with NFAI were evaluated for clinical, biochemical, and echocardiographic parameters at baseline and after 1 and/or 5 years of follow-up. Patients with MACS were managed either with active surveillance (AS, $n=23$) or unilateral adrenalectomy (ADRX, $n=11$), according to current recommendations.
Results
At baseline, patients with MACS showed higher left ventricular mass index (LVMi, $P=0.021$), interventricular septal (IVS) ($P=0.007$), and posterior wall (PW) thickness ($P=0.004$) compared to NFAI, along with higher prevalence of diastolic dysfunction and left ventricular hypertrophy ($P=0.050$ and $P=0.013$). Patients undergoing ADRX presented with larger adrenal mass diameters, higher prevalence of arterial hypertension, and lower ACTH levels ($P<0.001$ for all). After 1 year, the ADRX group showed a significant reduction in LVMi ($P=0.031$), IVS ($P=0.042$), and PW thickness ($P=0.037$), followed by a progressive increase to baseline values at the 5-year timepoint. The AS group showed overall long-term stability in cardiac parameters, while the NFAI group showed a significant, progressive increase of cardiac indexes through the 5-year follow-up. Accordingly, the ADRX showed a significantly higher decrease in

LVMi and PW thickness compared to the other two groups at the 1-year follow-up, even adjusting for sex and age ($P<0.001$, $P=0.003$). No significant inter-group differences were detected at the 5-year follow-up. In patients with MACS, linear regression analysis showed that unilateral adrenalectomy was the element most strongly associated with the 1-year improvement in LVMi ($R^2=0.423$, $P=0.017$) and PW thickness ($R^2=0.422$, $P=0.023$). The overall progression of the main cardiometabolic comorbidities remained comparable among the three groups.

Conclusions

Patients with MACS exhibit early cardiac remodelling compared to NFAI, independent of conventional risk factors. Unilateral adrenalectomy induced short-term improvement in cardiac parameters, which was not maintained on the long-term. Active surveillance in MACS resulted in long-term cardiac stability, likely reflecting the more intensive cardiovascular monitoring compared to NFAI, and underscoring the importance of cardiovascular monitoring to pursue individualized treatment strategies.

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P49

JOINT1287

Correlation of morning cortisol with HPA axis response to insulin-induced hypoglycemia in children

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Background

Diagnosis of adrenal insufficiency (AI) in children requires formal cortisol stimulation test which is time-consuming and costly. While morning cortisol levels has been proposed to predict hypothalamic–pituitary–adrenal (HPA) axis integrity in adults, data on children are limited. This study aimed to investigate the association between basal morning cortisol and peak cortisol response to the insulin tolerance test (ITT), the gold standard for diagnosing adrenal insufficiency, and to establish morning cortisol cutoff values for predicting AI in children.

Method

This retrospective study includes all children aged <18 years who underwent ITT to evaluate the cause of short stature. Subjects with prior steroid use and known pituitary or adrenal diseases were excluded. We collected data on age, sex, anthropometry, Tanner stages, glucose levels, baseline and peak cortisol levels, and cortisol increment (peak–baseline) during ITT. AI was defined as a peak cortisol level from ITT <18 mcg/dL measured by Chemiluminescence Immunoassay. The Mann–Whitney U test compared data between AI group and normal HPA group (nHPA). Spearman's rho correlation assessed association between variables. ROC analysis determined optimal cortisol cutoff values for predicting AI.

Result

Of the 108 subjects, 70 (64.8%) were male. The median age was 9.4 years (4.3–17.2). AI was diagnosed in 50 (46.3%) of the subjects. Compared to the nHPA, the AI showed significantly lower baseline morning cortisol (9.7 [4.7] vs. 12.6 [6.4] mcg/dL, $P=0.018$), and a significant smaller cortisol increment during ITT (3 [7.9] vs. 9.7 [10.7] mcg/dL, $P<0.001$). Baseline morning cortisol levels were positively associated with peak cortisol levels from ITT ($r=0.336$, $P<0.001$), particularly in the AI group ($r=0.535$, $P<0.001$). Peak cortisol levels correlated with cortisol increment ($r=0.45$, $P<0.001$), but not with age, anthropometry, Tanner stage, or gender. Regarding the morning cortisol levels, the cutoff of $<$ 6.3 mcg/dL showed highest sensitivity (34%) and specificity (86.2%), although the best cutoff to predict AI was <4.8 mcg/dL (sensitivity 22%, specificity 91.4%), and the best cutoff to predict nHPA was >16.7 mcg/dL (sensitivity 90% and specificity 31%)(AUC 0.632, $P=0.013$). The cortisol increment cutoff of $<$ 8.7 mcg/dL from ITT showed the best sensitivity (82%) and specificity (60%) to predict AI in children (AUC 0.737, $P<0.001$).

Conclusion

Basal morning cortisol levels and cortisol increment were well correlated with peak cortisol response to ITT and could be used to predict AI in children, potentially reducing the need for further unnecessary procedures. Further investigation in larger cohorts is warranted to validate these findings.

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P50

JOINT1137

Pseudohypoaldosteronism in infantile atopic dermatitis: a case series

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Recent literature has highlighted a potential association between severe atopic dermatitis (AD) in infancy and biochemical disturbances resembling pseudohypoaldosteronism (PHA), though the mechanisms behind these disturbances remain poorly understood. We present a case series of three children, aged three to seven months, who were admitted with severe exudative eczema and were found to be hyponatraemic (sodium levels 115–129 mmol/l) and hyperkalaemic (potassium levels 6.3–7.4 mmol/l) on routine blood testing. Screening for PHA revealed elevated aldosterone levels with hyperreninaemia and increased urinary corticosterone and aldosterone metabolites providing further evidence of activation of the renin–angiotensin system (RAS). In each case, these biochemical and hormonal disturbances resolved after optimising dermatological and nutritional management of their atopic presentations. Trans-epidermal sodium loss driving volume depletion has commonly been hypothesised to determine both hyponatraemia and RAS activation in severe eczema, but direct evidence in support of this mechanism remains sparse. In all three cases, the patients exhibited low urinary sodium levels despite elevated aldosterone and renin, suggesting a compensatory response to hypovolaemia rather than renal tubular resistance to aldosterone. We also explore other potential contributing factors, including gastrointestinal protein and sodium loss due to increased permeability in the gastrointestinal tract, which is common in children with severe eczema and food allergies. Chronic inflammatory states associated with severe AD may also induce dilutional hyponatraemia and disrupt potassium handling in the kidneys. Furthermore, age-related factors such as low muscle mass and the physiological unresponsiveness to aldosterone in infancy may exacerbate electrolyte imbalances and complicate the clinical picture. This case series contributes to the sparse but growing body of literature on pseudohypoaldosteronism-like disturbances in severe infantile atopic dermatitis. The findings underscore the multi-system impact of severe eczema, highlighting the importance of considering not only dermatological management but also biochemical and hormonal factors in the comprehensive treatment of infantile AD. These cases reinforce the need for a holistic, multidisciplinary approach to early management in order to prevent severe complications, including electrolyte imbalances and nutritional deficiencies, that can arise in the context of this chronic inflammatory condition.

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P51

JOINT3087

Real-life evaluation of efficacy and safety of modified-release hydrocortisone (MR-HC) in children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency: A national cohort study

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Background
Modified-release hydrocortisone (MR-HC) has been developed to mimic the cortisol rhythm and has recently been approved to improve the disease control in children with Congenital Adrenal Hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD), older than 12 years. Aim of this multicenter study is to assess the efficacy and safety of MR-HC in a national cohort of children.
Study population and methods
71 children with 21OHD (25M/46F; age 15.3 ± 2.4 years) were evaluated before and after 6 months of MR-HC. Fifty-four (76.1%) had classic form of 21OHD (66.2% salt wasting) and 17 (23.9%) the non-classic form. Before to switching to MR-HC, all patients were receiving conventional HC at an average dose of 16.0 ± 4.0 mg/m^2 per day. General wellbeing, adverse effects (AE), frequency of adrenal crisis (AC), Body Mass Index (BMI), systolic (SBP) and diastolic blood pressure (DBP), ACTH, 17-Hydroxyprogesterone (17OHP), Androstenedione, Renin, Insulin, HOMA IR levels and lipid profile were assessed before and after 6 months of MR-HC. Primary outcome was the change in 17OHP levels at 9.00 am; secondary outcomes included changes in other adrenal precursors, body mass index (BMI), insulin sensitivity, general wellbeing and the frequency of AE and AC.
Results
After 6 months of MR − HC, 17OHP (12.5 ± 26.0 vs 25.5 ± 35.0 ng/ml, $P = 0.005$) and ACTH (37.8 ± 56.9 vs 141 ± 233 pg/ml, $P = 0.001$) levels significantly decreased compared to pre − treatment values, despite the HC dose remained unchanged (15.80 ± 3.68 vs 16.0 ± 4.0 mg/m^2/day). Androstenedione (2.2 ± 1.8 vs 2.7 ± 1.9 ng/ml) and Renin (61.6 ± 54.0 vs 82.3 ± 85.0, pg/ml) levels also decreased, but these changes were not statistically significant. Insulin (14.9 ± 6.0 mcUI/ml vs 16.2 ± 7.0) and HOMA − IR (2.8 ± 1.56 vs 3.02 ± 1.7) showed slight, but not significant reductions. No significant changes were observed in BMISDS, SBP, DBP and lipid profile during MR-HC treatment. General wellbeing improved significantly from 77.5% to 96.6% after 6 months of MR-HC ($P = 0.005$). No severe AEs were reported, and the frequency of AC remained unchanged compared to conventional treatment.
Conclusions
Preliminary results suggest that MR-HC treatment improves general wellbeing and biochemical disease control in children with 21OHD, with no significant adverse effects. The findings also indicate beneficial effects on insulin sensitivity, although these results need to be confirmed in a larger cohort with a longer treatment duration.

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P52

JOINT2392

WHAT...IF? Organizing a focus group for young adults with congenital adrenal hyperplasia who underwent feminizing surgery in childhood and/or adolescence

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Background
Congenital adrenal hyperplasia (CAH) is a rare genetic disorder caused by an enzyme deficiency in the adrenal glands, resulting in insufficient cortisol and aldosterone production and high androgen levels. Girls with CAH are often born with virilized genitalia. For long, early feminizing surgery has been proposed to manage the situation. This practice has become a subject of medical and ethical debate while experiences of those who are directly impacted remain underrepresented in research.
Objective
To understand the perception of adult females diagnosed with CAH, who underwent genital surgery in childhood, on early feminizing surgery.
Methods
We organized a focus group, complemented with two individual interviews; all audio-recorded. The group discussion focused on participants' experiences with the surgery they had and their perception in the present debate. The recorded discussion was transcribed. The transcribed discussion was uploaded in NVivo, a software for data analysis. Thematic analysis, a structured method to identify and analyze discussions, elucidated themes across the data set on participants' experiences, views, opinions and values.
Results
Arguments pro early feminizing surgery — with the number of respondents who mentioned the argument between brackets — were societal participation (4), psychological well-being (4), reduced medical burden (3), body acceptance (3), potential need to explain their gender (3), align external genitalia with the experienced gender (3), challenge of determining the appropriate cut-off age (2), easier recovery at a younger age (2), preserving fertility and pregnancy (2), and reduced decisional distress (2). Arguments against feminizing surgery were autonomy (4), bodily integrity (2), complications (2), minimizing surgical interventions (2) and irreversibility (1). If their own daughter would have CAH, three women expressed a preference for surgery as early as possible.
Discussion
Participants underscored the importance of psychosocial support and the influence of family and societal acceptance on mental health, a positive self-image, and social participation. Participants proposed a preference for management of CAH that balances respect for patient autonomy and sensitivity to societal and medical contexts. The results indicated a divergence between the complex lived experiences of patients and the perspectives brought by activist movements, underscoring a gap in research on patient-reported outcomes in CAH.
Conclusions
This study highlights the necessity for more patient-centered management and further investigation into both surgical and non-surgical management options for CAH.

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P53

JOINT1017

Aldosterone synthase (CYP11B2) immunostaining predicts outcome in unilateral primary aldosteronism

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Background
The effectiveness of histopathological classification using CYP11B2 immunostaining in unilateral primary aldosteronism (PA) for predicting clinical and biochemical outcomes following adrenalectomy remains a topic of debate. To date, no studies have conclusively shown that HISTALDO influences hypertension remission, and its effect on biochemical success varies among different ethnic groups.
Methods
We conducted a cohort study involving 131 consecutive patients with unilateral PA who underwent unilateral adrenalectomy. Aldosterone-producing adrenal lesions were classified according to the HISTALDO criteria. Biochemical and clinical outcomes were assessed using the PASO criteria.
Results
Among the 131 adrenal lesions, classical and non-classical histology were identified in 101 (77.09%) and 30 (22.91%) cases, respectively. In the classical group, 89 cases were classified as aldosterone-producing adenoma (APA), and 12 as aldosterone-producing nodule (APN). Within the non-classical group, 27 cases (90%) had multiple aldosterone-producing micronodules (APM), and 3 cases (30%) had multiple APNs. Patients with classical histology were younger ($P = 0.028$) and predominantly female ($P = 0.028$) compared to those with non-classical histology. Classical histology was associated with higher rates of complete biochemical success (97.03% vs. 68.97%, $P < 0.001$) and complete hypertension remission (34.34% vs. 10.71%, $P < 0.001$) compared to non-classical histology. Although clinical and biochemical outcomes were similar between APA and APN, their immunohistological characteristics differed (fewer clear cells and stronger CYP11B2 staining in APN). In multivariable analysis, classical histology remained independently associated with complete biochemical ($P < 0.001$) and clinical ($P = 0.037$) success.
Conclusion
Classical histology was an independent variable associated with more severe PA, complete biochemical and hypertension remission in surgically treated patients

with unilateral PA. Moreover, the distinction between APA and APN did not differentiate outcome.

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P54

JOINT1349

High prevalence of CYP11B2-positive aldosterone-producing micronodules in subjects without known adrenal diseases

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Background
The zona glomerulosa (ZG) of the adrenal cortex synthesizes aldosterone, a key hormone involved in blood pressure regulation. Previous studies have shown an inverse correlation between age and both the continuity of aldosterone synthase (CYP11B2) expression and the area expressing CYP11B2. However, the significance of CYP11B2 discontinuity in the development of primary aldosteronism remains unclear. This study aimed to investigate patient demographics and explore the localization, symmetry, and clinical relevance of adrenal cortical lesions expressing CYP11B2.
Methods
This cross-sectional study included 145 consecutive autopsied cases from southern Finland without known adrenal diseases, all of whom had died from exogenic causes (trauma, suicide, or intoxication). Immunohistochemical CYP11B2 staining was performed on both adrenal glands and analyzed following the HISTALDO consensus guidelines. A four-grade classification system was used to assess CYP11B2 continuity: 1) diffuse CYP11B2 positivity (normal), 2) twenty or more aldosterone-producing micronodules (APMs $\geq$20), 3) APMs $<$ 20, and 4) aldosterone-producing nodules (APNs). Autopsy findings were recorded, and clinical data including diagnoses of hypertension and antihypertensive medication prescriptions from the past 10 years were obtained from national registries. This sub-study was registered at ClinicalTrials.gov (NCT05446779).
Results
The study cohort included 104 males (71.7%) and 41 females (28.3%), with a mean age of 53.7 years (range: 26.1–76.4 years). Among the participants, 12 (8.3%) exhibited bilateral diffuse CYP11B2 positivity, while APMs were identified in 131 subjects (90.3%). Of these, 42 cases (29.0%) had APMs $\geq$20 and 89 cases (61.4%) had APMs $<$20. Two cases (1.4%) with APNs were detected. Both APMs $\geq$20 and APMs $<$20 showed notable symmetry between the two adrenals, with concordant CYP11B2 continuity in 76.2% and 68.5% cases, respectively. CYP11B2 continuity did not associate with age, diagnosis of hypertension, or use of antihypertensives. Heart weight was significantly higher in subjects with APMs $<$20 compared to those with APMs $\geq$20 or diffuse CYP11B2 positivity ($P=0.048$ and $P=0.021$, respectively).
Conclusions
Bilateral diffuse CYP11B2 positivity, considered as normal ZG structure, was surprisingly rare. APMs were frequently observed in the adrenal glands, showing notable side-to-side symmetry. Heart weight was significantly associated with decreased CYP11B2 continuity. However, neither the diagnosis of hypertension nor the use of antihypertensive medications was related with the CYP11B2 continuity categories. Contrary to previous studies, age did not associate with CYP11B2 discontinuity. Our cross-sectional results indicate that bilateral CYP11B2 discontinuity is a frequent finding.

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P55

JOINT1623

Advancing adrenal tissue analysis: A comprehensive guide to immunohistochemical evaluation, RNA-scope, and digital pathology with QuPath

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Background
Histological analysis of adrenal tissue, particularly through immunohistochemical (IHC) staining and modern RNA-scope techniques, is pivotal in adrenal disease research and diagnosis. Traditionally, IHC evaluation relies on semi-quantitative methods such as the H-score, which offers the advantage of a straightforward, flexible, and numerical scaling system that integrates both the intensity and distribution of staining. However, these manual approaches are time-intensive, subjective, and prone to inter- and intraobserver variability, resulting in limited reproducibility.
Methods and results
To address these challenges, we developed a widely applicable protocol for adrenal tissue analysis based on automated cell detection using QuPath, an open-source digital pathology platform. Our method was evaluated for accuracy, robustness, and reproducibility and will additionally be assessed in direct comparison to the H-score. The protocol includes optimized cell detection strategies tailored to specific adrenal tissue types (normal gland ($n=3$), adenomas ($n=39$) and carcinomas ($n=240$), non-adrenal controls $n=40$)), adaptations for various unique staining patterns, assessment of tissue microarrays, and practical solutions for scenarios with restricted computational capacity. Furthermore, QuPath provides advanced AI tools to detect the presence of potentially confounding cells, such as blood cells, connective tissue or fat. We optimized these tools for adrenal tissue, offering practical insights to enhance analytical precision. QuPath is also capable of analyzing RNA-scope stainings ($n=59$ specimens, assessed for three targets respectively), which is traditionally performed semi-quantitatively, whereby a subset of cells and RNA spots are counted to calculate a spots-per-cell ratio. To enhance efficiency and reproducibility, the manufacturer recommends the use of software-based analysis. Utilizing QuPath's capabilities for automated cell detection and RNA spot identification significantly streamlines the evaluation process, providing a more representative and reliable assessment of RNA expression across entire tissue sections. Finally, we conclude our protocol by showcasing some of QuPath's visualization features on the adrenal gland, providing the necessary tools to get the most out of staining experiments.
Conclusion
Computational techniques have the potential to fundamentally revolutionize the assessment of adrenal tissue. With automated image analysis, large amounts of data can be evaluated more efficiently, reproducibly, and objectively, especially regarding marker expression. The additional use of artificial intelligence opens up the possibility of specifically recognizing distinct cell types and accounting for interfering tissue.

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P56

JOINT3703

Long-term outcomes and prognostic value of LC–MS/MS hormone profiling in the largest single-center cohort of adrenocortical carcinoma: a cohort study since 2000

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Background
Adrenocortical carcinoma (ACC) is a rare cancer with limited population-based studies. This study aimed to analyze the largest single-center ACC cohort over a 20-year period, investigating prognostic factors for clinical outcomes and the relevance of liquid chromatography tandem mass spectrometry (LC–MS/MS) for hormone measurement.
Methods
We conducted a cohort study of patients treated at our referral center from January 2000 to May 2024. Clinicopathological characteristics, including sex-

and age-related differences, were analyzed. Overall survival (OS) was assessed using Kaplan–Meier and Cox regression analyses. Hormone profiling via LC–MS/MS including 15 steroids was performed in a subgroup and compared with standard hormone assays.

Results

1516 ACC patients (median age 51 years, IQR 39–62; 62% female) were included. Median OS was 59 months (95%CI = 50.1–87.9), with ENSAT tumor stage, resection status, Ki67-index confirmed as independent prognostic factors ($P < 0.001$). No significant sex-related differences were found in OS, age at diagnosis, tumor stage, or metastasis patterns. However, men had larger tumors (median 12 (8–16) vs 10 (7–14) cm) that were more frequently incidentally diagnosed (39% vs 26%, $P < 0.001$, $\chi^2 = 23.06$). Young patients (< 16 years-old) had significantly longer OS (median not-reached) compared to young/adult (91 months, 95%CI = 69.3–122.7), adult (63 months, 95%CI = 48.6–77.8) and old patients (35 months, 95%CI 28.7–41.3) at multivariate regression (HR between 0.8 and 0.3, $P < 0.001$). Endocrine-inactive and androgens-secreting tumors were associated with significant better survival (111 months, 95%CI = 60.6–161.4, HR = 0.56, $P > 0.001$; and 105 months, 95%CI = 56.6–153.5, HR = 0.63, $P = 0.01$) than other hormone-secreting tumors (36 months, 95%CI = 30.3–41.6) at Cox regression. At diagnosis, metastases in liver, lymph nodes, and bone were associated with worse outcomes ($P < 0.01$), while lung metastases had no significant impact. In 78 patients evaluated with LC–MS/MS, a median of 3 (IQR 2–5) elevated steroids *per* patient was found and only 3 (3.8%) had complete negative hormonal profiles compared to 7 (8.9%) classified as inactive by standard immunoassays. Especially 11-deoxycortisol and 11-deoxycorticosterone were frequently detected (82% and 48%, respectively), also in patients with apparently inactive tumors. Increase of ≥4 steroids were associated with poorer OS (15 months, 95%CI = 7.6–22.4) than those with ≤3 increased steroids (31 months, 95%CI = 21.9–40.1; HR = 1.9, 95%CI = 1.1–3.8, $P = 0.04$) at multivariate regression.

Conclusion

While ACC is more frequent in women, our study suggest that sex-dimorphism has no impact on clinical outcome. Younger age, endocrine-inactive, and androgen-secreting tumors are associated with better survival. LC–MS/MS steroid panel diagnostic enhances hormonal detection and demonstrates that virtually all ACCs are endocrine active, improving diagnosis and potentially impacting patient management.

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P57

JOINT1418

Adrenalectomy reduces the risk of vertebral fractures in patients with adrenal adenoma and mild autonomous cortisol secretion

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Objective

Mild autonomous cortisol secretion (MACS) is associated with increased risk of vertebral fractures (VFx). However, the impact of recovery from MACS on bone health remains unclear.

Design

Retrospective Longitudinal Intervention Study (Study 1): A total of 53 patients with MACS were followed for 35.2 ± 18.6 months (mean ± S.D.). Among these, 31 patients underwent surgery (Study 1-GroupA), while 22 patients received conservative treatment (Study 1-GroupB). Prospective Randomized Study (Study 2): Fifty-one outpatients with MACS were randomly assigned to either adrenalectomy (Study 2-GroupA, 21 patients, 67% females, age 63 [56.5–72.5]) or a conservative approach (Study 2-GroupB, 28 patients, 78% females, age 69 [61–73]) and were followed for 24 months.

Methods

MACS was diagnosed in patients with adrenal incidentalomas > 1 cm and cortisol after 1-mg dexamethasone suppression test (F-1 mgDST) ≥ 1.8 μg/dL. At baseline and at the end of the follow-up we assessed: mineral metabolism, bone mineral density (BMD) at the lumbar spine (LS), total hip (TH) and femoral neck (FN) using Dual-energy X-ray Absorptiometry, and clinical and morphometric vertebral fractures (VFx).

Results

Study 1: Study 1-GroupB showed an increased incidence of VFx ($n = 11$) at the end of the follow-up when compared to Study1-GroupA ($n = 3$, $P < 0.05$). In both groups, BMD at LS, FN and TH were similar at baseline and at the end of follow-up. In Study 1-GroupB, a new VFx occurred in 50% of patients, including 2 out of the 5 patients treated with bisphosphonates; in GroupA, 3 patients (9.7%) experienced incident VFx, all having a prevalent VFx at baseline. Study 2: Patients in both groups were comparable for demographic features (age, sex, BMI), adenoma's size, cortisol secretion parameters (F-1 mgDST, urinary free cortisol, ACTH), prevalent VFx and BMD at baseline. After 24 months, in Study 2-GroupA, we observed significant increases in calcium and phosphate levels compared to baseline ($P = 0.03$ and $P = 0.04$, respectively). In Study 2-GroupB, no significant changes were noted when comparing baseline values with those after 24 months. Additionally, at the end of follow up, BMD remained stable across both groups. However, Study 2-GroupB showed a significantly higher incidence ($n = 7$, 25%) of VFx by the end of the follow-up period compared to Study 2-GroupA ($n = 1$, 4.8%, $P = 0.04$).

Conclusions

In patients with unilateral adrenal incidentalomas and MACS, adrenalectomy significantly reduces the risk of vertebral fractures.

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P58

JOINT3959

Pediatric adrenal incidentalomas: Insights from a multicenter study on diagnosis and outcomes

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Objective

Adrenal incidentalomas (AIs) are asymptomatic adrenal masses with a diameter of ≥1 cm that are detected incidentally during imaging without suspicion of adrenal gland disease. Most studies have focused on the characteristics of adult AIs and the recommendations for their diagnosis. However, the clinical characteristics of AIs in childhood differ greatly from those in adulthood. This multicenter study aimed to examine the clinical, laboratory and imaging characteristics of AIs in children to guide the clinical diagnosis and treatment.

Methods
The clinical data of pediatric AI cases admitted to participating hospitals from 2010 to 2024 was collected and analyzed retrospectively. The data analysis included the patient's sex, age; initial presentation, imaging, composition, size and site of the mass; tumor function; intervention/surgery and pathological/clinical diagnosis. All patients' radiographic images were reviewed by an experienced radiologist of the coordinating center. The determination of a malignant/benign tumor was primarily based upon histological findings from surgical resections.
Results
Nineteen children (68.4% male) were included,with a mean follow-up of 3.05 ± 2.83 years and mean age of 10.69 ± 4.24 (3.9–17.5) years. Abdominal ultrasound revealed almost all of the AIs (94.7%), while only one mass was detected with abdominal computed tomography. Most masses were <4 cm (68.4%), hormonally non-functional (84.2%) and excised (89.4%) by laparoscopic/laparotomic adrenalectomy. Seventeen cases (89.4%) were biopsy-confirmed, two (hemorrhage sequelae calcification and benign adrenal mass) were diagnosed clinically. These two cases who followed up without adrenalectomy remained clinically stable, with no increase in size. One patient who had adrenalectomy for bilateral pheochromocytoma developed adrenal insufficiency during follow-up. Among all the AIs, ganglioneuroma was the most common (63.2%). The mean age at ganglioneuroma diagnosis was 10 ± 4.64 years, most cases were male patients (75%) and most of them sized <4 cm (66.6%). The other diagnosed conditions were two adrenocortical neoplasia and one case each of pheochromocytoma, hemorrhagic sequela calcification, gastric duplication cyst, benign adrenal mass and adrenocortical-medullary hemorrhage. Both adrenocortical neoplasia cases were evaluated as suspicious for malignancy by the radiologist due to their heterogeneous internal structures, presence of hemorrhagic/calcific components, >4 cm size and heterogeneous contrast enhancement outside of adenoma characteristics.
Conclusion
Generally, most AIs are benign and poorly functional; often do not show any physical signs of excess/insufficient hormone secretion. In our multicenter study, ganglioneuroma was the most common type of pediatric AI. All of these cases were hormonally non-functional. Sixteen patients (84.2%) were regularly followed and all remained stable throughout the surveillance period.

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P59

JOINT821

Adrenomedullary stem cells can instigate the formation of steroidogenic adrenal cortex through paracrine signalling

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Adrenal disorders, such as congenital adrenal hyperplasia or Addison's disease, can require lifelong hormone replacement therapy and may result in potentially life-threatening complications. Although steroid cell replacement strategies could be attractive therapeutical approaches, the generation of steroid hormone-producing cells *in vitro* remains inefficient. The adrenal glands consist of two interdependent tissues of distinct developmental origin: the adrenal cortex, which arises from the intermediate mesoderm during development, and the adrenal medulla, which originates from the trunk neural crest, migrating from the neural folds. We recently demonstrated that SOX2+ cells of the postnatal adrenal medulla have stem cell properties throughout life, generate new chromaffin cells, and promote chromaffin cell proliferation through paracrine secretion of WNT6. It is not known if this inductive potential of neural crest-derived adrenomedullary stem cells (AMSCs) extends to the influence of cell fate and regulation in the cortex. We present here that altering the metabolic activity of AMSCs through genetic mutation in the succinate dehydrogenase complex, leads to changes in their paracrine secretion properties. Mutant AMSCs of postnatal mice influence surrounding mesenchyme, leading to the generation of new accessory adrenal structures *in vivo*, that include a capsule and adrenal cortex expressing steroidogenic markers. These results confirm that postnatal mesenchyme can remain competent to generate new adrenal cortex *in vivo,* and that key signals, secreted from mutant AMSCs, can influence steroidogenic differentiation. Taken together, these findings can be harnessed to improve the efficiency of regenerative approaches for adrenal disorders relying on the generation of steroid-producing cells.

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P60

JOINT3229

Adrenal insufficiency associated with mutations in haem biosynthesis genes

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Mutations in the 8 haem biosynthetic pathway genes are traditionally known to cause a group of diseases known as porphyria. While Primary Adrenal Insufficiency (PAI), an intrinsic adrenal defect in glucocorticoid synthesis ± mineralocorticoid synthesis, is linked to mutations in more than 25 genes. Over the last few decades, there have been tantalising case reports linking porphyria with defects in steroidogenesis. We identified seven families (11 individuals) with defects in haem biosynthetic enzymes who exhibit flagrant adrenal insufficiency (AI), with or without porphyria. 1) a kindred ($n=4$) from Egypt with biallelic mutations in protoporphyrinogen oxidase (*PPOX*) p.(Glu339Lys), who have variegate porphyria along with severe AI. 2) Three kindreds with mutations in coproporphyrinogen oxidase (*CPOX*), with variable presentations (i) a female with p.(Pro367Ala) mutation, (ii) siblings of Kurdish descent homozygous for p.(Ser28*) mutation, one of which had no clinical manifestations of HCP but has severe AI, and (iii) a patient with HCP from France who presented with AI aged 64. 3) Three adult patients with mutations in Hydroxymethylbilane Synthase (*HMBS*) who presented with AI during acute hepatic porphyria attacks. We hypothesized that reduced enzyme activity may cause AI through reduction in the level or activity of steroidogenic CYP450 enzymes due to the lack of haem, toxicity of accumulated intermediate porphyrins, and/or the increased oxidative stress these may cause. We investigated the underlying mechanism, employing knockdown and knockout *PPOX* and *CPOX* human adrenal cell lines (H295R) plus an animal model of *PPOX* deficiency to measure steroid perturbations, enzyme activity and levels of oxidative stress. PPOX knockdown significantly reduces cortisol output in our cell model, whereas CPOX knockdown does not, likely due to differences in residual enzymatic activity. CRISPR knockout of these genes was unsuccessful, consistent with the lethal nature of homozygous null mutations in humans and other mammals, highlighting their essential role in survival. In heterozygous PPOX mice, mimicking an acute porphyria attack by administering 5-aminolevulinic acid (ALA) blunted the Synacthen response in both WT and mutant animals.
Conclusion
Although we have not fully delineated the mechanism, our finding of a link between mutations in haem biosynthesis genes and PAI indicates that testing adrenal function in porphyria patients and their families might be warranted. Furthermore, haem biosynthesis genes should be considered for inclusion in genetic testing panels for isolated adrenal insufficiency.

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P61

JOINT3261

Lipoid congenital adrenal hyperplasia due to mutations in StAR: Genotype and phenotype in 10 Vietnamese patients

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Background
Lipoid congenital adrenal hyperplasia (LCAH) is the most severe form of congenital adrenal hyperplasia. It is characterized by severe adrenal insufficiency and gonadal steroidogenesis impairment. Most cases of lipoid CAH are caused by recessive mutations in the gene encoding a steroidogenic acute regulatory protein (*StAR*).
Objectives
To identify variants of *StAR* and to describe the phenotype and genotype of patients with LCAH.

Patients and methods
This is a case series study of 10 cases from 9 unrelated families. The study included mutation analysis using whole exome sequencing or panel sequencing, description of clinical manifestations, karyotyping, and biochemistry tests.
Results
Seven of 10 cases have a female appearance. Among them, 4 have a karyotype of 46,XX, ovaries, and uterus on pelvic ultrasound; 3 have a karyotype of 46,XY and testis. 2 of 10 have a male-typical appearance and 46,XY, and testis. 1 of 10 has bilateral cryptorchidism, truth micropenis, hypoplasia of the scrotum, and 46,XY. Six of ten patients presented with severe adrenal insufficiency in early infancy (under 6 months old). Remain cases presented the first adrenal crisis from 15 months to 6.5 years of age. The investigations showed very high plasma ACTH levels (440–1551 pmol/l), and salt losing with hyponatremia (117–127 mmol/l) on admission, while the plasma 17OHP level was normal or decreased. All patients have good responses to glucocorticoid and mineral corticoid replacement therapy. Nine different pathogenic/like pathogenic variants in the *StAR* gene were identified including c.577C>T (p.R193X), c.649A>G (p.R217G), c.545G>A (p.R182H), c.562C>T (p.R188C), c.496A>T (p.I166F), c.11C>G (p.A4G), c.784del (p.Q262RfsX59), c.466ã 11T>A, and Del exon 1-3. Homozygous mutations were identified in 6 probands and compound heterozygous mutations were identified in 3 probands.
Conclusions
The phenotype of LCAH can be classic or non-classical form. The clinical manifestations include early/severe or later onset of adrenal insufficiency and female external genitalia or male-typical genitalia in 46, XY. Molecular testing using next-generation sequencing helps confirmation of the LCAH – a rare cause of adrenal insufficiency, with effective treatment and genetic counseling.

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P62

JOINT1863

Growth-promoting therapy in congenital adrenal hyperplasia due to 21-hydroxylase deficiency: Real-world data from the I-CAH registry

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Introduction
Individuals with congenital adrenal hyperplasia (CAH) often experience reduced final adult height due to androgen excess (AE). AE induces early puberty, accelerates bone age, and leads to premature epiphyseal fusion. Growth-promoting therapies aim to mitigate sex-steroid effects and improve height outcomes. We aim to evaluate the use of growth-promoting therapies in CAH patients and their impact on height outcomes using real-world data from the I-CAH registry.
Methods
A retrospective analysis was conducted on 162 CAH patients from I-CAH registry from 33 centres in 19 countries, who were on growth-promoting therapies. Data on types of treatment agents, dose, and age at treatment initiation were analysed. Height outcomes were assessed using change of height standard deviations (s.d.s) corrected for bone age (BA), and height deviation from the mid-parental height (MPH) after treatment.
Results
The cohort included 162 patients (93 males, 57%; 69 females,43%) diagnosed at a median age of 0.22 years (IQR: 0.04–3.55), with growth-promoting therapy initiated at a median age of 7.75 years (IQR: 5.73–9.14). Median average hydrocortisone equivalent glucocorticoid (GC) dose before treatment was 13.56 mg/m^2/day (IQR: 11.41–16.4), with 113 patients (70%) receiving fludrocortisone in combination with GC. Adherence issues with GC therapy were reported in 40%. Growth-promoting therapies included GnRH analogues ($n=104$, median initiation age: 8.01 years), aromatase inhibitors (AIs) ($n=54$, 7.68 years), growth hormone (GH) ($n=34$, 7.45 years), cyproterone acetate ($n=38$, 6.83 years), and spironolactone ($n=8$, 8.83 years), administered alone or in combination. Seventeen different drug combinations were used. Letrozole was the most used AI (69%, $n=36$) at a dose of 2.5 mg (97%, $n=35$). GH was administered at a median dose of 40 mcg/kg/day (range: 25–50), while median doses for cyproterone acetate and spironolactone were 50 mg/day (range: 25–200) and 100 mg/day (range: 25–150), respectively. After a mean treatment duration of 3.83 years (s.d. 2.14), significant improvements in height outcomes were observed. Mean height s.d. adjusted for BA increased significantly from -2.36 pre-treatment to -1.44 post-treatment (Δ height s.d.: 0.92, $P<0.00001$). Similarly, height s.d.s deviation from MPH improved significantly from -1.64 pre-treatment to -0.65 post-treatment (Δ height deviation: 0.65, $P<0.00001$).
Conclusion
This real-world study demonstrates the diverse use of growth-promoting therapies in CAH management and their potential to improve height outcomes by reducing the height deficit relative to BA and MPH. However, lack of a unifying approach emphasizes the need for standardized treatment strategies to improve patient outcomes through establishing evidence-based guidelines.

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P63

JOINT316

Influence of glucocorticoid replacement and dosage on infection rates and adrenal crises in patients with adrenal insufficiency

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Introduction
Patients with adrenal insufficiency (AI) have been shown to suffer from an increased susceptibility to infections. Conventional hydrocortisone replacement therapy may be the main cause as it is associated with temporary cortisol under- and overexposure leading to immunodysregulation and -suppression. Both effects may be reduced with dual-release hydrocortisone (Plenadren®), which improves the adaption to the circadian rhythm of cortisol. Aim of this study was to assess the effect of different hydrocortisone preparations on infection rates and thus also on the number of adrenal crisis (AC).
Material and methods
Patients with AI were contacted via a group practice for endocrinology, several self-helping groups in Northern Germany and the online network 'Glandula'. The test subjects were given a self-developed questionnaire regarding their infections in the past year, AC since their diagnosis and their glucocorticoid replacement dosage. The results were analyzed using Excel and SPSS.
Results
Eighty-eight patients (84% women, 16% men) with primary (53.4%), secondary (43.2%) and tertiary (3.4%) AI participated in this study. The results showed a 56.8% reduction in infections over 12 months in patients with Plenadren® compared to conventional hydrocortisone ($P=0.012$). Furthermore, patients with secondary AI had 56.4% more infections than those with primary AI ($P=0.04$). Overall, even though patients with Plenadren® had significantly higher medication doses (23.2 vs. 25.7 mg; $P=0.022$), no dosage-effect could be shown on the frequency of infections. Regarding the ACs, no differences were observed between the medications.
Conclusions
Our study suggests that the improved cortisol exposure under Plenadren® may indeed lead to fewer infections. However, this did not result in a lower rate of AC. The impact of glucocorticoid replacement dosage in the prevention of infections and AC remains unclear underlining the need of further confirmatory studies.

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P6

JOINT3423 Systemic treatment and outcomes in metastatic pheochromocytomas and paragangliomas of a multicenter Spanish cohort

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Introduction
Pheochromocytomas (PHEOs) and paragangliomas (PGLs), collectively known as PPGLs, are rare endocrine tumors with significant clinical variability. Around 10–15% of PHEOs and 35–40% of PGLs exhibit metastatic behavior. Due to their heterogeneity, treatment must be tailored to each patient individually.
Methods
This study aim to describe the general characteristics, treatments strategies, and response in a cohort of 49 patients with metastatic PPGLs. It is a retrospective study (2010–2024) conducted at two reference NET centers in Spain.
Results
Among the 49 patients, 51% with a mean age of 52.7 years (s.d.:8.4). The mean age at diagnosis was 40.9 years (s.d. 19.1). PHEO was the primary tumor in 25 patients. The most common reasons leading to diagnosis were incidental findings (23.1%), hypertension (20.5%), cervical mass (15.4%), and abdominal pain (15.4%). A total of 51% of cases were functional, with the majority exhibiting a noradrenergic phenotype (76%). At diagnosis, 44.9% of patients had metastases, with the most frequent metastatic sites being bone (32.7%), lymph nodes (26.5%), liver (22.4%), and lungs (14.3%). Systemic treatment was not administered to 14.3% of patients. Among those treated, the main indications were disease progression (PD)(59.5%), high tumor burden (31%), and tumor functionality (9.5%). Most patients (43.2%) received only one line of treatment. The remaining patients received more than one line: 23.8% received two, 16.7% three, 9.5% four, 4.8% five, and 4.8% seven First-line treatments included somastotin analogs (SSA)(40.5%), radionuclide therapy (33.3%), and chemotherapy (26.2%).No significant differences were observed between the reason for treatment initiation and the choice of first-line therapy ($P=0.316$). However, differences were found between the reason for starting treatment and the best radiological response achieved ($P=0.01$), with a higher partial response (PR) rate in patients with a high tumor burden compared to those with disease progression (38.4% vs 8%). PR was seen in 27.2% of the patients receiving chemotherapy and 28.5% of those treated with radioligands, compared to 5.88% with SSA ($P=0.14$). After first-line treatment, 63.1% of patients experienced disease progression, with a median progression-free survival of 25.6 months (s.d. 21.2). Significant differences were observed depending on the type of treatment received (SSA:11 months, radionuclide therapy:16.4 months, chemotherapy:7.2 months)($P=0.02$).
Conclusions
The most common indication for initiating systemic treatment in PPGLs is radiological disease progression. However, initial tumor burden appears to be the most influential factor in predicting radiological response. Prospective studies are needed to determine the optimal timing for initiating systemic treatment in PPGLs.

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P65

JOINT3742

Factors influencing the time to achieve target mitotane concentration

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Mitotane is an adrenolytic drug used as adjuvant therapy in patients with adrenocortical carcinoma (ACC) at high risk of recurrence or as first-line treatment for unresectable tumors. Its antineoplastic efficacy correlates with plasma concentration, making the early achievement of the therapeutic threshold (14 mg/l) crucial. However, interindividual variability in mitotane pharmacokinetics poses challenges in reaching this target concentration within an optimal timeframe. This study aimed to identify factors influencing the time required to achieve therapeutic mitotane levels.
Methods
We retrospectively analyzed 51 patients with ACC aged 18 to 72 (median 54 years) ENSAT stage I–IV treated with mitotane for at least 6 months. In stage I there was 1 patient, stage II 17 patients, stage III 17 patients and in stage IV 16 patients. 34 patients recived mitotane monotherapy and 17 of them recived combination of mitotane with chemoterapy (EP or EDP protocol). In 82% of the patients we used high dose approach, and in 18% low dose approach of mitotane therapy. Mitotane concentrations were obtained from Lysosafe service which provides a centralized analysis of mitotane levels using high-performance liquid chromatography (HPLC).
Results
The median time to achieve the target plasma mitotane concentration was 89 days (30–300, IQR 49–129). There was no significant difference in the time required to reach the target mitotane concentration between patients treated with the high-dose and low-dose approaches (median 86 days (range 26–300 days) vs. 92.5 days (range 32–275 days), respectively). Similarly, the time to reach the target mitotane concentration was not influenced by age at diagnosis, body mass index, ENSAT stage, tumor size, or tumor hormonal activity. Although patients receiving mitotane in combination with chemotherapy reached the target concentration more slowly than those receiving mitotane monotherapy (median 113 days (range 32–174) vs. 85 days (range 32–300)), this difference was not statistically significant.
Conclusion
No clinical parameter was found to significantly impact the time required to achieve therapeutic mitotane levels. However, given the relatively small sample size, our study may have been underpowered to detect subtle differences. Larger, multicenter studies with a greater number of patients are needed to more comprehensively evaluate this issue.

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P66

JOINT372

Diurnal aldosterone and potassium intake in third trimester are associated with higher blood pressure in offspring up to 5 years of age

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Background
Offspring blood pressure (OBP) may be programmed during pregnancy. Accordingly, maternal third trimester 24-hour (24 h) urine (u-) aldosterone levels are associated with feto-placental trophic effects. Furthermore, high potassium and low sodium intakes are generally recommended in adults with normal renal function. We hypothesized that maternal 24 h u-aldosterone levels were positively associated with OBP and maternal intake of potassium and sodium may influence the association.
Objectives
To investigate associations between maternal third trimester 24 h u-aldosterone, potassium and sodium intakes and OBP.
Methods
In the prospective Odense Child Cohort, 475 mother–child dyads had 24 h u-aldosterone from gestational week 29 and OBP (systolic (SBP) and diastolic (DBP)), at ages 3 and 18 months and 3 and 5 years. Maternal potassium and sodium intakes were calculated from 24 h u-potassium and u-sodium excretions.
Results
Increased maternal 24 h u-aldosterone associated with higher SBP in offspring at ages 3 months ($\beta = 0.54$ mmHg (95% CI: 0.29; 0.79)) and 18 months ($\beta = 0.24$ mmHg (95% CI: 0.03; 0.44)). One thousand mg/day increase in maternal potassium intake was associated with an average increase in offspring SBP of 0.68 mmHg (95% CI: 0.02; 1.34) up to 5 years of age (pooled), with significant associations only in girls ($\beta = 1.14$ mmHg (95% CI: 0.21; 2.08)). No significant association was seen between maternal sodium intake and OBP.
Conclusions
Elevated maternal 24 h u-aldosterone and higher dietary potassium intake were associated with higher OBP, but within normal range, in young children, and girls were more susceptible to maternal potassium intake.

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P67

JOINT3835

Activation of calcium signaling, using chemogenetic tools, leads to the development of hyperaldosteronism and adrenal remodeling in mice

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Primary aldosteronism (PA) is the most frequent form of secondary hypertension and is due to autonomous aldosterone production by the adrenal gland. The most frequent genetic cause of aldosterone producing adenoma (APA) are somatic mutations in the potassium channel KCNJ5. They affect the ion selectivity of the channel, with sodium influx leading to cell membrane depolarization and activation of calcium signaling, the major trigger for aldosterone biosynthesis. To investigate how *KCNJ5* mutations lead to the development of APA, we developped a mouse model expressing specifically in the adrenal cortex, using a Cyp11b2-Cre mice generated in our laboratory, a chimeric ion channel receptor named α7-5HT3-R formed by the ligand binding domain of the α7 nicotinic acetylcholine receptor fused to the ion pore domain of the serotonin receptor 5HT3a. (Cyp11b2-Cre::α7-5HT3-R). The activation of the α7-5HT3-R by a selective agonist, the uPSEM-817, leads to sodium entry into the cells. In an adrenocortical cell model (H295R-S2 cells), we previously demonstrated that the expression of α7-5HT3-R leads to an increase of sodium entry into the cells, resulting in cell membrane depolarization, the opening of voltage-gated calcium channel, an increase in intracellular calcium concentration, and an upregulation of *CYP11B2* expression and aldosterone biosynthesis. Additionally, we found that this sodium influx reduces cell proliferation and promote apoptosis. Moreover, RNA sequencing and steroidome analyses revealed unique profiles associated with sodium entry, with only partial overlap with changes induced by angiotensin II and potassium. These findings suggest that additional events may be required for the development of an APA with *KCNJ5* mutation. In Cyp11b2-Cre::α7-5HT3-R mice, four weeks of treatment with uPSEM-817 induces, in both male and female, an increase in plasma aldosterone and 18-hydroxycorticosterone concentrations associated with an increase in *Cyp11b2* expression and to a lesser extent, a disorganization of the adrenal cortex. After four weeks of treatment, we did not observe an increase in blood pressure or cardiac remodeling. Further investigations and longer treatments are ongoing to thoroughly characterize this mouse model. This mouse model, in which we can modulate calcium entry, provides a valuable tool for dissecting the mechanisms underlying APA development and assessing new therapeutic strategies.

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P68

JOINT1315

Investigating the role of insulin and adipose tissue in regulating adrenal steroidogenesis in response to metabolic diseases

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Metabolic syndrome is characterized by the hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis, leading to increased steroidogenesis. The molecular signaling mechanisms underlying HPA axis alterations in metabolic diseases remain poorly understood. In this study, our objective was to investigate how changes in signaling molecules within both plasma and adipose tissue contribute to the regulation of adrenal steroidogenesis in metabolic diseases and elucidate the modified response of adrenocortical and pituitary cells. Using a mouse model of obesity induced by a high-fat diet (HFD), we aimed to pinpoint the onset of changes in steroid hormone response. We investigated the adrenal glands and plasma of mice at different time points up to 16 weeks of HFD. We observed a significant increase in adrenal gland weight along with increased levels of corticosterone in mouse plasma. These changes were preceded by elevated insulin concentrations in the mouse plasma as early as 8 weeks of HFD. Further, our findings revealed increased expression of *Lep* (leptin), and decreased expression of *Adipoq* (adiponectin) in the adipose tissue surrounding the adrenal upon 16 weeks of HFD. To explore the direct impact on adrenocortical cells, we treated primary adrenocortical cell-derived spheroids with insulin and adiponectin. We observed that insulin induced an increase in spheroid diameter along with an increase in mRNA expression of steroidogenic genes, indicating enhanced cell expansion and steroidogenesis, while adiponectin decreased the spheroid diameter, indicating an inhibitory effect on steroidogenesis. We have previously shown that insulin can enhance ACTH secretion in primary pituitary cells. To elucidate the underlying mechanism of how insulin acts in these *in vitro* systems, we performed bulk RNA sequencing of adrenocortical and pituitary cells with and without insulin stimulation. When comparing insulin-induced

differentially expressed genes (DEGs) in both cell types, we observed upregulation of genes related to cholesterol biosynthesis and fatty acid transport. This could indicate that insulin stimulates *de novo* cholesterol biosynthesis, the precursor for steroid synthesis. In adrenocortical cells, insulin-induced DEGs were uniquely attributed to cholesterol transport, inner mitochondrial membrane and respiratory chain, and steroid synthesis. Hence, an overall effect of insulin on cholesterol metabolism could be crucial for regulating cholesterol transport for subsequent steroid synthesis in adrenocortical cells. Together, our results underscore the crucial role of insulin and adipose tissue in regulating adrenal gland function in metabolic diseases contributing to a comprehensive understanding of HPA axis activity in these conditions.

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P69

JOINT1521

Medical treatment of hypercortisolism with relacorilant: Final results of the phase 3 GRACE study

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Relacorilant is a selective glucocorticoid receptor modulator in development for the treatment of patients with endogenous hypercortisolism. The objective of the phase 3, randomized-withdrawal (RW) GRACE study (NCT03697109) was to assess the efficacy and safety of relacorilant in patients with hypercortisolism and hypertension and/or hyperglycemia (diabetes/impaired glucose tolerance). Patients who achieved prespecified response criteria in the 22-week open-label (OL) phase were then eligible to enter the 12-week, double-blind placebo-controlled RW phase. The primary endpoint was defined as loss of response in hypertension control between relacorilant and placebo and was assessed at the end of the RW phase. There were 152 patients enrolled in GRACE ($n=31$ with hypertension; $n=50$ with hyperglycemia; $n=71$ with both). During the OL phase, rapid and sustained improvements in hypertension and hyperglycemia were observed, along with improvements in several other cortisol-related comorbidities. Patients who continued to receive relacorilant in the RW phase maintained significant improvements in blood pressure and glycemic measures. The primary endpoint was met with an odds ratio of 0.17 (95% confidence interval: 0.04–0.77; $P=0.02$) in favor of relacorilant. The most common adverse events (AEs) observed were back pain, headache, arthralgia, insomnia, and pain in extremity; these AEs were mostly mild to moderate in severity. No cases of relacorilant-induced irregular vaginal bleeding with endometrial hyperplasia, adrenal insufficiency, or QT prolongation were reported. Significant and sustained improvements in hypertension, hyperglycemia, and other manifestations of cortisol excess were observed during relacorilant treatment. Treatment with relacorilant was well tolerated in both the OL and RW phases of GRACE.

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P70

JOINT1256

PLK1 and multi-CDKs dual inhibition as a novel approach for the treatment of adrenocortical carcinomas

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Background

Adrenocortical carcinomas (ACC) are highly aggressive malignancies with limited treatment options. Polo-like kinase 1 (*PLK1*) and cyclin-dependent kinases (*CDKs*) 1/2/4 are among the most overexpressed genes in ACC human samples. We have previously demonstrated the efficacy of PBD-targeting PLK1 inhibitor (PLK1i) poloxin in ACC cell lines (H295R, MUC-1, CU-ACC2).

Aims and methods

We tested the efficacy of 1) two PLK1i, i.e. the polo-box domain (PBD)-targeting poloxin and the kinase domain (KD)-targeting plogosertib; 2) two CDK inhibitors (CDKi), i.e. dinaciclib (targeting preferentially CDK1/2) and the CDK1-cyclin B1 inhibitor cucurbitacin E (CurE); 3) the combination of plogosertib and dinaciclib. Their efficacy was evaluated in four ACC cell lines, including H295R, MUC-1, and the newly generated TVBF-7 and JIL-2266. Increasing drug concentrations for 72 h. Cell proliferation and apoptosis were assessed by BrdU incorporation and caspase 3/7 activity, respectively, compared to basal condition. The "SynergyFinder" tool was used to analyse two-drugs combinations.

Results

PLK1i poloxin reduced proliferation at very high doses, achieving a maximum effect at 100μM ($P<0.01$ in MUC-1 and TVBF-7; $P<0.001$ in H295R and JIL-2266), and increased apoptosis at 10μM ($P<0.05$ for all). At considerably lower concentrations, plogosertib dose-dependently reduced cell proliferation ($P<0.05$ at 100 nM in MUC-1 and JIL-2266; $P<0.01$ at 750 nM in H295R and TVBF-7) and increased apoptosis ($P<0.05$ for H295R, TVBF-7, and JIL-2266 at 1μM). CDKi dinaciclib markedly reduced cell proliferation at low nanomolar doses ($P<0.05$ at 20 nM in

MUC-1 and JIL-2266, and at 100 nM in TVBF-7; $P<0.01$ at 100 nM in H295R), and increased apoptosis ($P<0.05$ in MUC-1, TVBF-7, and JIL-2266 at 200 nM). CurE dose-dependently reduced proliferation in all ACC cells, but its effects were less pronounced than dinaciclib ($P<0.05$ at 100 nM in MUC-1 and TVBF-7; $P<0.01$ at 100 nM in H295R and JIL-2266). In line with the observed differences in treatment sensitivity among cell lines, qRT-PCR analysis showed that CDK1/2 and PLK1 mRNA expression was particularly high in MUC-1 and JIL-2266. Synergistic suppression of cell proliferation by combined treatment with PLK1i plogosertib and CDKi dinaciclib was observed in H295R ($P<0.05$) and TVBF-7 ($P<0.01$) cell lines.

Conclusion

Plogosertib and dinaciclib were the most effective inhibitors in all cell lines, representing interesting novel targeted treatment options for ACC. Moreover, the combination of these drugs showed a synergistic effect, suggesting a potential benefit of using both PLK1i and multi CDKi that need to be further investigated *in vivo*.

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P71

JOINT2327

Is muscle strength an overlooked parameter in patients affected by mild autonomous cortisol secretion (MACS)? A prospective study

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Background

Adrenal incidentalomas are a growing clinical concern due to their increased prevalence in imaging studies. While most are non-secreting adenomas (NFAA), a significant proportion are associated with mild autonomous cortisol secretion (MACS), linked to various comorbidities, including metabolic and musculoskeletal alterations. The specific impact of MACS on skeletal muscle health, body composition, and quality of life (QoL) remains poorly understood.

Objective

To evaluate the effects of mild cortisol excess on skeletal muscle health, body composition, and QoL in patients with adrenal incidentalomas associated with MACS compared to those with NFAA and healthy controls.

Participants and methods

This cross-sectional case–control study enrolled 62 participants: 21 with MACS, 21 with NFAA, and 20 controls. Skeletal muscle strength was assessed using hand-grip strength, sit-to-stand test and the MRC scale. Body composition was analyzed through bioelectrical impedance analysis (BIA), measuring fat free mass (FFM), muscle mass (MM), and fat mass (FM). QoL was evaluated using EQ-5D and SARC-F questionnaires. Statistical comparisons were performed between groups, and correlations with cortisol levels were explored.

Results

Participants were demographically and anthropometrically comparable across groups. Patients with MACS exhibited a higher prevalence of osteopenia and osteoporosis than NFAA and controls (61.9% vs. 28.6% and 25%, respectively; $P=0.036$). Although no significant differences were observed in FFM, MM, or FM, MACS patients demonstrated lower muscle strength scores on the MRC scale for biceps and quadriceps than controls ($P=0.040$ and $P=0.0397$, respectively). Cortisol levels positively correlated with adenoma size ($r=0.347$, $P=0.0243$) but not with muscle strength parameters, despite a clear trend towards less suppression of cortisol values. QoL measures revealed trends toward greater functional impairments in MACS patients, though without statistical significance.

Conclusion

Mild cortisol excess in MACS patients is associated with subtle impairments in muscle strength and a higher prevalence of skeletal health issues, highlighting the potential subclinical impacts on musculoskeletal health and QoL. These findings underscore the clinical significance of MACS and highlight the need for multidisciplinary management strategies for the disease.

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P72

JOINT2754

Exploring the impact of pathogenic variants and cortisol secretion on M2-like tumor-associated macrophage polarization in adrenocortical adenomas

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Background

Prevalence of M2-macrophages has been described in normal and tumor adrenal tissues, likely modulated by cortisol autocrine/paracrine effects. However, their infiltration in adrenocortical adenomas (ACA) and comparison with normal adrenal glands (NAG) remain poorly characterized. This study aimed to evaluate tumor-associated macrophages (TAM) in ACA and assess the impact of ACA-pathogenic variants (PVs) and cortisol hypersecretion on their polarization.

Methods

Immunohistochemistry for CD163 and CD206 (M2-specific markers), and CD68 (pan-macrophage marker) was performed. Immunostaining was quantified using QuPath-0.5.1 pixel classification (thresholds 0.15–0.30) and expressed as mean percentage of positive pixels. PV in *CTNNB1, PRKACA,* and *GNAS* were detected by Sanger sequencing from matched fresh-frozen ACA. Associations between TAM, clinicopathological features, PV status, hormone levels and circulating monocytes were analyzed. Additionally, myeloid transcriptomic profiles from single-nucleus RNA sequencing (snRNA-Seq) data (DOI:10.1002/ctm2.1798) were examined using Seurat R package and differential gene expression analysis.

Results

A cohort of 103 ACA and 8 NAG-adjacent to ACA was analyzed. In ACA, CD163 staining was higher than CD206 and CD68 (6.83% vs. 1.62% and 1.71%, $P<0.001$). Conversely, in NAG CD206 was higher than CD68 (8.41% vs. 5.6%, $P=0.008$), but similar to CD163. Matched ACA-NAG comparisons revealed in ACA reduced CD206 (2.3% vs. 7.46%, $P=0.008$) and CD68 (2.14% vs. 4.43%, $P=0.012$), while CD163 remained unchanged, resulting in an increased CD163/CD206 ratio in ACA (2.28% vs. 0.76%, $P=0.017$). Same result was found at snRNA-Seq levels for CD206 (1.21 in ACA vs 1.48 in NAG, $P<0.001$), without difference in CD163. ACA harbouring *CTNNB1* and *PRKACA/GNAS* PVs had a higher CD163/CD68 ratio compared to PV negative cases (60% vs 33%, $P=0.022$), an association observed exclusively in women, suggesting potential sex-specific differences in macrophage infiltration. ACA with *PRKACA* PVs showed lower CD206 (0.5% vs. 1.79%, $P=0.003$) and, consequently, higher CD163/CD206 ratio (17.4% vs 3.2%, $P=0.002$) than those without. These results were consistent when considering cortisol-producing ACA only. Similarly, low CD206 was found also at snRNA-Seq in ACA with *PRKACA* PV (0.73 vs 1.27, $P=0.003$). Finally, CD68 inversely correlated with 24 h-urinary free cortisol ($\rho=-0.245$, $P=0.04$), with lower CD68 in patients with overt Cushing's syndrome ($P=0.018$). No correlation between number of circulating monocytes and TAM was found.

Conclusion

This study provides a comprehensive characterization of M2-like TAM in ACA, revealing distinct macrophage infiltration with higher CD163/CD206 ratio compared to NAG. TAM polarization is influenced by PVs and cortisol excess, with sex-specific differences, offering new insights into ACA microenvironment

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P73

JOINT1173

Diagnostic accuracy of urinary free cortisol and cortisone excretion for the diagnosis of neoplastic hypercortisolism

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Background
Quantification of urinary free cortisol excretion is one of the recommended initial screening tests for diagnosing hypercortisolism. The use of liquid chromatography–tandem mass spectrometry (LC–MS/MS) allows for the simultaneous quantification of both urinary cortisol and cortisone. This study aims to determine the optimal cut-off values for urinary free cortisol (UFCortisol) and urinary free cortisone (UFCortisone) in the diagnosis of neoplastic hypercortisolism and to determine whether either one has superior diagnostic accuracy.
Methods
In this retrospective study, we analyzed data from subjects who were screened for endogenous hypercortisolism at Amsterdam UMC between December 2015 and February 2022. Subjects had been instructed to collect urine for 24 hours on two consecutive days. UFCortisol and UFCortisone concentrations were measured using an in-house developed LC–MS/MS method. The average of both collections was used to determine the diagnostic accuracy. Confirmation of the diagnosis of neoplastic hypercortisolism was based on (postoperative) clinical parameters and histopathology, while the diagnosis was excluded based on a lack of progression of clinical signs during follow-up of at least 12 months. The diagnostic accuracy was evaluated by ROC-curve analysis.
Results
We included 426 subjects without neoplastic hypercortisolism (test indication: 136 clinical signs/symptoms, 274 adrenal incidentaloma, 9 pituitary incidentaloma, 2 genetic predisposition, 5 unclear) and 27 subjects with neoplastic hypercortisolism (test indication: 23 clinical signs/symptoms, 2 adrenal incidentaloma, 2 pituitary incidentaloma) in which UFCortisol was measured. In a subgroup of 304 subjects without and 17 subjects with neoplastic hypercortisolism UFCortisone was measured as well. The median UFCortisol concentration was 369 nmol/24 h (range 47–8987) for subjects with and 63 nmol/24 h (1.3–614) for subjects without neoplastic hypercortisolism ($P<0.001$). The median UFCortisone concentration was 606 nmol/24 h (131–1174) for subjects with and 190 nmol/24 h (13–863) for subjects without neoplastic hypercortisolism ($P<0.001$). For UFCortisol, a cut-off value of 120 nmol/24 h provided optimal diagnostic accuracy with a sensitivity of 88.9% (95% CI 0.771–1.000) and specificity of 85.9% (0.826–0.892). The optimal cut-off value for UFCortisone was 300 nmol/24 h with a sensitivity of 94.1% (0.829–1.000) and specificity of 87.8% (0.841–0.915). The sum of UFCortisol and UFCortisone provided a slightly higher diagnostic accuracy at a cut-off of 460 nmol/24 h with a sensitivity of 94.1% (0.829–1.000) and specificity of 93.0% (0.901–0.959).
Conclusion
We established cut-off values for UFCortisol and UFCortisone for the diagnosis of neoplastic hypercortisolism. UFCortisone had similar diagnostic accuracy to UFCortisol, but the sum UFCortisol + UFCortisone seemed to perform slightly better.

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P74

JOINT1946

Increased mortality in patients with primary adrenal insufficiency: a systematic review and meta-analysis

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Introduction
Primary adrenal insufficiency (PAI) is mainly due to autoimmune adrenalitis in developed countries and the most common inherited form is congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. There is controversy on long-term outcomes in PAI, with earlier studies showing that mortality was not different from the general population and more recent studies showing higher mortality. The primary aim of this study is therefore to synthetise the evidence on long-term mortality in PAI. The secondary aims are to analyse mortality due to cardiovascular and infectious diseases, along with time trends in mortality.
Methods
A database search of Medline, Cochrane, Embase and Web of Science was conducted for studies on mortality in PAI, including CAH. Two reviewers conducted an initial screening of the titles and abstracts. Thereafter, each reviewer examined the selected articles in full text. Observational studies reporting all-cause mortality in comparison with a control group or general population were included. The extracted data was systematically synthetised. The study quality was assessed independently by two reviewers, following the Newcastle-Ottawa quality assessment scale. The protocol for this systematic review complies with the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines and was registered in PROSPERO (CRD42023416253)[1].
Results
Totally, 5463 articles were identified. After title and abstract screening, 54 articles were reviewed in full text and nine were included in the systematic review. Cardiovascular disease, infections, neoplasms and adrenal crises were the most common causes of death. Of the nine studies, two were removed due to overlapping population. The meta-analysis included therefore 7 studies and in total 10211 patients (6178 with autoimmune PAI and 4033 with CAH). Four studies were cohort studies (6085 patients), assessing mortality using hazard ratios (HR), with a pooled HR of 2.51, 95% CI: 1.47–4.31, $I^2=86.1\%$. Three studies were population-based (4126 patients) that assessed mortality using standardised mortality ratios (SMR), with a pooled SMR of 2.49, 95% CI: 0.99–6.28, $I^2=97.9\%$. Cause-specific mortality and time-trend analyses were not performed due to lack of data or small sample size.
Conclusions
This is the first systematic review and meta-analysis studying mortality in patients with PAI. The analysis shows a 2.5 times higher mortality among patients with PAI compared to controls or general population.
Reference
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P75

JOINT1304

Prediction of lateralisation in primary aldosteronism – a decision tree model for bypassing adrenal vein sampling in bilateral disease

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Background
Subtyping primary aldosteronism (PA) into unilateral and bilateral disease is essential for effective treatment, as unilateral PA can be treated with adrenalectomy, while bilateral PA is managed medically. The gold standard, adrenal vein sampling (AVS), is creating a bottleneck because it is technically challenging and only available in specialized centers.
Aim
To create a predictive score for identifying bilateral PA with a high specificity to bypass AVS, while ensuring a high sensitivity for unilateral disease.
Methods
Retrospective observational study of patients, who underwent AVS at the University Hospital Basel, Switzerland between 2015 and 2023. A decision tree

model, using *rpart* (R version 4.4.2), was used to predict the likelihood of bilateral disease.
Results
A total of 164 patients with PA underwent AVS. 20 patients were excluded due to insufficient selectivity of AVS, leading to a total of 144 patients that were included in the analysis (38% female, median age 51[45;59]). Final diagnosis, based on AVS results, was unilateral in 68% ($n=98$) and bilateral in 32% ($n=46$) of patients. The classification decision tree with the highest accuracy was built based on the following predictors: *unilateral adrenal mass, potassium, diastolic blood pressure, age, glomerular filtration rate (GFR).* The model achieved an overall accuracy of 81%, with a specificity of 95% and sensitivity of 52% for bilateral disease. Assuming a distribution of 50% of uni- and bilateral disease, this decision model would allow to bypass AVS in 50% of bilateral diseases, translating into 25% total reduction in AVS exams. This comes with a price of 5% of patients with unilateral disease not undergoing AVS and surgery (benefit ratio 8:1). Feature importance analysis indicated diastolic blood pressure, GFR, unilateral adrenal mass, and potassium as most influential variables, while age contributed minimally to the model.
Conclusion
Our findings indicate that a decision tree model, based on variables: *unilateral adrenal mass, potassium, diastolic blood pressure, age, and GFR* can serve as an effective tool for predicting bilateral PA. Importantly, our model works with robust clinical parameters and is not dependent on variables from validation tests (e.g. saline loading test) This classification model has the potential to **first**, minimize the need for complex AVS procedures in patients with bilateral disease, **second**, optimize AVS resources for patients with unilateral disease, and **third** reduce health care costs associated with AVS diagnostics. Prospective validation of this score is necessary.

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P76

JOINT699

The genetic and functional analysis of CYP21A2 mutants in congenital adrenal hyperplasia

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Congenital adrenal hyperplasia (CAH) is a genetic disease inherited in an autosomal recessive manner. Over 90% of CAH cases are caused by reduced activity of 21-hydroxylase encoded by *CYP21A2*, a cytochrome P450 protein which catalyzes the conversion of 17-hydroxyprogensterone (17-OHP) to 11-deoxycortisol and progesterone to 11-deoxycorticosterone (11-DOC), leading to the production of cortisol and aldosterone. Clinically, three distinct phenotypes are identified: the salt-wasting, the simple virilizing, and the nonclassical (NC) phenotype. Typically, the phenotype is dictated by the specific variant present in the milder allele. Therefore, the presence of a severe mutation cannot always be inferred from the phenotype in some cases of NC-CAH, which may lead to the severe symptom associated with significant neonatal mortality and morbidity. Furthermore, discordance between the phenotype and the identical genotype can be observed within families. Protein stability, enzymatic function, and gene expression regulation may contribute to this mechanism. It is necessary to obtain sufficient experimental evidence using computational and functional analysis of mutants to elucidate the molecular pathogenic mechanisms and improve clinical diagnosis. Five novel disease-associated mutants in CYP21A2 were selected from ClinVar by analyzing their positions on the surface of protein structure in PyMOL. Conservation and chemical properties of these amino acid substitutions were predicted using ConSurf, PolyPhen-2, SNAP2, Meta-SNP, Predict SNP, and MutPred2. The structure stability of CYP21A2 variant was calculated by the FoldX tool. Changes in enzymatic activity were measured by the conversion of 17-OHP to 11-deoxycortisol and progesterone to 11-DOC in HEK293T cells. The expression levels of CYP21A2 were determined by Western Blot. Three selected mutations showed less than 50% of WT activity: L308V, R401G, and R436C exhibited 30%, 40%, and 26% of WT activity, respectively. These three mutations showed similar reductions in enzyme activity for both 17-OHP and progesterone conversion: for 17-OHP conversion, L308V, R401G, and R436C exhibited 11%, 43%, and 12% activity, respectively; and for progesterone conversion, L308V, R401G, and R436C exhibited 20%, 27%, and 12% activity, respectively. Mutations E162G and S373N showed 58% and 99% of WT activity, respectively. E162G showed increased expression compared to WT, while the other mutations showed decreased expression. The reduced activity observed for variants L308V, R401G, and R436C shows their potential pathogenicity in CAH. The observed differences in protein expression may be related to gene expression regulation, mRNA degradation, or protein stability. These findings contribute to our understanding of the molecular mechanisms underlying CAH caused by CYP21A2 deficiency.

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P77

JOINT3917

The impact of alternative treatment approaches on final adult height in patients with congenital adrenal hyperplasia

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Introduction
Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder, most commonly caused by 21-hydroxylase deficiency (21-OHD). Chronic androgen excess in CAH patients accelerate epiphyseal maturation, and may cause early puberty and epiphyseal fusion which negatively affects growth potential. While conventional therapies help to manage hormonal imbalances, alternative therapies may optimize growth outcomes. This study aimed to evaluate the effects of additional treatment strategies on final height in CAH patients.
Methods
We retrospectively reviewed records of 57 patients (F/M=31/26) with molecularly confirmed classical CAH due to 21-OHD. Among these, 38 patients with predicted adult height (PAH) shorter than target height (TH), due to early puberty and/or advanced bone age, received additional therapies, including anastrozole, cyproterone acetate, GnRHa, and growth hormone (GH) (Group 1). The remaining patients received only conventional hydrocortisone/mineralocorticoid therapy (Group 2). Anthropometric data were compared between groups.
Results
The median age at diagnosis of CAH was 0.1 (range:0–10.3) years and; age at the initiation of alternative therapies in group 1 was 9.2 (range:4.6–11.1) years. In Group 1, 55% received cyproterone acetate, 45% anastrozole, 77.5% GnRHa, and 15% GH. The median treatment duration in Group 1 was 2.3 (range:0.6–7.3) years. Thirty-two patients (82.4%) in Group 1 and 11 (64%) in Group 2 have reached adult height. A significant difference in pre-treatment height SDS was observed between the groups (0.97 [range:−1,1 to 5.3] vs. 0.64 [range:−1.5 to 2.7], respectively; $P=0.02$), with an accelerated somatic growth noted in Group 1. Before alternative therapies, the median PAH SDS was −1.5 (range:−5.5 to 1.9) in Group 1 and −2.3 (range:−4.3 to 3.7) in Group 2, with no significant difference. As expected, the bone age/chronological age ratio before treatment was significantly higher in Group 1 (1.3 [range 1–2.5] vs. 1.0 [range 1.3–1.1], $P<0.001$) with accelerated somatic growth. The comparison of the difference between target height SDS and final height SDS revealed a median of 0.8 (range:−2.8 to 2.4) in Group 1 and 0.1 (range:−2.6 to 2.5) in Group 2, with no statistical significant difference. Final height SDS was −1.5 (range:−3.9 to 0.9) in Group 1 and −1.5 (range:−4.2 to 1.4) in Group 2. It was similar in both groups, and somatic growth acceleration regressed with alternative therapies.
Conclusion
Our data suggest growth-promoting therapies such as aromatase inhibitors, cyproterone acetate, GH and GnRHa appear to be effective in enhancing adult height in appropriately selected cases.

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P78

JOINT1366

Diagnostic work-up of paediatric adrenocortical tumours – International consensus through a modified Delphi process

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Background

Paediatric Adrenocortical Tumours (pACTs) are potentially devastating neoplasms of the adrenal cortex. The incidence of pACTs is about 0.2–0.3 cases per million children per year in most countries. Most pACTs are hormonally active and most often present with androgen excess. Data suggest that pACTs that solely produce androgens have better survival than tumours that concomitantly produce other steroid classes. Although a thorough endocrine work-up is recommended, there is no consensus on how this should be performed, nor is there guidance on imaging modalities or the extent of genetic investigations.

Aim

To seek international consensus on the initial diagnostic work-up in children and young people with pACTs.

Methods

A modified three-step Delphi consensus method was applied to develop statements from an international group of pACT experts (Delphi panel), comprising 28 participants from Europe, the Americas, and Asia selected by their clinical merit and peer-reviewed publications in the field of pACTs. Electronic surveys were created by the steering committee (members of the European Network for the Study of Adrenal Tumours [ENS@T], KIDS working group) and circulated to the panel. Levels of agreement and disagreement were rated on a six-point Likert response scale with the opportunity to give feedback. After each round, results were discussed within the ENS@T-KIDS group, and questions were reformulated if no consensus (defined as agreement by at least 70%) was reached.

Results

Of the 28 voting members, 24 participated in round 1 (86%), 23 in voting round 2 (82%) and 24 in round 3 (86%). Based on a literature review, 45 statements were formulated by the steering committee and electronically distributed to the Delphi panel for voting. The statements cover four categories: (I) General Aspects and Clinical Assessment (17 statements); (II) Endocrine Work-up (including methodology and assessment of hormone excess; 15 statements); (III) Radiology (7 statements) and (IV) Genetics (6 statements). Of the 45 statements voted upon in round one, only eight did not reach consensus. These eight statements were revised and voted upon in round two, with seven reaching consensus. One statement was further revised based on panel/committee feedback and reached a consensus on round three.

Discussion and conclusion

The diagnostic work-up of rare pACTs varies amongst different centres and countries and partly depends on local resources and individual experiences. For the first time, we have developed expert-based consensus statements formulating a diagnostic pathway to guide a unified approach with practical considerations for the work-up of pACTs.

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P79

JOINT3426

Once-daily low-dose prednisolone has lower cardiovascular risk than conventional hydrocortisone replacement therapy in adrenal insufficiency: A double-blind randomised controlled trial

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Background

Current Endocrine Society guidelines recommend thrice-daily hydrocortisone for the management of adrenal insufficiency. Prednisolone is suggested as a second-line treatment but previous studies have evaluated its use at greater than 5 mg. We have safely used low-dose prednisolone (2–4 mg) for over 10 years, culminating in this study to address the current vacuum of evidence.

Methods

Patients with adrenal insufficiency were recruited to this double-blind, randomised crossover study. Participants received 4 months of low-dose prednisolone (2–4 mg) with matching placebo at noon and in the afternoon, or 4 months of standard regimen hydrocortisone (10 / 5 / 2.5 mg). They were then crossed over to the alternative medication for the second study period. Observations (including weight, waist–hip circumference, blood pressure), biochemical data for cardiometabolic health and bone turnover, and subjective health data (SF-36 and Addisons Quality of Life (Addi-QoL)) were collected. Baseline and end-point data were collected at days 1, 30 and 120 of each study period, on both medications.

Results

A significant treatment difference of -1.87 Kg ($P=0.002$) in weight was detected in association with prednisolone treatment. There were further significant reductions in waist circumference and HbA1c of -2.26 cm ($P=0.010$) and -1.23 mmol/mol ($P=0.001$). Bone formation markers were suppressed on prednisolone with a treatment difference of -1.22 µg/l ($P=0.035$) in osteocalcin levels and -13.8 ng/l ($P<0.001$) in Procollagen 1 N-Terminal Propeptide. Bone resorption was also suppressed with Urinary N-telopeptide levels, decreasing by -9.34 nmol/mmol ($P=0.002$) with prednisolone. There was no significant difference in blood pressure, high-sensitivity troponin and CRP, between the treatments. Data from SF-36 survey and Addi-QoL questionnaire demonstrated that subjective health outcomes were unaffected by both hydrocortisone and prednisolone.

Discussion

We demonstrate evidence that low-dose prednisolone is associated with weight loss and reductions in HbA1c, suggesting superior cardiovascular outcomes compared to standard hydrocortisone treatment. This study is limited by the use of short-term markers, but is an important stepping-stone in normalising the use of prednisolone in adrenal insufficiency. Importantly, there were no adverse effects on wellbeing. These results could be explained by the reduced steroid exposure seen with low-dose prednisolone treatment. Alternatively, once-daily dosing may mimic the normal diurnal rhythm of physiological cortisol secretion better than thrice-daily hydrocortisone.

Conclusion

Once-daily low-dose prednisolone is an alternative to standard-regimen hydrocortisone. Further studies should be completed using low-dose prednisolone, focussing on longer term outcomes such as bone-mineral density and real-world mortality.

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P80

JOINT3989

Evaluation of the overnight dexamethasone suppression test in a large cohort of patients with incidentally discovered adrenal nodules

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Introduction

Incidentally discovered adrenal nodules are detected in 1–7% of abdominal imaging studies. The 2023 ESE guidelines recommend the 1-mg overnight

dexamethasone suppression test (ODST) for screening autonomous cortisol secretion (ACS). Previous studies suggest 20–50% of adrenal nodules patients will fail an ODST which, in the absence of clinical evidence of Cushing's syndrome (CS), is termed mild autonomous cortisol secretion (MACS). Herein, we report findings from a large cohort of patients with adrenal nodules.
Methods
512 patients (239 males, 273 females) referred between 2019 and 2023 were included. Patients with a positive ODST (cortisol $\geq$50 nmol/l) had dexamethasone level measured on the same sample to rule out false positives (defined as dexamethasone $\leq$3.7 nmol/l). Patients with abnormal ODST and dexamethasone levels >3.7 nmol/l were investigated for additional evidence of ACS defined as at least two of the following: elevated 24-hour urinary free cortisol, elevated late-night salivary cortisol, 0900 h plasma ACTH <10 pg/mL, suppressed DHEAS level.
Results
Of 512 patients, 52 were excluded due to incomplete data, leaving 460 participants. ODST was normal in 292 (63.5%) and abnormal in 168 (36.5%). Among the abnormal ODST group, 18/168 false positives were identified through dexamethasone measurement, while 150/168 with adequate dexamethasone levels were referred to the specialist adrenal multidisciplinary team (MDT) for further evaluation. Of the 150 patients, 40/150 were not recommended for further investigation by the MDT, and 14/150 declined additional assessment. Among the remaining 96 patients, 65 had no further clinical or biochemical evidence of ACS, while 31 had findings suggestive of ACS, including 3 with overt Cushing's syndrome (CS). The median cortisol level in patients with additional positive biochemical evidence of ACS was significantly higher at 102 nmol/l compared to 79 nmol/l in the abnormal ODST-only group who had no other clinical or biochemical evidence of ACS ($P=0.0019$).
Conclusion
This study highlights the need to consider new biomarkers to better detect MACS and stratify those at highest cardiovascular risk. Furthermore, a revision of the current ODST cortisol cut-off with further analysis needed to improve diagnostic accuracy and evaluate the clinical and economic impact of MACS screening.
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P81

JOINT1467

Thyroid hormone regulation of adrenal androgens: Observations from the H295R cell model and pediatric CAH patients

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Introduction
Thyroid hormones (THs) play an essential role in the development, cellular differentiation and metabolism of the human body. Although TH action on various tissues has been well-described, the effect on the adrenal glands remains less understood. Recent studies have indicated a regulatory role for THs in adrenal cortex development and function. However, the regulation of adrenal androgen production by THs has yet to be clarified.
Aim
To investigate the regulatory role of THs on androgen synthesis in human adrenocortical carcinoma H295R cells and to correlate TH levels to circulatory androgens in pediatric patients with congenital adrenal hyperplasia (CAH).
Methods
H295R cells were incubated with triiodothyronine (T3) [10^{-9} M] in serum-free media for either 48 h or 72 h. Gene expression was assessed by mRNA-sequencing (cutoff value for padj < 0.001), and steroid profiling of cell supernatants was examined via liquid chromatography–mass spectrometry (LC–MS). In addition, serum samples of pediatric CAH patients with 21-hydroxylase deficiency were analyzed, obtained from a prospective, observational multi-center cohort study. At 1 or 2 consecutive visits, a targeted and untargeted panel of conventional adrenal and additional peripheral steroids were measured by LC–MS. Data of 83 visits from 70 children (39 boys, 31 girls; 33 prepubertal, 37 postpubertal) were available. Mean age was 11.0 [1.2; 18.9] years and BMI z-score was 0.51 [−1.84; 2.91]. Free thyroxine (fT4) was measured via chemiluminescence immunoassays. Regression analyses were adjusted for age, sex, BMI-z-score, pubertal status (pre- and postpubertal), CAH subtype (salt-wasting, simple-virilizing, late-onset) and treatment quality (under-, over- and well-treated).
Results
T3 downregulated dehydroepiandrosterone (DHEA) and DHEA-sulfate production in H295R cells (fold changes 0.71 and 0.63 respectively; $P<0.01$), reflecting changes in the transcriptome profile of upregulated *HSD3B2* (log2FC = 1.24) and downregulated *CYP17A1* (log2FC = −0.42) and *PAPSS2* (log2FC = −0.49) gene expression. Likewise, in our CAH patients, we found a weak negative correlation for fT4 and serum DHEA (R^2 =0.251; $P=0.014$), androstenedione (R^2 =0.368; $P=0.018$) and androsterone (R^2 =0.323; $P=0.036$).
Discussion
We show that T3 downregulates adrenal androgen secretion in H295R cells, mediated by changes in the expression of key steroidogenic enzymes. Furthermore, we found weak negative correlations between fT4 levels and serum androgens in pediatric patients with CAH. Together, these results indicate that THs may play a role in adrenal androgen production.
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P82

JOINT2558

24-hour blood pressure profiles in patients with adrenal insufficiency

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Background
Patients with adrenal insufficiency (AI) have an increased risk of cardiovascular diseases, largely attributed to supraphysiological hormone replacement therapy.
Objective
This study evaluated 24-hour blood pressure (BP) profiles in patients with primary (PAI) and secondary AI (SAI) based on ESC/ESH hypertension thresholds and dipping status. BP profiles were correlated with glucocorticoid (GC) and mineralocorticoid (MC) replacement, cumulative GC dose/week (calculated from daily GC dose and frequency of dose adjustments), plasma steroid profiles, salivary cortisol (SC) day profiles, urinary cortisol as well as routine clinical and biochemical parameters.
Methods and results
We analysed 246 patients (76% PAI; mean age 50±15 years; 69% female). 52% of the subjects either had a preexisting diagnosis of arterial hypertension (22%) or exhibited pathologically elevated blood pressure on 24-h BP measurement (30%). Among patients on antihypertensive treatment ($n=53$, 22%), 60% had elevated 24 h-BP, compared to 41% of untreated patients ($n=187$) ($P=0.01$). The prevalence of elevated 24 h-BP was higher among SAI compared to PAI (58% vs. 41%, $P=0.02$). Nighttime hypertension was more frequent than daytime hypertension (48% vs. 35%), even in patients without previously diagnosed hypertension (42% vs. 30%). One-third were non-dippers, regardless of antihypertensive therapy. No significant differences in GC or MC dose regimens or GC preparations were observed between patients with elevated or normal 24 h-BP. However, both 24-hour diastolic BP and extent of nocturnal dipping positively correlated with cumulative GC dose/week ($r=0.2$, $P<0.01$; $r=0.14$, $P=0.03$). Inverse dippers were more frequent with evening GC use (20% vs. 6%, $P=0.02$). Morning SC levels were significantly higher in patients with elevated 24 h-BP, particularly in patients on short-acting GC and in patients with quantifiable steroid precursors. Logistic regression analyses identified AI etiology, glomerular filtration rate (GFR), body weight, and the frequency of GC dose adjustments as significant predictors of elevated 24-hour BP in the entire cohort. Except for AI etiology, these factors remained significant predictors in subgroups of patients not on antihypertensive treatment and in those with PAI.
Conclusion
Of the subjects, 52% either had a preexisting diagnosis of arterial hypertension or exhibited elevated 24-h BP levels. Frequency of GC dose adjustments was a consistent predictor of hypertension, implying a negative impact of recurrent cortisol spikes on BP regulation. The higher morning SC levels observed in hypertensive patients on short-acting GC and in those with quantifiable steroid precursors suggest that delayed cortisol metabolism and/or residual adrenal function may additionally contribute to increased blood pressure.
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P83

JOINT1642

GC–MS urinary steroid metabotyping of aldosterone deficient states

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Introduction
Disorders of isolated deficient aldosterone action involve insufficient production of aldosterone (aldosterone synthase defects type 1 and type 2 (corticosterone methyl oxidase (CMO) I and II)), as well as pseudohypoaldosteronism (PHA) featuring end-organ hormone resistance. Aldosterone is a key regulator of sodium–potassium homeostasis and blood pressure. Deficient action is characterized by hypotension, hyponatremia, hyperkalemia, and dehydration. We investigated whether gas chromatographic–mass spectrometric (GC–MS) urinary steroid metabolome analysis allows for delineation of these entities.
Method
We quantified 44 urinary steroid metabolites from spot urine (μg/l) by targeted GC–MS from 124 infants with aldosterone deficient states (24 CMO I, 26 CMO II, 74 PHA; aged 3–348 days) and 138 matched controls. Relative enzymatic activities were calculated from precursor/product metabolite ratios. Data preprocessing included log2 transformation, Z-score standardization, and quantile normalization, followed by logistic regression and decision tree analysis.
Results
Male patients dominated in all diseases (68%). All entities peaked around the end of the neonatal period (wk4) with CMO manifesting up to six months and PHA extending until the end of the first year of life. Elevated corticosterone metabolite levels distinguished patients best from controls. PHA showed grossly elevated metabolites of aldosterone and its precursors. The ratio between corticosterone and aldosterone metabolites discriminated best between CMO subtypes and PHA. The ratio between 18-hydroxylated corticosterone and aldosterone metabolites differentiated CMO II from CMO I. Decision tree (rpart) analysis identified various sequential classifiers distinguishing controls, PHA, CMO I and CMO II, with high specificity (94%) and sensitivities (96%, 92% and 77%), respectively.
Conclusions
GC–MS urinary steroid metabotyping from spot urine provides a non-invasive and highly reliable new diagnostic tool for delineating aldosterone deficient states in young infants. Various metabolites and metabolite ratios effectively discerned controls, patients with CMO I, CMO II and PHA. The quantitative biomarkers we found allow for a steroid metabolomics based precision medicine approach.

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P84

JOINT317

Metabolic associations of premature adrenarche 4 years after menarche

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Premature adrenarche (PA) is associated with increased adiposity and adverse metabolic profiles at presentation. Recent LC–MS/MS studies have demonstrated adrenal production of potent 11-oxygenated C19 androgens. However, evidence is conflicting about whether girls with PA are at higher risk of developing permanent metabolic dysfunction.
Objective
Does hyperandrogenism in childhood resulting from PA lead to metabolic dysfunction in young adulthood?
Methods
Girls from the prospective observational Growth and Obesity Chilean Cohort Study (GOCS, all with normal birth weight) who had DHEAS measured at age ∼7 ($n=504$, 68%) were studied at 4 years after menarche (4yPM, age ∼16 yr). Subjects were classified by DHEAS concentrations at age 7 into HD ($>75^{th}$ percentile) or normal DHEAS (ND, $\leq 75^{th}$ percentile) subgroups. This definition of PA subgroups allowed identification of PA independently from factors influencing clinical manifestations (*e.g.,* ethnicity or tissue sensitivity).
Results
At 4 YPM girls with HD at 7 years ($n=96$) exhibited higher BMI SDS ($P<0.01$), waist circumference (WC)/height ($P<0.05$), WC/hip ratio ($P<0.05$), and a 47% higher mean DHEAS concentration compared to ND girls. Nevertheless, glycemia, insulin, HOMA-IR, total cholesterol and its subfractions, triglycerides, testosterone, SHBG, FAI, LH, FSH, AMH, and all C19 11-oxo steroids (11-OHA4, 11-OHT, 11-KA4,1-KT) did not differ between the groups. Girls with HD 4YPM did not show greater frequency of metabolic syndrome score in the crude and adjusted models (covariates: birth weight SDS, age at menarche, and BMI at age ∼7) but a higher blood pressure. Furthermore, there was no correlation between HD at age ∼7 and C19 11-oxo concentrations at 4 YPM nor with concentrations of C19 11-oxo above the 75^{th} percentile. Linear regression analysis showed inverse correlations of 11-KA and 11-KT with metabolic score, WC, and triglycerides that were lost after adjustment for covariates. 11-KA4 showed an inverse correlation with glycemia in raw and adjusted models (β −0.02, 95%CI −0.04 to −0.006).
Discussion
Our observations indicate that girls with HD at the age of adrenarche continue to display higher levels of DHEAS after puberty completion but not of the more bioactive 11-oxygenated adrenal androgens. Apart from trends, the unfavorable metabolic signature at adrenarche appeared to diminish at 4 yr post menarche.

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P85

JOINT695

Myocardial microcirculation and left ventricular function in former and current female androgenic anabolic steroid users: A cross-sectional study

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Background and aim
Impaired myocardial microcirculation, measured by myocardial flow reserve (MFR) has recently been demonstrated in male androgenic steroid (AAS) users. Illicit use of AAS has disseminated to women, though the knowledge on the impact on cardiac function is virtually none. Therefore, the purpose of this study was to investigate cardiac microcirculation and systolic function in current and former female AAS users and compare with female controls with no former AAS use. Coronary artery calcium score was assessed as a secondary outcome.
Methods
This cross-sectional study included recreational strength trained females who were grouped according to their history of illicit AAS use. MFR was investigated using rest and adenosine stressed cardiac rubidium 82 (^{82}Rb) positron emission tomography/ computed tomography (PET/CT). Impaired and subclinical impaired myocardial microcirculation was evaluated using cutoffs of MFR less than 2 and less than 2.5, respectively. Left ventricular ejection fraction (LVEF) was evaluated at rest and during stress, and as LVEF-reserve, calculated as LVEF-stress minus LVEF-rest. Coronary artery calcium score was determined from a non-contrast breath-hold CT.
Results
A total of 54 women, 20 current users (mean (s.d.): 34 (10) years), 17 former users (37 (9) years) and 17 controls (37 (8) years) were included. The accumulated use of AASs were similar between current users (median (IQR): 58 (13–166) weeks) and former users (58 (33–117.5) weeks, $P=0.67$). There were no differences in mean MFR between groups ($P=0.79$). Further, the prevalence of impaired MFR (current users: $n=1$ (5.0%), former users: $n=1$ (5.9%), controls: $n=0$ (0.0%), $P>0.99$), and subclinical impaired MFR (current users: $n=3$ (15.0%), former users: $n=2$ (11.8%), controls: $n=3$ (17.6%), $P>0.99$) did not differ between groups. Mean (s.d.) LVEF-rest and LVEF-stress was reduced in current users (64 (7) % and 72 (7) %) compared to controls (70 (6) %, $P=0.01$ and 78 (19) %, $P=0.01$). In contrast, no significant differences were observed in LVEF-rest and LVEF-stress between former users (68 (5) %, $P=0.47$ and 75 (4) %, $P=0.47$) and controls. No differences were detected in LVEF-reserve ($P=0.92$) and coronary artery calcium score (median (range): current users: 0 (0–2.5), former users: 0 (0–44), controls: 0 (0–0), $P=0.14$) between the three groups.
Conclusion
In this study, there were no group differences in MFR and coronary artery calcium score. However, an impaired left ventricular function demonstrated by a reduced LVEF-rest and LVEF-stress, was found among current female users of AASs compared to female controls.

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P86

JOINT1444

Predictors of increased vulnerability for adrenal crises in patients with chronic adrenal insufficiency – long-term follow-up of an initial prospective study

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Background
Despite increasing patient education, the prevalence and mortality of adrenal crises (AC) remain high in individuals with adrenal insufficiency (AI). Effective prevention is limited by the absence of established risk profiles. A previous 2-year prospective study identified a positive history of AC as the sole significant risk factor for future AC.
Objective
This study aims to reassess the frequency and predictors of AC over a long-term follow-up period (14 years) within the original study population.
Materials and methods
Patients from the initial prospective study ($n=423$) were re-contacted for a 14-year follow-up via questionnaire. AC prevalence was calculated per 100 patient-years (py). Parameters assessed included glucocorticoid (GC) and mineralocorticoid (MC) replacement therapy, dose regimen, possession of an emergency card and hydrocortisone injection, education status, regular GC dose adjustments, comorbidities, and co-medications.
Results
A total of 200 patients responded (70% female, 55% primary AI). AC prevalence increased from 8.8 AC/py to 11.6 AC/py. Seventeen (8.5%) patients died during the observation period. No significant differences were observed in disease duration, GC replacement dose, or changes in GC dose/preparation between patients who experienced AC and those who did not during the observation period. The highest risk for recurrent AC was observed in patients with a history of AC at baseline compared to those without prior AC (OR 7.1, 95% CI 2.3–21.6). Logistic regression identified AI etiology, prior AC history, type 2 diabetes mellitus, hypothyroidism, and frequency of regular GC dose adjustments as significant predictors of AC. Except for AI etiology, these factors remained significant predictors of AC in the subgroup of patients primary AI.
Conclusion
This study confirms previous findings that a history of AC is the strongest predictor of future AC and identifies additional risk factors contributing to individual vulnerability. These results support the development of personalized risk assessment and prevention strategies for AC.

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P87

JOINT2906

Treatment of children and adolescents with congenital adrenal hyperplasia with hydrocortisone modified-release hard capsules

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Context
The standard treatment for congenital adrenal hyperplasia (CAH) in childhood includes hydrocortisone and, for salt-wasting CAH, fludrocortisone supplementation. Regular monitoring and dose adjustments are essential to prevent over- or under-dosing during growth and puberty. Conventional fast-acting hydrocortisone often fails to adequately suppress the early morning surge of 17-OH progesterone (17OHP), and the requirement for three daily doses poses adherence challenges. In 2021, the European Medicines Agency approved hydrocortisone modified-release capsules (HMRC, Efmody®) for children aged 12 and older with CAH. Its modified release allows for twice-daily dosing, with the highest dose at bedtime, better replicating physiological cortisol secretion by achieving peak levels in the early morning.
Objective
To investigate growth, pubertal development, safety, long-term disease control and dosage of hydrocortisone and fludrocortisone in children and youth with CAH treated with HMRC and monitored by 17OHP saliva profiles.
Methods
This study is a retrospective, descriptive analysis of CAH patients treated at a single-center outpatient clinic. Linear mixed models (LMMs) are used to compare the average growth rate of parental target height and BMI before and after switching to hydrocortisone modified-release capsules (HMRC). Additionally, average dosage, blood pressure, and 17OHP level before and after switch are calculated using LMMs. The LMMs account for patient heterogeneity in time-dependent changes. Pubertal status is assessed using breast stage in females and testicular stage in males.
Results
Since September 2021, 42 children with CAH (22 males) have been treated with hydrocortisone modified-release capsules (HMRC). At the time of treatment switch, the median age was 11 years (IQR 8–14), with 16 children classified as prepubertal, 17 as pubertal, and 9 as postpubertal. Prior to the switch, growth rates were accelerated (0.10 z-scores/year, CI: 0.04–0.15, $P<0.001$), whereas a deceleration was observed afterward (-0.05 z-scores/year, CI: -0.15 to 0.04), particularly in (pre-)pubertal patients (0.13 vs. -0.12). The average hydrocortisone dosage increased by 3.25 mg/m^2 per day upon switching from immediate-release hydrocortisone to HMRC. Morning 17OHP levels suggested underdosage before the switch (323 ng/l, CI: 250–396) and improved control afterward (228 ng/l, CI: 167–289, $P<0.01$). No increase in adrenal crises was observed.
Conclusion
HMRC treatment in children with CAH improves morning pre-dose 17OHP levels, while growth rates align more closely with the parental target height. No significant adverse effects or severe complications were observed. Further research is needed to assess long-term outcomes and quality of life.

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P88

JOINT1321

AZD1775: effect of monotherapy or EDP-M combination in the treatment of ACC preclinical models

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Adrenocortical carcinoma (ACC) is a rare and aggressive endocrine cancer. The current treatment for advanced ACC is represented by EDP-M (etoposide, doxorubicin, cisplatin + mitotane), but its efficacy is limited and new therapeutic approaches are needed. Previous *in vitro* findings of our group showed that AZD1775, an inhibitor of the G2/M checkpoint gatekeeper Wee1, reduces proliferation and increases apoptosis in ACC cell lines and primary cultured cells. Aim of this study was to test in vitro, in vivo, and ex-vivo the effects of the combined AZD1775+EDP-M therapy, as well as to validate AZD1775 antitumoral efficacy in a preclinical mouse model of ACC. In human ACC H295R cells the coincubation of AZD1775 and EDP-M showed synergistic effects in reducing both cell viability and cell proliferation (HSA Synergy Score 11.86 and 17.63, respectively). The growth of H295R-derived tumor xenografts in athymic nude mice was significantly reduced after single or combined treatment vs. control group (tumor volume increase in untreated +168(32–253)% after 21 days, +24.5(7–75)% in AZD1775 group, +53(6–116.8)% in EDP-M group, and +45.5(13–84.5)% in AZD1775+EDP-M group). All treatments were well tolerated and histological examination of hearts and kidneys of treated animals did not reveal signs of toxicity. Interestingly, AZD1775 was the most efficient drug in inducing tumor cell necrosis. At last, ex vivo primary cultures of untreated and AZD1775+EDP-M treated tumor xenografts were incubated with single or combined drugs. Cell proliferation assays demonstrated that cells derived from mice treated with combination therapy for 21 days were less responsive to AZD1775 or to EDP-M compared to cells derived from untreated mice, suggesting the possible onset of resistance mechanisms. Interestingly, the co-incubation of these cells with AZD1775+EDP-M maintained a strong inhibitory effect (−60.7% of cell proliferation in pre-treated cells vs −80.7% in naïve cells). In conclusion, we showed the high efficiency of AZD1775 therapy on H295R xenografts, which resulted comparable to EDP-M monotherapy, without

any off-target toxicity. Furthermore, the combined therapy AZD1775 + EDP-M synergistically reduced cell proliferation and viability in vitro, impaired tumor growth of H295R xenografts, and was efficient even upon re-exposure of cells derived from treated mice. Our data support AZD1775 as a novel therapeutic option for ACC, as well as its combination with EDP-M as a useful strategy to enhancing drug efficacy, possibly reducing the therapeutic dose, minimizing side effects and preventing the development of drug resistance.

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P89

JOINT1535

Adrenalectomy ameliorates cardiovascular profile in patients with mild autonomous cortisol secretion: results of a RCT

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Context
The best therapeutic approach in patients with mild autonomous cortisol secretion (MACS) is debated.
Objective
To evaluate the effect of adrenalectomy on blood pressure (BP), glycometabolic control, cardiac structure and coagulation factors in patients with MACS.
Design
Prospective randomized controlled trial.
Setting
Outpatients.
Patients
Patients with adrenal incidentaloma (AI) >1 cm and cortisol after 1 mg dexamethasone suppression test (F-1 mgDST) between 1.8 (50 nmol/l) and 5 μg/dL (138 nmol/l).
Intervention
Randomization to adrenalectomy (Arm-A) or conservative approach (Arm-B).
Main outcomes measure
BP, coagulation factors, echocardiography and glycemic control, parameters and medical therapy changes assessed at baseline and 12 months after recovery or observation, in Arm-A and Arm-B, respectively.
Results
Fifty-one subjects (23/28 in Arm-A/Arm-B) were enrolled. At follow-up the prevalence of BP improvement was higher in Arm-A (43.5%) than in Arm-B patients (14.3%, $P=0.020$). The improvement of BP control was 5.4-fold more frequent in Arm-A patients (CI, 1.16–24.9 $P=0.031$), regardless of confounding factors. Left ventricular (LV) mass and Left atrial (LA) area decreased at follow-up in Arm-A (96.4 ± 28.8 vs 87.6 ± 25, 6 g/m^2, $P=0.039$; 28.4 ± 9.9 vs 22.6 ± 12.4 cm^2, $P=0.037$, respectively), whereas they remained stable in Arm-B. At the end of follow-up, Arm-A patients had a lower prevalence of altered anti-coagulant parameters (10% vs 50%, respectively, $P=0.005$). The improvement of ≥ 1 out of hypertension, LV hypertrophy or LA dilatation and coagulation state was observed in 82.5% of patients of Arm-A and in 49.1% of Arm-B group ($P=0.015$)
Conclusion
In patients with MACS surgery ameliorates BP, cardiac structure, and coagulation factors

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P90

JOINT2462

Assessing hypothalamus–pituitary–adrenal axis in Prader-Willi syndrome: experience in a tertiary care centre

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Background
Central adrenal insufficiency (CAI) is a severe endocrinological manifestation reported in Prader Willi Syndrome (PWS). To date there is no consensus on the most reliable dynamic test to assess the adrenal function or whether to treat CAI. We aimed to evaluate adrenal function using morning plasma cortisol (MPC) and Low-Dose Tetracosactrin Stimulation Test (LDTST) in a paediatric PWS cohort; we also evaluated the usefulness of Glucagon stimulation test (GST) in those in transitional age who reached adult height.
Methods
We retrospectively analysed MPC and ACTH levels in 94 GH-treated PWS patients (48:M, 46: F), aged 0.5–17.9 years, followed at San Raffaele Hospital over the past 16 years. An MPC level of ≥ 60 ng/mL was considered normal; a LDTST test was performed if MPC was lower than 60 ng/ml on two MPC measurements. A cortisol peak <180 ng/mL after LDTST was suggestive of CAI. We also assessed hypothalamic–pituitary–adrenal (HPA) function in those patients undergoing GST during transitional age at adult height achievement; in this case adrenal insufficiency was considered as peak of cortisol <167 ng/mL, according to prior studies.
Results
The median MPC and ACTH levels were 75.5 ng/mL [54; 109] and 16 pg/ml [12; 22.38], respectively. No patients showed laboratory abnormalities suggestive of CAI, such as hypoglycaemia, hyponatremia, or hyperkalaemia. Only one patient (1%) presented abnormal weight loss, albeit in absence of anorexia, fatigue or salt cravings. Eight subjects (8.5%) underwent LDTST: median basal and peak cortisol levels were 40 ng/ml [30.5; 55.75] and 185 ng/ml [149.3; 217.3], respectively. Four out of eight patients (50%) showed a pathological test response, although the cortisol peak was not indicative of severe CAI. These patients were advised to take hydrocortisone only during acute illness or stressful events. Total of nine patients (9.5%) underwent GST during transitional age, all showing an adequate cortisol response (median peak 198 ng/ml [172.5; 216]).
Conclusions
This study suggests that CAI, despite rare, is a potentially life-threatening endocrinological manifestation in PWS. Considering its subtle presentation, monitoring adrenal function in PWS patients is crucial. Morning basal cortisol alone has a limited diagnostic value for CAI, but it appears useful as an initial step in CAI screening. To improve diagnostic accuracy, we believe that a dynamic stimulation test should be performed in every PWS patient at least once. Further studies are needed to establish defined criteria for diagnosis and treatment of CAI.

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P91

JOINT3006

Intraocular pressure and risk of glucocorticoid-induced ocular hypertension are increased in children with congenital adrenal hyperplasia

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Background
Children with classical congenital adrenal hyperplasia (CAH) require lifelong glucocorticoid (GC) treatment. An important side-effect of steroids is GC-induced ocular hypertension, which may cause irreversible blindness known as GC-induced glaucoma.
Aim
This study aimed to evaluate the intraocular pressure (IOP) and the risk of GC-induced ocular hypertension in pediatric patients with congenital adrenal hyperplasia (CAH), a condition requiring long-term GC therapy due to impaired adrenal steroid synthesis.
Method
The study included patients aged 4–21 years diagnosed with salt-wasting or simple virilizing CAH and receiving hydrocortisone therapy, along with age-matched healthy controls. Data including GC dosages, auxological parameters, and levels of serum androstenedione (AS) and 17-hydroxyprogesterone (17-OHP) over the past year for all patients. IOP was measured using an Icare tonometer, with intraocular hypertension defined as a peak IOP of ≥ 21 mmHg in either eye. IOP levels were compared among CAH patients based on hydrocortisone dosage (≥ 15 mg/m^2/day as high dose; <15 mg/m^2/day as maintenance dose).
Results
The median ages of CAH patients ($n=26$) and controls ($n=45$) were 12 ± 5 and 11.5 ± 2.9 years, respectively ($P=0.63$). No difference was observed between the groups in terms of age and gender ($P=0.63$, $P=0.8$, respectively). IOP levels were significantly higher in CAH patients (20 ± 3 mmHg) compared to healthy controls (13.8 ± 3 mmHg) ($P<0.001$). Fourteen of CAH patients (53%) had intraocular hypertension; among these, three were treated with dexametasone

(daily doses were 0.25 mg, 0.375 mg, and 0.5 mg). Age, gender, mean 17-OHP and AS levels over the past year of patients with intraocular hypertension were similar with those of normotension subgroup. However, the change in BMI SDS over the past year was significantly higher in patients with intraocular hypertension ($P=0.005$). Median IOP levels were similar ($P=0.5$) between the high dose hydrocortisone ($n=9$) and maintenance dose ($n=14$) groups. The correlation analyses revealed no significant associations between IOP and age, disease duration, AS, or 17-OHP levels. However, a positive significant correlation was observed between BMI SDS change over last year and IOP ($r=0.5$, $P=0.008$).

Conclusion

In patients with CAH, systemic GC can cause increased IOP which indicates the need for IOP screening of these children. Increase in BMI can be an additional risk factor.

Keywords: CYP21A2; adrenocorticotropic hormone; androgens; glaucoma

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P92

JOINT4004

Analysis of novel ventricular repolarization parameters in Cushing's syndrome: A comparative study

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Introduction

Cardiovascular complications are leading causes of morbidity and mortality in Cushing's disease, including hypertension, myocardial infarction, stroke, dilated-hypertrophic cardiomyopathy, heart failure, pulmonary embolism, and arrhythmias. Electrocardiography (ECG) remains one of the most reliable methods for assessing cardiac electrical activity. The Tpeak-end (Tp-e) interval, which represents the time from the peak of the T wave to its end, is a repolarization parameter that reflects both global and transmural repolarization. An increased Tpe interval has been shown to predict in-hospital and long-term mortality in patients with acute myocardial infarction. These ECG parameters have been associated with poor prognosis and mortality in various diseases beyond cardiovascular conditions. This study aimed to evaluate changes in ventricular repolarization parameters on ECG in patients with Cushing's syndrome.

Methods

This study included 45 patients with ACTH-dependent or ACTH-independent Cushing's disease, along with a control group matched for age and gender. Patients with known cardiovascular diseases, those using antiarrhythmic drugs, and those with electrolyte disturbances were excluded. All participants underwent a standard 12-lead ECG (filter 40 Hz, 25 mm/s, 10 mm/mV). An experienced cardiologist measured heart rate, P-wave duration, QRS complex, T-wave duration, PR interval, Tp-e interval, and QT interval.

Results

A total of 83 participants were included, comprising 41 patients with Cushing's syndrome (Female/Male: 32/9) and 42 healthy controls. Among the patients, 27 had ACTH-independent and 14 had ACTH-dependent Cushing's disease. P-wave duration, Tp-e interval, and Tp-e/QT and Tp-e/QTc ratios were significantly increased in the Cushing's group compared to controls ($P<0.001$). Additionally, the QTc interval and P-wave duration showed a significant negative correlation with midnight salivary cortisol levels.

Conclusion

Our study found that P-wave duration, Tp-e interval, and Tp-e/QT and Tp-e/QTc ratios were elevated in patients with Cushing's syndrome compared to control subjects. These findings suggest that ECG changes linked to ventricular arrhythmias and mortality may be present in Cushing's syndrome, highlighting the need for further investigation and monitoring of these patients.

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P93

JOINT2103

Assessment of adrenal function after glucocorticoid therapy for childhood onset first episode nephrotic syndrome

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Background

Adrenal insufficiency (AI) is a significant concern in children having prolonged glucocorticoid therapy for childhood onset first-episode nephrotic syndrome. As AI results in impaired cortisol response during stressful conditions, which can lead to life-threatening adrenal crisis if stress dose of corticosteroid is not administered on time. Therefore, this highlights the need for regular monitoring of adrenal function after discontinuing steroid therapy.

Objectives

1. To assess the proportion of children having adrenal insufficiency within 5 days after discontinuing steroid therapy for first episode nephrotic syndrome and again after 6–8 weeks.
2. To assess features of steroid toxicity at both time points.

Methods

This study included 40 children with first-episode nephrotic syndrome who received standard corticosteroid therapy as per ISPN guidelines. Adrenal function was assessed within 5 days and again at 6–8 weeks after discontinuing steroids by measuring 0800 h basal and 1-hour post ACTH stimulation serum cortisol levels (obtained after 25 IU I/M injection of Acton Prolongatum). Basal serum cortisol < 3 µg/dL were considered low and suggestive of adrenal insufficiency. Confirmed adrenal insufficiency was defined as post-stimulation serum cortisol $<$ 18 µg/dL. Steroid toxicity features were also assessed at both time points.

Results

Mean basal and post-stimulated cortisol levels increased significantly from first to second assessment ($P<0.001$ for both) indicating progressive adrenal recovery with time after discontinuing steroid therapy. Low basal cortisol was present in 42.5% cases at first and 2.5% cases at second assessment. Adrenal insufficiency was present in 52.5% within 5 days of stopping steroids which decreased to 27.5% at 6–8 weeks. Steroid toxicity at first assessment included moon face (97.5%), buffalo hump (25%), hirsutism (42.5%), pre-hypertension (25%) and hypertension (12.5%) which was reduced to 72.5%, 10%, 22.5%, 7.5%, and 5% respectively by the second assessment. Impaired fasting sugar was seen in 17.5% at first and 12.5% at second assessment. No children were overweight, obese, diabetic or showed clinical symptoms of adrenal insufficiency during study period. Hypertension and impaired blood sugar were significantly associated with adrenal insufficiency at the first assessment, but not at the second.

Conclusion

Over half of the children had adrenal insufficiency soon after stopping steroids, with more than a quarter still affected at 6–8 weeks. This highlights the need for regular adrenal function monitoring post-steroid therapy to prevent adrenal crisis and optimize the use of stress-dose steroids. The study also demonstrates the reversible nature of steroid-related side effects after treatment cessation.

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P94

JOINT2341

Insights into the health provision for children with congenital adrenal hyperplasia in the UK and implementation of longitudinal collection and analysis of real-world data

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Background
Congenital adrenal hyperplasia (CAH) is one of the commonest forms of primary adrenal insufficiency, around 70 children being diagnosed every year in the UK. Our national survey indicated variations among clinicians in the management of children and young persons with CAH. We wanted to use the SDMregistries to gain further insight regarding the current practice of CAH clinical management in children in the UK.
Methodology
We launched a 5-year-project in 03/2022, collecting annually longitudinal data from the SDMregistries platform on UK patients under 18 with 21-hydroxylase deficiency, the most common form of CAH.
Results
The first data extraction in 09/2022 provided data from 44 eligible patients (5 centres), with a median of 8 patients per centre (range 3–15). The second data extraction in 03/2024 showed an increase in participation, including 96 patients from 15 centres, with a median of 4 patients per centre (range 1–20). Of these, only 68 (70%) had sufficient data to allow an analysis of the replacement medication. We analysed information related to medication and height standard deviation scores (SDS) for age and sex. The mean daily glucocorticoid (GC) dose was 12.0 ($\pm$3.8 S.D.) mg/m^2 per day hydrocortisone-equivalent, with broad variations between centres ranging from 7.7 ($\pm$1.2) to 19.1 ($\pm$7.7) mg/m^2 per day. The dose decreased with age by 0.2 mg/m^2 per day per year, and depended upon centre; it also varied with sex, doses used in girls being lower by 1.1 mg/m^2 per day compared to boys. We identified different GC administration regimes, with variation in the time of administration of the first daily hydrocortisone dose between 04:00 and 09:00, and six centres using midnight doses. Total daily fludrocortisone doses ranged between 50 and 300 μg/day, with significant variation between centres ($R^2=0.44$, $P<0.01$). Generalised additive model fit showed height SDS fluctuated with age, starting from -0.6 in infancy increasing to 0.7 at 10 years and then decreasing to -1.0 at 17.5 years.
Conclusions
These preliminary findings warrant further investigation to establish potential different approaches and analyse outcomes. Thus, we are implementing a strategy to increase recruitment by actively engaging UK centres involved in the management of CAH patients under 18 into recording their data in I-CAH. Data will be collected and analysed annually, to assess the current level of care provision and inform the development of national CAH standards. This work will help to develop a standardised approach to hormone replacement in CAH and create a framework for benchmarking management at national and international level.

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P95

JOINT2738

Increased prevalence and incidence of psychiatric and sleep disorders in patients with non-functional adrenal tumors

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Importance
Current research has yet to elucidate the potential relationship between non-functional adrenal tumors (NFATs) and various mental health conditions, including psychiatric and sleep-related disorders. An increase could be hypothesized due to very mildly abnormal cortisol secretion in patients with NFATs.
Objective
To investigate the prevalence and incidence of psychiatric and sleep-related disorders in individuals diagnosed with NFAT.
Design, setting, and participants
A national retrospective register-based study was conducted on patients diagnosed with NFAT in Sweden from 2005 to 2019 and controls without adrenal tumor diagnosis, followed until death or the conclusion of 2020. Individuals diagnosed with adrenal hormonal excess were excluded from the study.
Exposures
NFAT diagnosis.
Main outcomes and measures
Primary study outcomes were the prevalence and incidence of any psychiatric and sleep disorders after adjustment for sex and age. The secondary outcomes were sleep disorders, substance abuse disorders, psychotic disorders, mood disorders, anxiety and stress-related disorders.
Results
Among 33 348 cases, 18 510 (55.5%) were women, and the median (IQR) age was 68 (59; 74) years. Among 144 983 controls, 80 942 (55.8%) were women, and the median (IQR) age was 67 (59; 74) years. Previous psychiatric and sleep disorders were more prevalent in patients diagnosed with NFAT compared to controls (odds ratio (OR) 1.74, 95% CI 1.69–1.80, adjusted OR 1.71, 95% CI 1.66–1.77). Similar increases were found in all secondary outcomes. During the follow-up period (5.4 years (IQR 2.5–8.8)), the incidence of psychiatric and sleep disorders was higher in patients with NFAT than in controls (hazard ratio (HR) 2.06, 95% CI 1.97–2.15, adjusted HR 2.03, 95% CI 1.94–2.13). Similar increases were found in all secondary outcomes.
Conclusion and relevance
NFAT was associated with an increased risk of psychiatric and sleep disorders.

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P96

JOINT1080

Macrophage polarisation in patients with autonomous cortisol excess

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Background
Adrenal Cushing's syndrome (CS) is characterized by chronic, endogenous cortisol excess, which disrupts innate and adaptive immune functions. This dysregulation is observed as increased monocyte and reduced lymphocyte counts. However, the effects of "subclinical" CS in patients with cortisol-producing adenomas (CPA) and mild autonomous cortisol secretion (MACS) remain insufficiently understood. We hypothesize that macrophage polarization and activation may be altered in these patients, potentially leading to significant immune dysfunction.
Methods
Our cohort included 14 patients, i.e. 5 with CPA-MACS, 4 with CPA and overt CS (CPA-CS), and 5 sex- and age-matched patients with endocrine-inactive adenomas (EIA) as controls. Serum samples were collected during standard visits, centrifuged within 1–2 hours from collection, and stored at -80 °C. Primary human macrophages were polarized to an M1-like inflammatory state by adding TNFα (10 ng/ml) and IFNγ (20 ng/ml), followed by co-treatment with 10% serum from patients with adrenocortical adenomas. The macrophages were incubated for 24 hours, and inflammatory and anti-inflammatory cytokine levels and gene expression were measured using ELISA and RT-qPCR techniques. Cytokines and gene expression levels were correlated with clinical parameters (e.g. age, sex, tumour size) and degree of cortisol secretion (e.g. cortisol after overnight dexamethasone test, ACTH, and DHEAS levels).
Results
Pro-inflammatory markers such as TNFα exhibited a slight decrease in M1-polarized macrophages exposed to serum from both CPA-MACS ($P=0.1916$) and CPA-CS ($P=0.1217$) patients when compared to controls. A similar pattern was observed for IL6, with significant reductions noted in CPA-MACS ($P=0.0389$) and CPA-CS ($P=0.0283$) serum-treated macrophages compared to EIA. Gene expression data indicated non-significant trends in IL6 reduction in both CPA groups (CPA-MACS: $P=0.0794$, CPA-CS: $P=0.1302$). Additionally, GILZ (glucocorticoid-induced leucine zipper) gene expression was modestly elevated in CPA-CS patients ($P=0.2830$), though no change was observed in CPA-MACS ($P=0.9921$). The pro-resolving M2-like marker CD163 showed slight increases in gene expression in both CPA-MACS ($P=0.1761$) and CPA-CS ($P=0.1545$) groups compared to EIA controls. Notably, CD163 expression was strongly correlated with GILZ ($P<0.0001$) and the anti-inflammatory marker

CD64 ($P=0.0038$). The ratio of IL6 to CD163, reflecting M1-to-M2 polarization, was elevated in CPA-CS samples ($P=0.0614$). Additionally, CD163 expression correlated with post-ONDST cortisol levels ($P=0.0153$) and tumour size ($P=0.08$).

Conclusions

Both CPA-MACS and CPA-CS patients demonstrated suppression of M1-like inflammatory markers and a shift towards M2-like polarization, which could contribute to immune dysregulation. Further experiments with a larger cohort and additional functional assays are ongoing to identify the mechanisms driving these immune alterations.

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P99

JOINT3614

Aldosterone, renin and their ratio (ARR) in patients with newly diagnosed and untreated hypertension

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Background

Primary hyperaldosteronism (PA) is more prevalent than previously recognized. The prevalence of PA in patients with undiagnosed and untreated hypertension (HT) is less known. In a prior population-based study, REFINE-REYKJAVIK study (RRS), carried out in Iceland 2005–2006, 8815 men and women born between 1935 and 1985, and living in the Reykjavik area, were randomly drawn from the Icelandic national registry. Of those, 6941 (73%) individuals attended the study. Thereof, 420 participants were diagnosed with previously unrecognized and untreated HT. The aim of the presented study is to evaluate serum aldosterone (s-aldosterone), plasma renin (p-renin) and their ratio (ARR) taken at baseline and the difference between participants with HT in comparison to normotensive (NT) counterparts.

Methods

As part of RRS, systolic (SBP) and diastolic (DBP) blood pressure was measured at baseline, and HT diagnosed if SBP was over 140 mmHg and/or DBP over 90 mmHg. Blood samples were collected between 08 and 10 AM (68%), 10–12 AM (30%) and few after 12 PM (1.5%). The specimens, initially cooled for up to maximum of 6 hours before being frozen at -80°C and stored. S-aldosterone and p-renin was measured in the 402 HT patients and the 207 NT participants. A Mann–Whitney U test was implemented in comparing the groups. Statistics were performed by using datatab.net.

Results

The mean value for s-aldosterone was 253.09 pmol/l $\pm$ 167.58 in HT ($n=402$) and 267.5 pmol/l $\pm$ 170.8 in NT ($n=207$), the difference was not significant ($P=0.817$). The mean value for p-renin was 11.15 mIU/l $\pm$ 11.32 in HT and 13.56 mIU/l $\pm$ 11.2 in NT. The difference was significant $P<0.001$. The ARR in the HT group was 39.95 $\pm$ 39.11 and 29.64 $\pm$ 23.49 in the NT group, the difference was significant, $P=0.005$. Mean serum potassium levels for the groups was 4.22 mmol/l $\pm$ 0.28 in HT and 4.19 mmol/l $\pm$ 0.27 in NT, the difference was not significant $P=0.952$.

Discussion

These findings show that p-renin was significantly lower in the HT group compared to the NT group and ARR was thus significantly higher in individuals with newly diagnosed and untreated HT compared to NT counterparts. These findings emphasize the importance of using aldosterone, renin and ARR in patients with newly diagnosed HT. As PA seems to be largely underdiagnosed; these findings support the need to screen for PA at the time of diagnosis of HT.

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P100

JOINT1780

Incidental adrenal nodules: A single-center study on the prevalence and radiological predictors of phaeochromocytoma

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Introduction

Phaeochromocytomas are increasingly diagnosed incidentally during cross-sectional imaging for other indications. Biochemical confirmation can be obtained via plasma free metanephrines or a 24-hour urine collection for normetanephrine and metanephrines. However, recent ESE guidelines suggest biochemical testing may not be necessary for patients with clear radiological features of an adrenal adenoma.

Methods

A retrospective analysis was conducted on the radiological and biochemical data of patients with incidentally discovered adrenal nodules reviewed at Cambridge University Hospital from 2019 to 2024.Only cases with formal radiological characterization of the adrenal nodule via unenhanced CT, dedicated CT adrenal imaging, or MRI were included. Data collected included age, gender, plasma metanephrines, laterality, tumour size, histology, genetics, and follow-up.

Results

A total of 631 patients were included, with 296 males (47%) and 335 females (53%). Of these, 507 (80.34%) had nodules with attenuation <10 Hounsfield units (HFU) or signal dropout on MRI. 61 patients (9.66%) had densities between 10 and 20 HFU, and 63 (10%) had densities >20 HFU. Most nodules (94.45%) were <4 cm in size, with 35 (5.55%) >4 cm. 521 nodules (82.56%) were unilateral and 110 (17.43%) bilateral. The mean age was 66 years (range 21–91). Two patients (0.4%) with radiologically characterized lipid-rich adenomas had abnormal plasma metanephrine results (<2 times the upper reference range), one of whom was on Venlafaxine. Both cases are pending further evaluation, with a low clinical suspicion for phaeochromocytoma. Among the 631 patients, 7 (1%) were diagnosed with phaeochromocytoma, all of which had nodules with densities >20 HFU on unenhanced CT scan adrenal glands. 4 were females and 3 males. It is important to mention that two ($\sim$28%) were reported as adenomas on washout studies but later confirmed as non-secretory pheochromocytomas. Histological analysis showed retained SDHB immunoreactivity in all cases. Genetic testing in five patients revealed an NF1 gene mutation in one with composite pheochromocytoma.

Conclusion

This study found a 1% prevalence of phaeochromocytoma in patients with incidentally discovered adrenal nodules. All confirmed cases had unenhanced nodules with densities >20 HFU. Histological analysis showed retained SDHB immunoreactivity, and genetic testing revealed an NF1 mutation in one patient. Two patients with lipid-rich adenomas had equivocal plasma metanephrine results, with further testing pending. Washout characteristics were unreliable in distinguishing benign from indeterminate lesions. These findings support the ESE guidelines, suggesting biochemical testing can be excluded in patients with radiologically characterized lipid-rich adrenal adenomas on unenhanced CT imaging of adrenal glands.

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P101

JOINT3916

Effects of prednisolone administration on clock gene expression and indices of circadian rhythms in healthy human subjects

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Background

States of glucocorticoid (GC) excess and circadian clock disruption disorders – as observed in shift workers and following chronic stress and sleep deprivation – both confer an increased risk of developing abdominal obesity, type 2 diabetes and cardiovascular disease. Animal studies have demonstrated that GCs regulate circadian clocks providing a potential mechanism for GC side effects however, experimental data in human models are sparse.

Objective

To investigate the impact of exogenous GC exposure in human subjects on clock gene expression in muscle and fat in concomitance with assessment of circadian variations in peripheral interstitial glucose levels, blood pressure, cortisol levels and sleep quality.

Design

Randomized double-blinded crossover trial with ten healthy males aged 18–34.

Intervention

Prednisolone 25 mg/day in two daily doses or placebo in random order for five days with 6 week washout.

Results
During placebo treatment, an expected large difference was observed between morning and evening expression levels of all four clock genes investigated in adipose tissue and skeletal muscle (table). Prednisolone profoundly flattened the diurnal change in expression levels of all genes. Prednisolone treatment led to increased nocturnal interstitial glucose (placebo 6.6±0.8 vs prednisolone 8.2±0.9 mmol/l, $P<0.001$) and elevated nocturnal nadir of systolic blood pressure (placebo 116±7 vs. prednisolone 123±14, $P=0.05$).
Conclusion
Prednisolone twice daily abolished the normal fluctuations in the expression levels of core clock genes in skeletal muscle and adipose tissue. This was accompanied by disturbed sleep, and altered daily patterns of glucose levels and blood pressure. Our findings add important human data supporting GC-induced circadian disruption in metabolic tissues.

Parameter	Placebo		Prednisolone	
	Fold difference morning vs evening	P-value	Fold difference morning vs evening	P-value
Adipose tissue – ($2^{-\Delta\Delta CT}$)				
Per3	3.3 (2.4 to 4.5)	<0.001	1.3 (0.9 to 1.8)	0.11
Reverb-Beta	3 (2.3 to 3.9)	<0.001	1.3 (1 to 1.7)	0.04
Bmal1	0.3 (0.2 to 0.4)	<0.001	1 (0.7 to 1.4)	0.99
Npas2	0.4 (0.3 to 0.6)	<0.001	0.8 (0.6 to 1.1)	0.20
Skeletal muscle – ($2^{-\Delta\Delta CT}$)				
Per3	2.6 (2 to 3.5)	<0.001	1.1 (0.8 to 1.4)	0.59
Reverb-Beta	1.8 (1.3 to 2.3)	<0.001	0.9 (0.7 to 1.2)	0.56
Bmal1	0.4 (0.3 to 0.6)	<0.001	0.7 (0.5 to 1)	0.05
Npas2	0.5 (0.3 to 0.8)	<0.01	0.7 (0.5 to 1.2)	0.20

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P102

JOINT646

Metabolomic profiling of premature adrenarche reveals a unique acylcarnitine-dominated signature

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The mechanisms and regulatory factors underlying adrenarche, the development of the zona reticularis in the adrenal cortex, remain largely unknown. Children with premature adrenarche (PA) are typically taller and have a higher body fat percentage compared to peers with normally timed adrenarche. Notably, their growth acceleration and rapid weight gain can often be traced back to infancy, suggesting the possibility of early metabolic programming as a contributing factor. To explore this, we compared 16 girls with PA and 27 control girls, at the mean ages of 7 and 9 years, in a longitudinal study using a liquid chromatography mass spectrometry (LC–MS)-based untargeted metabolomics approach. PA was defined by at least one clinical sign of androgen action, accompanied by a serum DHEAS concentration exceeding 1 µmol/l, with other causes of androgenic signs ruled out. Both groups were comparable regarding background characteristics, including standardized body size at birth and diagnosis (length/height and BMI), basic biochemical parameters (glucose, insulin, and lipids), and dietary nutrient intake. Metabolites were analyzed from serum samples using LC–MS. Metabolomics data from PA girls at age 7 was compared to control girls at age 7 ('age-matched' comparison) and in addition also at age 9, when the control group exhibited adrenarchal signs ('event-matched' comparison), using linear mixed-effects models. In the age-matched comparison, 93 metabolite features differed significantly between the groups, with 74 being higher and 19 lower in PA girls. In the event-matched comparison, 128 metabolite features differed significantly between the groups, with 95 being higher and 33 lower in PA girls. Notably, 23 metabolites were identified in both comparisons, including 22 being consistently higher and 1 lower in PA girls. Among the 22 metabolites that were higher in PA girls, acylcarnitine metabolites were predominant, along with several fatty acid and steroid metabolites. The sole metabolite that was lower in the PA girls was a sulfate conjugate of the bacterial metabolite p-cresol. These findings suggest a potential involvement of fatty acid beta-oxidation in mitochondria and/or peroxisomes, and gut microbiome in the development of PA.

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P103

JOINT844

The determination of steroid levels directly in the tissue of bilateral adrenocortical lesions reveals discrepancies with circulating levels

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Introduction
Bilateral adrenocortical lesions, either primary including macronodular adrenocortical disease (BMAD) and pigmented nodular adrenocortical dysplasia (PPNAD), or secondary to Cushing's disease (CD), are responsible for steroid hypersecretion of variable intensity, evaluated by plasma or urine assays. In a subgroup of BMAD, *ARMC5* pathogenic variants are associated with more severe clinical, radiological and biological phenotypes. The aim of our work was to better describe steroidogenesis alterations in these bilateral lesions by directly assessing steroid content in the adrenocortical tissue.
Material and methods
An intratissular profile of 14 steroids (4 glucocorticoids, 3 mineralocorticoids, 5 androgens, 2 precursors) was determined using LC–MS/MS (*Thermo Fisher* ™) on 38 fresh-frozen tissue samples collected from patients undergoing adrenalectomy (6 *ARMC5*-WT BMAD, 7 *ARMC5*-altered BMAD, 9 PPNAD including 8 with *PRKAR1A* pathogenic alteration, 7 from adrenal hyperplasia due to CD), and 9 normal adrenals (NA) as controls).
Results
CD presented higher intratissular glucocorticoids and androgens concentrations than NA, in accordance with circulating levels. Intratissular steroids levels were globally lower in *ARMC5*-altered BMAD than in *ARMC5*-WT BMAD (cortisol: median [IQR] =5976 [3201–16741] vs. 26971 [18069–44509] nmol/kg of tissue, $P=0.02$). Surprisingly, intratissular testosterone was elevated (between 256 and 595 nmol/kg vs. 40.3 [15.6–99.7] nmol/kg of tissue in NA) in 4/9 PPNAD (2F/2M) despite neither evidence of clinical nor biological hyperandrogenism. Intratissular concentrations of mineralocorticoids precursors in BMAD were higher than in PPNAD.
Discussion
Our results confirm the hypothesis of a less efficient steroidogenesis in *ARMC5*-altered BMAD, in which the higher tumoral mass may contribute to systemic hypercortisolism. Despite normal plasmatic concentrations, we observed elevated intratissular levels of testosterone in some PPNAD, as well as mineralocorticoid precursors in BMAD. These discrepancies between intratissular and circulating steroid concentrations might reflect the underlying and little-known mechanisms leading to steroidogenesis alterations in these bilateral adrenocortical nodular diseases, and also raise the question of a specific steroid export dysregulation.

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P104

JOINT1468

Circulating GDF-15 is elevated in adrenal cushing's syndrome but not in cushing's disease

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Context
Growth/differentiation factor 15 (GDF-15) is a cytokine involved in immunosuppression and anorexia and secreted primarily in response to mitochondrial dysfunction. Recent studies suggest its potential implication in the hypothalamic–pituitary–adrenal axis.
Objective
To investigate the potential role of GDF-15 in adrenal steroid dysregulation in Cushing's syndrome (CS).
Design
Case–control study.
Methods
Circulating GDF-15 concentrations were assessed in plasma from 25 patients with confirmed overt CS (16 pituitary, 9 adrenal) and 30 age-, BMI-, and sex-matched patients in whom CS was ruled out.
Results
Plasma GDF-15 was significantly higher in CS compared to the control group (644 pg/ml [487.3–797.6] *vs* 520.9 pg/ml [353.2–665.9], $P=0.033$). GDF-15 plasma concentrations were positively correlated with age ($r=0.423$, $P<0.001$), HbA1c ($r=0.329$, $P=0.014$), serum cortisol following dexamethasone suppression test (DST) ($r=0.484$, $P<0.001$), and late-night salivary cortisol ($r=0.334$, $P=0.014$), while negative correlations were observed with ACTH ($r=-0.310$, $P=0.023$) and DHEA-S ($r=-0.538$, $P<0.001$). In multivariate linear regression, age ($B=8.955$, $P=0.045$), DST ($B=7.980$, $P=0.050$) and DHEA-S ($B=-58.215$, $P=0.035$) emerged as independent predictors of GDF-15 concentration ($R^2=0.311$, $P=0.002$). Plasma GDF-15 was significantly higher in adrenal CS compared to pituitary CS (797.6 pg/ml [723.0–1212.2] *vs* 523.2 pg/ml [441.3–668.1], $P=0.002$). Binomial logistic regression identified GDF-15 as an independent predictor of adrenal CS diagnosis (OR = 1.005, $P=0.040$). ROC analysis revealed that the diagnostic accuracy of GDF-15 approached that of DHEA-S and ACTH.
Conclusion
This study identified elevated GDF-15 concentrations in patients with adrenal CS. This observation may reflect cellular stress in response to adrenal steroid dysregulation and could be an additional contributor to immunosuppression in CS.

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P105

JOINT3744

Unravelling the sexually dimorphic role of adrenocapsular progenitor cells during stress adaptation of the adult adrenal gland

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Chronic stress is a pervasive concern in the modern society. The HPA axis dysregulation in chronic stress and psychiatric disorders is tightly linked with hypertrophy and hyperplasia of the adrenal gland. These stress-induced cellular adaptations might employ and could be a result of capsular progenitor behaviour. However, little is known about the contribution of resident progenitor cells to these stress-induced cellular changes. In this study, we aim to unravel the mechanisms involved in the regulation of adreno-capsular progenitors during acute and repeated restraint stress. To that aim, we used a tamoxifen inducible *Gli1:CreERT2/R26R:eYFP* mouse line to lineage trace and monitor *Gli1*$^+$ adrenocortical progenitors during restraint stress in the adult adrenal cortex *in vivo* using both sexes. Our results reveal migratory patches of *Gli1*$^+$ spindle-like cells towards zona glomerulosa (zG) in the cortex of stressed male mice. These patches resemble the adrenocortical neoplasms previously described in literature and express GATA4, a common marker of the adrenogonadal primordium. Further, significant upregulation of the capsular markers *Nr2f2* and *Rspo3*, a signaling molecule involved in the control of cell renewal in the tissue, was noted in the adrenal cortex of those mice. Concerning female mice, it is already known that *Gli1*$^+$ cells contribute to the tissue renewal under homeostatic conditions. Preliminary results suggest that the subcapsular patches of *Gli1*$^+$-derived eYFP$^+$ cells are rather reduced in the cortex of stressed female mice compared to the control group. Overall, this may suggest that in female mice the process of capsular progenitor cell recruitment is reduced when the need for increased steroid production occurs. Notably, beside the reduced recruitment of capsular progenitor cells, we additionally observed significant upregulation of *Cyp11b2*, *Dab2* and the Wnt target *Lef1,* which may indicate a higher response of the zG in female compared to male mice. Lastly, our preliminary results from single-cell RNA sequencing data from stressed and non-stressed mice from both sexes confirm the sexually dimorphic response of the capsule during restraint stress. By further analysing these data, we aim to shed light on molecular factors involved in the paracrine communication between the capsule and the rest of the cortex in stress that could potentially regulate directly or indirectly the stress response and the steroid production.

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P106

JOINT328

Diagnostic genotyping of CYP21A2 gene employing Short Read-NGS: Benefits and Limitations

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Introduction
Short Read Next Generation Sequencing (SR-NGS) has been widely applied in the genetic diagnosis of several mendelian disorders. Nevertheless, one of the major disadvantages remains the inability to fully discriminate genes from their pseudogenes/homologous genes. To date, SR-NGS is not widely used in the diagnostic genotyping of the *CYP21A2* gene due to its highly homologous pseudogene, thus rendering the PCR-based sequencing and MLPA analysis the recommended *CYP21A2* genotyping methodologies. The aim of this study is to assess one of the first SR-NGS assays developed for the genotyping of the *CYP21A2* gene and to present the results of 151 samples referred to the Laboratory of Molecular Endocrinology for *CYP21A2* genotyping employing the above-mentioned technique.
Patients and methods
A total of 172 subjects were studied. Subjects were categorized in 2 groups; the Pilot and the Study Group. The Pilot Group, employed for the assessment of the SR-NGS assay, consisted of 21 samples, previously analyzed using PCR-based sequencing and MLPA analysis. The Study Group consisted of 151 subjects referred for *CYP21A2* genotyping. Both Groups underwent Long Range PCR followed by SR-NGS. Two different bioinformatic pipelines for variant calling (varscan mpileup2cns and GATK HaplotypeCaller functions) were employed in the Study Group. Filtration of the data was performed using VarAFT v2.17. In cases with suspicion of *CYP21A2* gene duplication/deletion MPLA analysis was also employed.
Results
The pilot study assessment of the SR-NGS assay resulted in a sensitivity and precision of 100%. Minor differences were observed in the use of the two different bioinformatics pipelines. No alteration was observed in the frequencies of cases harboring duplication of the gene when compared to cases carrying two copies of the *CYP21A2* gene. Advantage of this methodology is the identification of variants in regions with heterozygous deletions/insertions that could not be covered by PCR-based sequencing. In the Study Group, pathogenic variants were identified in 54.3% of cases while duplications in 4.6%.
Discussion
This study verifies that the application of the SR-NGS assay for *CYP21A2* genotyping presents high sensitivity and precision, short turnaround time and cost effectiveness compared to the PCR based sequencing. Both bioinformatic pipelines can be employed for the SR-NGS data analysis although the GATK algorithm exhibits higher accuracy. MLPA analysis is still required for the

identification of deletions/duplications of the *CYP21A2* gene. Hence, the presented SR-NGS assay and MLPA can be employed for the *CYP21A2* diagnostic genotyping.

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P107

JOINT1929

Elevated bone turnover in primary aldosteronism: a role for aldosterone-dependent phosphate changes?

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Background
Aldosterone excess has been implicated in the regulation of bone metabolism, with different studies indicating reduced bone mass in patients with primary hyperaldosteronism (PA) compared to those with essential hypertension (EH). Some authors suggest that these alterations may be linked to aldosterone-induced parathyroid hormone (PTH) release. Additionally, increased levels of 24-hour urinary calcium have been proposed as a mechanism contributing to bone loss. However, it remains unclear whether this 24-hour urinary calcium is a direct effect of aldosterone or a compensatory response to elevated PTH levels. Existing data on bone turnover in PA patients are limited and often conflicting. This study aimed to investigate calcium–phosphorus metabolism and bone turnover markers in PA patients compared to a cohort of EH controls.
Methods
We conducted a retrospective, multi-center study involving 37 patients with PA and 46 EH controls. PTH, 24-hour urinary calcium, alkaline phosphatase (ALP), C-terminal telopeptide (CTX), calcium, phosphate, 25-OH vitamin D, plasma aldosterone concentration, plasma renin activity, and the aldosterone-to-renin ratio were measured in all participants. Bone turnover has been evaluated in the absence of interfering anti-hypertensive medications in both PA and EAH patients.
Results
The two study groups were comparable in terms of age, gender, and BMI. Serum ALP levels were similar between the groups (73 U/L [62–91] in PA vs. 70 U/L [55–73] in EH, $P=0.26$), as were 25-OH vitamin D levels (27.6 ng/ml [15–34] in PA vs. 19.9 ng/ml [16–28.5] in EH, $P=0.33$) and PTH levels (52 pg/ml [41–61] in PA vs. 59 pg/ml [44–71] in EH, $P=0.25$). As expected, 24-hour urinary calcium was significantly higher in PA patients (201 mg/kg/day [149–299]) compared to those with EH (165 mg/kg/day [107–230]). Notably, the PA group exhibited significantly elevated CTX levels compared to EH controls (617 ng/ml [447–779] vs. 410 ng/ml [280–560], $P<0.005$). Additionally, calcium levels were higher (9.3 mg/dl [8.9–9.6] vs. 9.1 mg/dl [8.8–9.3], $P=0.03$), while phosphorus levels were lower in PA patients (3.0 mg/dl [2.6–3.5] vs. 3.5 mg/dl [3.2–3.7], $P<0.001$).
Conclusion
Patients with PA demonstrate increased skeletal turnover compared to EH controls, which does not appear to be linked to elevated PTH levels. These findings suggest that alterations in bone metabolism among PA patients may be partially PTH-independent and potentially driven by other factors, such as changes in phosphorus metabolism induced by aldosterone, as indicated by the lower phosphorus levels observed in this cohort.

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P108

JOINT2438

Serum inflammation-based scores in adrenal incidentalomas: the role of salivary cortisol rhythm dysregulation

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Background
Alteration of serum inflammation-based scores, used as surrogate markers of systemic inflammation, has been associated with hypercortisolism in recent studies. However, the role of altered circadian rhythm of cortisol in the context of mild autonomous cortisol secretion (MACS) has not been investigated so far.
Aim
To evaluate the association between inflammation-based scores and salivary cortisol daily rhythm in patients with MACS and non-secreting (NS) adrenal tumors.
Methods
We included 85 benign adrenal tumors, classified as NS ($n=25$) and MACS ($n=60$) according to the cortisol values after 1 mg dexamethasone suppression test (DST) $\leq$ or >1.8 mcg/dl, respectively. On an ordinary day, each subject collected saliva samples at the following times: 0700 (awakening), 0715, 0730, 1000, 1230, 1400, 1600, 1930, 2100, and 2300 (bedtime). Salivary cortisol was measured by liquid chromatography–tandem mass spectrometry. The following serum inflammation-based scores were calculated: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and systemic immune-inflammation index (SII; platelet count * NLR). Cortisol AUC (AUC) was used as a surrogate marker to assess overall (0700–2300), morning (0700–1600) and evening (1600–2300) cortisol exposure. Student *T*-test, Pearson's correlation and generalized linear models adjusted for sex, age, body mass index, presence of altered glucose metabolism, and smoking status were used to analyze the relationship between serum inflammation-based scores and cortisol measures.
Results
Evening cortisol AUC was positively correlated with post-DST cortisol levels ($R=0.23$; $P=0.037$). Cortisol levels at 1930 and 2100, and evening AUC were higher in patients with MACS than in those with NS tumors ($P<0.001$ for all). NLR and SII were positively associated with cortisol overall ($R=0.29$, $P=0.010$), morning ($R=0.26$, $P=0.024$) and evening ($R=0.29$, $P=0.009$) AUCs, while PLR only directly correlated with evening AUC ($R=0.23$, $P=0.043$). Generalized linear models showed that higher post-DST cortisol levels were significantly associated with increased NLR ($B=0.160$; 95% CI: 0.011–0.308; $P=0.035$) and reduced LMR ($B=-0.160$; 95% CI: -0.271 to -0.048; $P=0.005$). Increasing overall and evening cortisol AUCs were significantly directly associated with NLR ($B=0.285$, 95% CI: 0.0.059–0.510, $P=0.013$, and $B=0.306$, 95% CI: 0.100–0.512, $P=0.004$; respectively). Additionally, evening cortisol AUC directly associated with SII values ($B=0.406$, 95% CI: 0.107–0.705, $P=0.008$). Active smoking showed an independent direct contribution over NLR ($P<0.001$) and SII ($P=0.006$).
Conclusion
Cortisol exposure, particularly in the evening, is associated with surrogate markers of increased systemic inflammation in patients with benign adrenal incidentalomas.

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P109

JOINT3980

Spectrum of Presentation of 46,XY Sex Reversal and Adrenal Insufficiency: Case Report with Literature Review

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Introduction
CYP11A1 (P450scc) deficiency is a rare and complex disorder associated with primary adrenal insufficiency and 46,XY disorders of sex development (DSD).
Objective
This study delineates the clinical spectrum and genetic underpinnings of 46,XY sex reversal and adrenal insufficiency, using a detailed case presentation and comprehensive literature review.
Methods
We present a case of congenital adrenal hyperplasia (CAH) due to P450scc deficiency in a patient with complete 46,XY DSD. This case prompted a review of similar reported cases focusing on the onset of adrenal insufficiency (AI), clinical presentations, and gonadal management.

Results
Our index case involves a 4-year-old child, assigned female at birth, presenting with recurrent vomiting, hypoglycemia, fatigue, and hyperpigmentation of the lips and hand creases. Clinical examination revealed clitoromegaly. Laboratory tests indicated mild hyponatremia, low cortisol, elevated ACTH, diminished steroidogenesis across all pathways, low aldosterone, and elevated renin. Diagnosis of primary adrenal insufficiency was established, and treatment with hydrocortisone and fludrocortisone was initiated. Chromosomal analysis confirmed a 46,XY karyotype. Pelvic MRI showed no female internal genitalia and bilateral inguinal gonads. Whole exome sequencing revealed a homozygous variant in CYP11A1, confirming P450scc deficiency. The literature review included 25 cases, all demonstrating mutations in the CYP11A1 gene. The mean age at presentation of AI was 3.7 years, ranging from neonates to 18 years. The most common clinical presentations involved ambiguous genitalia or undervirilization (90%) and signs of adrenal crisis or insufficiency (50%). Genital appearances varied, with micropenis, cryptorchidism, and bifid scrotum being prevalent. Approximately 60% had non-palpable or undescended testes. Gonadal management typically involved surveillance or gonadectomy, based on malignancy risk and anatomical findings, with no established timing for surgery.
Conclusion
This case report and literature review underscore the heterogeneity in presentation and genetic variability of 46,XY sex reversal and adrenal insufficiency. Importantly, mutations in the CYP11A1 gene were present in all cases reviewed, highlighting the critical role of genetic analysis in diagnosis. Early genetic screening and multidisciplinary management are crucial for optimizing patient outcomes, suggesting a need for further research into tailored therapeutic approaches.

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P110

JOINT2864

Diagnostic accuracy of urinary aldosterone, independent of sodium intake, for the diagnosis of primary aldosteronism

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Introduction
Primary aldosteronism (PA) is an underdiagnosed cause of secondary hypertension. Diagnosis is typically performed in three steps: screening, confirmatory testing (CT), and subtype classification. Twenty-four-hour urinary aldosterone (uAldo) after an oral sodium load is one of the available confirmatory tests. This test requires an intake of 6 grams/24 hours of sodium for three days to achieve urinary sodium (uNa) >200 mmol/24 hours. However, in some cases, intravenous (IV) or oral sodium administration may have detrimental effects on the cardiovascular system.
Objective
To assess the diagnostic utility of uAldo in PA, independent of sodium loading.
Materials and methods
We carried out an observational study of patients suspected of having PA based on an aldosterone-to-renin ratio (ARR) $\geqq$ 30 ng/dl/ng/ml/h or an aldosterone-to-direct renin concentration ratio $\geqq$ 3.7 ng/dl per mU/l between 2018 and 2024. All patients underwent a confirmatory test (either the captopril test or IV saline infusion, depending on physician preference and/or comorbidities), and antihypertensive treatment change, and were advised to follow a normal-sodium diet for the three days preceding the confirmatory test. Additionally, uAldo and uNa were measured from a 24-hour urine sample collected the day before. The diagnostic performance of uAldo was analyzed independently of uNa levels.
Results
77 patients were included, 47 (64.9%) of whom were women; 94.8% had hypertension. A total of 39 individuals (50.6%) had a positive confirmatory test for PA. Baseline renin was suppressed in 76.6% of patients at the beginning of the confirmatory test, and 33.8% had uNa >200 mmol/24h. The group with a negative confirmatory test had a lower median uAldo than the group with a positive confirmatory test (8.3 μg/24h, IQR [4.5–12.1] vs. 11.7 μg/24h, IQR [8.5–19.3], $P<0.05$). A uAldo cutoff of >6.6 μg/24h had a sensitivity of 87.1% and a specificity of 36.8%. A uAldo >14 μg/24h had a sensitivity of 46.1% and specificity of 84.2%. The area under the ROC curve (AUC) was 0.70 (95%CI 0.59–0.81).
Conclusions
uAldo, regardless of uNa levels, showed acceptable diagnostic performance. Despite the absence of prior sodium loading, most patients had suppressed renin, ensuring independent aldosterone production. A uAldo >14 μg/24h strongly suggests the diagnosis of PA in patients with a positive screening test and a normal sodium diet, while a uAldo <6 μg/24h makes PA unlikely.

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P111

JOINT2770

Adrenocortical carcinoma following long-term stable adrenocortical adenomas: a rare phenomenon in a large cohort

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It remains debated whether adrenocortical adenomas (ACAs) might represent a precursor to adrenocortical carcinomas (ACCs) or whether ACCs arise 'de novo' from adrenocortical tissue. Sporadic cases of malignant transformation of pre-existing ACA after prolonged latency have been reported, highlighting the unpredictable malignant potential of few benign tumors. This study retrospectively investigates the prevalence of prior imaging-based ACA diagnosis in the largest single-center ACC cohort, including 1516 patients referred to our center since January 2000. We identified 3 patients (0.2%) with documented ACA that remained stable for $\geqq$2 years but were later histologically confirmed as ACC. All 3 patients were female, with a median age of 33 years at ACA diagnosis and 40 years at surgery. Tumors averaged 3.3 cm initially, and median follow-up was 7 years (range:4–14 years).
Case 1: A 39-year-old woman was diagnosed with a 4.5 cm left ACA in 2003. The lesion remained stable during the first 8 years of regular follow-up. However, following a 5-year gap in surveillance, the lesion grew to 6 cm and exhibited a new inhomogeneous appearance at CT imaging. Surgical tumor resection confirmed a high-grade ACC (Ki67:20%; Weiss score:9) with p53 positivity at immunohistochemistry. She died 2 years later from synchronous lung adenocarcinoma.
Case 2: A 33-year-old woman had a diagnosed of 3.7 cm non-functioning right ACA in 2014. After 3 years, although the lesion did not significantly change in size, the patient underwent adrenalectomy because of the development of hypercortisolism (cortisol after 1 mg-DST:16.6 μg/dl). Histology revealed low-grade ACC (Ki67:2–5%; Weiss score:3). She remains disease-free under active surveillance.
Case 3: A 33-year-old woman was diagnosed with a 1.6 cm left ACA in 2014, which remained stable until 2016. Hormonal evaluation was incomplete at diagnosis. By 2021, the lesion had grown significantly to 7.5 cm and hypercortisolism was detected (cortisol after 1-mg-DST:17 μg/dl). Adrenalectomy confirmed a high-grade ACC (Ki67:10–40%; Weiss score:8). A somatic pathogenic variant in *CTNNB1* (p.Ser45Ala) was found. Since 2021, she has been undergoing mitotane and systemic therapies due to disease progression. Determining whether these ACCs arose from the malignant transformation of pre-existing ACAs, developed de novo, or were initially misdiagnosed remains challenging. However, these cases emphasize the exceptionally low likelihood of malignant transformation in benign-appearing, size-stable adrenal lesions, despite the high prevalence of benign adrenal tumors. Additionally, one case describes a rare occurrence of hormonal hypersecretion developing over time.

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P112

JOINT1515

Metabolic syndrome in patients treated for primary adrenal insufficiency

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Primary adrenal insufficiency (PAI) requires lifelong steroid substitution however, standard replacement regimens do not perfectly mimic the physiological glucocorticoid secretion. Under-replacement is life-threatening, while long-term steroid excess leads to adverse effects, including metabolic consequences, which may contribute to increased mortality. The current study was designed to assess the frequency of the metabolic syndrome (MS) in patients conventionally treated for PAI. General Polish population displays 33% and 39% prevalence of MS in women and men, respectively. This cross-sectional analysis comprised 239 individuals (69 males, 170 females) suffering from PAI. Their mean age was 48.2 ± 14.8 years and mean disease/treatment duration 10.8 ± 11.2 years. All patients were on hydrocortisone (HC): mean daily HC dose was 23.1 ± 7.1 mg, adjusted for body mass 0.34 ± 0.12 mg/day/kg, and cumulative HC dose was 94.6 ± 98.1 g during treatment. Central obesity (waist circumference 94/80 cm) was found in 148 (61.9%) patients (123 females and 25 males), hypertension in 37 (15.5%), decreased circulating HDL cholesterol in 64 (26.8%), elevated triglycerides in 90 (37.6%), and hyperglycemia in 57 (23.8%) individuals (19 prediabetes, 15 type 2 diabetes, 23 type 1 diabetes). Overall, 62 (25.9%) subjects displayed MS, including 54 (31.8%) females and 8 (11.6%) males ($P = 0.0013$), however, mean age in the studied women was also significantly higher (51.7 ± 13.8 *vs.* 39.7 ± 13.7 years; $P < 0.0001$). Female were older, but their PAI onset was also later than males (40.7 ± 13.2 years *vs.* 30.1 ± 12.0 years; $P < 0.0001$), therefore mean treatment duration remained similar in both sexes ($P = 0.3717$). Once pre- and postmenopausal women were considered, the proportion of MS reached 14.7% and 43.1%, respectively ($P < 0.0001$). Daily HC doses were similar in patients with and without MS ($P = 0.3382$), however, once total HC dose was evaluated, MS patients displayed significantly higher cumulative HC intake (123.4 ± 112.4 *vs.* 84.5 ± 90.8 g, $P = 0.0088$), which supports the primordial role of disease duration. Finally, in a multiple linear regression model comprising age, disease duration, gender, PAI form (isolated or polyglandular) and HC dosage, only age appeared significant predictor of MS ($P < 0.001$). In conclusion, MS does not specifically affect patients with PAI, however, post-menopausal women seem at increased risk. This is mainly due to their advanced age, and obviously lack of protective estrogen effects, while HC treatment within the current dose recommendations does not seem primordial for MS development. Therefore, conventional but still reasonable HC dosage in PAI does not imply considerably elevated risk for MS, although postmenopausal women should be carefully monitored with this regard.

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P113

JOINT886

Oral Contraceptives: A Key to reducing androgen levels in women with classic CAH

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Background

Androgen excess in 21-hydroxylase deficiency (21OHD) remains challenging. Combined oral contraceptives (OCs) containing ethinylestradiol and progestin are known to affect both ovarian and adrenal androgen levels. In a pilot study, we observed a positive effect of combined OCs on the androgen status in women with classic congenital adrenal hyperplasia (CAH). Therefore, we aimed to prospectively investigate how combined OCs affect the steroid metabolome in young women with classic 21OHD.

Methods

We enrolled women aged 11-26 with classic 21OHD treated with hydrocortisone and mostly fludrocortisone from eight international centres who planned to start combined OCs. The study comprised three visits, including blood-drawing and 24-h-urine sampling: baseline (Visit-1, prior to OCs), three cycles post-OC-initiation (Visit-2), and six cycles post-initiation (Visit-3). Liquid chromatography-mass spectrometry (LC–MS) and gas-chromatography mass spectrometry (GC–MS) were utilized for steroid analysis. Differences in steroid metabolite levels across the three visits were assessed using the Friedman-test.

Results

The 17 participating young women had a median age of 18.7 years (range 11-26 years). Compared to before OC-intake, we saw a substantial decrease in plasma 17α-hydroxyprogesterone, androstenedione, dehydroepiandrosterone, testosterone (all $P < 0.001$) and 11-ketotestosterone ($P = 0.004$) under OCs, whilst cortisol levels increased. The levels of relevant urinary androgen metabolites, including 11-oxo-pregnanetriol, also showed a significant decrease (Table 1). Between visits 1 and 3, seven out of 17 (41%) women could reduce their hydrocortisone doses.

Conclusion

Our results suggest that combined oral contraceptives have a significant potential in lowering androgen levels, thereby improving the steroid metabolome in women with classic 21OHD. OC-treatment could therefore serve as an effective supplementary therapy in women with 21OHD, particularly in those with an unsatisfactory steroid profile.

Table 1: Urine metabolites (nmol/24h).

	Median (P25-P75)			
Urine metabolites	**Visit-1**	**Visit-2**	**Visit-3**	**P-value**
Androsterone	767.9 (398.5–1619.2)	131.6 (39.0–632.1)	77.9 (35.3–537.0)	<0.001
Etiocholanolone	469.7 (310.8–781.8)	83.1 (32.1–473.8)	57.3 (31.4–405.0)	0.002
11-Oxo-etiocholanolone	258.8 (187.9–359.0)	98.5 (77.4–166.9)	97.7 (60.1–173.2)	0.002
11β-OH-androsterone	740.3 (367.8–1474.5)	112.1 (73.1–480.8)	106.4 (61.8–278.8)	<0.001
11β-OH-etiocholanolone	169.9 (114.4–211.5)	100.7 (60.1–181.8)	100.9 (72.7–139.2)	0.029
11-Oxo-pregnanetriol	233.4 (64.7–402.6)	23.3 (6.2–183.9)	18.3 (10.8–59.2)	<0.001

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P114

JOINT2395

Exploring the role of glucocorticoids and androgens in the regulation of brain immunity using zebrafish models of impaired steroidogenesis

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Background

The role of steroid hormones in the pathophysiology of neurological problems is well established, however, the mechanisms involved in their development are not well understood. More recently, there has been increasing evidence on the important involvement of brain immunity in health and disease. We aimed to study the role of steroid hormones in the regulation of neuro-immunity, using established zebrafish models of cortisol deficiency.

Methods

We analysed adult brains from two zebrafish lines with differentially impaired steroidogenesis: 21-hydroxylase deficiency (*cyp21a2*−/−), which are cortisol deficient and have normal sex hormones, and side-chain cleavage enzyme deficiency (*cyp11a2*−/−), which are deficient in both cortisol and sex hormones, developing as infertile males. We extracted brain RNA and conducted paired-end sequencing, followed by transcriptome study by Gene Set Enrichment Analysis (GSEA) to identify dysregulated biological processes.

Results

In the *cyp21a2*−/− zebrafish, we found that cortisol deficiency impacted on the regulation of immune processes within the brain in a sex-specific manner. When compared to wild-type (WT) siblings the brains of mutant males showed wide upregulation of the immune response, including biological processes involved in the immune cell chemotaxis, response to cytokines, response to other organisms. By contrast, these processes were downregulated in the *cyp21a2*−/− female brains and in the *cyp11a2*−/− brains. In addition, granulocyte activation and leukocyte

differentiation were also upregulated in the *cyp21a2−/−* male brains, however, they were not found to be dysregulated in the other groups. We then compared male against female brain transcriptomes within the WT and *cyp21a2−/−* groups. Immune processes including the major histocompatibility (MHC) complex assembly, immune cell differentiation, activation, T-cell proliferation, response to biotic stimulus, macrophage migration, were downregulated in males compared to females only in WT fish, but not in cortisol deficient mutants. Moreover, leukocyte chemotaxis and migration were downregulated in WT males but upregulated in *cyp12a2−/−* males compared to females.
Conclusion
Our results indicate that cortisol deficiency has a different impact on the regulation of brain immunity in male zebrafish compared to females, or to androgen-deficient males. The differential dysregulation of the immune response in the brains of our mutant lines would indicate that androgens have a cortisol-dependent suppressive effect on brain immunity in zebrafish. Further research into the role of sex hormones and their relationship with glucocorticoids in regulating the immune response is warranted to better understand sex-specific patterns in the development of neurological conditions, and the relevance of replacement therapies in patients with steroid deficiencies.

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P115

JOINT241
Effect of very low LDL cholesterol levels on steroid metabolome
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Introduction
Recommended cholesterol levels in cardiovascular prevention are continuously being lowered by clinical guidelines. Cholesterol is an essential substrate for the synthesis of steroid hormones. The aim of the study was to explore the adrenal glands' ability to adapt to cholesterol deficiency as a substrate.
Methods
Thirty-six male patients on high-intensity hypolipidemic therapy with LDL-C levels of 0.5±0.3 mmol/l, documented for at least one year, were selected. Exclusion criterion was corticosteroid therapy, including local application, in the previous year and ageless than 18 years. The Synacthen (1-24 ACTH) test (10 μg) was performed, and 17 steroid hormones were measured at baseline and following stimulation at 0, 30, and 60 minutes. Additionally, baseline levels of ACTH, TSH, fT4, insulin, C-peptide, fasting blood glucose, and glycated hemoglobin were determined. All steroid measurements at baseline and after stimulation were performed using Liquid Chromatography-Mass Spectrometry (LCMS). The data obtained were statistically processed.
Results
Results showed a correlation between steroid hormones (sex hormone-binding globulin, testosterone, cortisol, 11-deoxycortisol, 11-deoxycorticosterone, 17α-hydroxyprogesterone) and LDL cholesterol levels, but no adrenocortical insufficiency was observed. These findings prove a correlation between LDL cholesterol and adrenal steroids, and highlight the safety of hypolipidemic therapy in clinical practice. We also, unexpectedely observed the association between various hormones (androstenedione, dehydroepiandrosterone, cortisol, cortisone, 11-deoxycorticosterone, 17α-hydroxyprogesterone, dihydrotestosterone) and HDL cholesterol levels.
Conclusion
The adrenal glands are capable of full adaptation to a profound cholesterol deficiency using it as a substrate for steroid hormone synthesis. Long-term hypolipidemic therapy does not induce adrenocortical insufficiency.
Keywords
Cholesterol, Synacthen test, adrenal glands, adrenocortical insufficiency
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P117

JOINT1454
Performance of plasma renin assays in guiding mineralocorticoid dosing in children with adrenal insufficiency
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Background
Plasma renin is measured in paediatric patients with salt-wasting adrenal insufficiency (AI) to assess the efficacy of mineralocorticoid (MC) replacement. Plasma renin is recommended as a useful marker to monitor MC replacement and can be measured as either plasma renin concentration (PRC) or activity (PRA). Our department currently measures PRC using immunoassay in paediatric patients, and PRA using LC-MS/MS in adults.
Objective
Here, we sought to compare the clinical utility of PRC and PRA concentrations in paediatric patients with AI taking MC replacement.
Methods
Samples from patients less than 18-years old ($n=129$, m:f=69:60) requested for PRC were selected randomly. PRC was measured using the IDS-iSYS chemiluminescence immunoassay, PRA was measured by LC–MS/MS. The PRC and PRA values for each sample were reviewed using published reference ranges and categorised into low, normal and high results. Samples which showed disagreement between PRC and PRA results were divided into patient groups. Samples collected from patients attending the adrenal clinic were clinically reviewed by local endocrinologists to determine if MC dosing would differ based on PRC or PRA results.
Results
Of the samples analysed, 96 (74%) exhibited concurrence between their PRC and PRA interpretation. Samples that displayed disagreement ($n=33$, 26%) included 17 collected from adrenal clinic patients. Of these, eight resulted in a different clinical decision concerning MC replacement based on PRA compared to PRC. In each of these instances, adjustments to MC dose was strongly supported by serum sodium and blood pressure centiles when based on PRA. In several instances, PRC had been overlooked by clinicians and MC dose had been adjusted in preference to other conventional parameters such as blood pressure and serum electrolytes. Thus, PRA provided reassurance that clinicians had correctly assessed MC replacement.
Conclusions
Using the current methodology and normative ranges, our investigation found PRA performed superiorly to PRC for assessing MC replacement in paediatric patients, based on supporting biochemical and clinical parameters. Our results indicated that use of PRA may help to standardise practice when assessing MC replacement, which would have immediate patient benefit through improved blood-pressure and electrolyte control. Further work is planned to corroborate these results in a wider pool of patients.

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P118

JOINT382
Familial hypercholesterolemia in Chinese children and adolescents: a multicenter study
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Background
Familial hypercholesterolemia (FH) is an inherited disorder mainly marked by increased low-density lipoprotein cholesterol (LDL-C) concentrations and a heightened risk of early-onset arteriosclerotic cardiovascular disease (ASCVD). This study seeks to characterize the genetic spectrum and genotypeã phenotype correlations of FH in Chinese pediatric individuals.
Methods
Data were gathered from individuals diagnosed with FH either clinically or genetically at multiple hospitals across mainland China from January 2016 to June 2024.
Results
In total, 140 children and adolescents (mean age of 6.00 years) with clinically and genetically diagnosed FH were enrolled in the study, with 87 distinct variants identified in the *LDLR*, *APOB* and *PCSK9* genes. Among the variants, 11 variants were newly identified worldwide, with 9 classified as 'pathogenic' or 'likely pathogenic', and 2 classified as 'variants of uncertain significance'. Additionally, the 5 most common variants in the study were c.1448G>A (p.W483*), c.1879G>A (p.A627T), c.1216C>A (p.R406R), and c.1747C>T (p.H583Y) in the *LDLR* gene, as well as c.10579C>T (p.R3527W) in the *APOB* gene, accounting for 49.29% (69/140) of all patients. These variants are primarily observed in the Asian or Chinese population and are distinct from those present in Caucasian groups. In this cohort, 105 patients were diagnosed with heterozygous FH (HeFH), while 35 were diagnosed with homozygous FH (HoFH). Finally, only 28.57% of the patients (40/140) were using lipid-lowering medications with 33.33% of HoFH patients

initiating treatment after the age of 8. Additionally, only 3 compound heterozygous patients (2.14%) underwent liver transplantation because of significantly high lipid levels.
Conclusion
This study reveals the variable genotypes and phenotypes of children with FH in China and illustrates that the genotypes in the Chinese population differ from those in Caucasians, providing a valuable dataset for the clinical genetic screening of FH in China. Furthermore, the older age at diagnosis and treatment highlights the underdiagnosis and undertreatment of Chinese FH pediatric patients, suggesting that early identification should be improved through lipid or genetic screening, and that more timely and regular pharmacological treatments should be implemented.

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P119

JOINT1309

Effect of cholecalciferol and calcium supplementation on blood pressure in young Infertile but otherwise healthy men

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Introduction
Vitamin D plays a crucial role in bone and mineral homeostasis, but its effect on cardiovascular health and blood pressure (BP) in particular remains unclear with studies presenting conflicting results. Most studies have focused on hypertensive patients, but this study aims to assess the effect of cholecalciferol supplementation on BP in young men.
Materials and methods
The Copenhagen Bone-Gonadal Study, a double-blinded RCT (NCT01304927), included 330 healthy infertile men with $25(OH)D_3$ insufficiency who received either cholecalciferol supplementation or placebo for 150 days. The primary endpoint was semen quality. BP was measured using standardized conditions after five minutes of rest, with an average of three consecutive measurements used for analysis. Correlations between vitamin D metabolites and BP were assessed using Pearson's correlation, and intervention effects were analyzed using *t*-tests and ANOVA.
Results
The cohort consisted of 300 men (mean age 35 years), and no correlations were found between systolic BP and $25(OH)D_3$ ($r=0.037$, $P=0.53$) or $1,25(OH)_2D_3$ ($r=-0.0042$, $P=0.94$) at baseline. There was no difference between the treatment and placebo groups after 150 days in systolic BP (127 mmHg vs 127 mmHg, $P=0.87$) or diastolic BP (81 mmHg vs 82 mmHg, $P=0.23$). Even in men with vitamin D deficiency (<25 nmol/l), supplementation with cholecalciferol and calcium did not affect BP (127 mmHg vs 127 mmHg, $P=0.85$). No differences were found in subgroups when stratifying according to baseline $25(OH)D_3$ levels, SCORE2 categories, or changes in in serum $25(OH)D_3$ (all $P>0.05$).
Conclusion
There was no correlation between vitamin D metabolites and BP. Cholecalciferol supplementation for 150 days did not significantly affect BP in infertile men, regardless of baseline $25(OH)D_3$ status or cardiovascular risk using SCORE2, implying that high-dose supplementation is not beneficial for BP regulation in young and overall healthy men.

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P120

JOINT1698

Persistent renin suppression after unilateral adrenalectomy in patients with primary aldosteronism

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Background
Suppressed renin levels in medically treated patients with primary aldosteronism (PA) are associated with a worse cardiometabolic outcome. This study investigates the prevalence and outcome of persistent renin suppression after adrenalectomy in patients with unilateral PA.
Methods
We included 77 patients that underwent adrenalectomy for PA and evaluated postoperative renin recovery. Patients were divided into tertials based on their renin concentration at the first follow-up, approximately six months after adrenalectomy. We compared histopathology using CYP11B2 staining according to histopathology of primary aldosteronism consensus (HISTALDO), biochemical and clinical outcomes according to the PASO (Primary Aldosteronism Surgical Outcome) criteria and improvement of comorbidities and end-organ damage at short- and long-term follow-up ranging from six months to three years postoperatively.
Results
Renin concentrations were <8mU/l, between 8 and 16mU/l, or >16mU/l at first follow-up in the respective groups. Patients with renin concentrations <8mU/l had twice as often non-classical histopathology, comprising multiple aldosterone-producing nodules, aldosterone-producing micronodules and aldosterone-producing diffuse hyperplasia, as the other two groups together (8/26 (30.8%) vs. 1/25 (4%) vs. 3/26 (11.5%); $P=0.024$) and less frequently complete biochemical remission (normalisation of aldosterone-to-renin ratio and correction of hypokalaemia) at their first follow-up ($P<0.01$). There were no differences in the clinical outcome, long-term biochemical outcome, and improvement of end-organ damage and comorbidities.
Conclusions
In our study, suppressed renin concentrations <8mU/l occurred in one third of PA patients six months after adrenalectomy. Despite a worse short-term biochemical outcome, long-term biochemical and clinical outcomes, including comorbidities and end-organ damage, do not appear to be associated with postoperative renin concentrations.

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P121

JOINT1402

Establishing the prevalence of non-classical congenital adrenal hyperplasia using serum 21-deoxycortisol concentrations

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Background
The prevalence of non-classical congenital adrenal hyperplasia (NCCAH) is estimated to be 0.1–0.2% in the Netherlands, mostly established using serum 17-hydroxyprogesterone (17-OHP) concentrations. However, it could be questioned whether this prevalence is accurate as 17-OHP measurement does not reflect optimal sensitivity and specificity for the diagnosis of NCCAH. Recently, 21-deoxycortisol (21-DOCL) has been proposed to be a valid diagnostic discriminator for both classical and non-classical CAH.

Objectives
To establish the prevalence of NCCAH in the Netherlands using serum 21-DOCL concentrations.
Methods
Steroid hormone concentrations were measured using LC–MS/MS in participants from the Netherlands Epidemiology of Obesity (NEO) study, which contained an oversampling of participants with overweight and obesity. We examined 21-DOCL concentrations in participants not using corticosteroids (3416 women and 3096 men) and used a cut-off value of 0.5 nmol/l for the diagnosis NCCAH. To rule out potential selection bias of our overweight population, prevalence rates were calculated by weighing toward distribution of body mass index in the general population.
(Preliminary) results
Based on 57 participants with a 21-DOCL concentration ≧0.5 nmol/l, the weighted prevalence was 0.94% [95% CI 0.65%–1.35%] in this population. A sub analysis showed a prevalence of 0.86% [95% CI 0.49%–1.50%] in women and 1.04% [95% CI 0.65%–1.66%] in men. When comparing the groups of participants with 21-DOCL concentrations ≧0.5 nmol/l to those with lower 21-DOCL concentrations, mean testosterone, androstenedione and 17-OHP concentrations were higher in participants with 21-DOCL concentrations ≧0.5 nmol/l.
Conclusions
The prevalence of NCCAH established based on serum 21-DOCL concentrations seems to be 5- to 10-fold higher than the previously estimated prevalence based on serum 17-OHP concentrations in the general population. This is relevant information since, in women particularly, there might be an underdiagnosis of NCCAH and possibly overdiagnosis of polycystic ovary syndrome (PCOS) due to overlapping clinical symptoms between NCCAH and PCOS.

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P122

JOINT1578

Can the plasma aldosterone/potassium ratio predict primary aldosteronism in patients scheduled for confirmatory testing?

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Introduction
Primary aldosteronism (PA) is a common cause of endocrine hypertension, yet there are some difficulties in diagnosing the disease. A single normal or low aldosterone/plasma renin activity (PRA) ratio (ARR) alone may not be sufficient to exclude the diagnosis of primary aldosteronism (PA) (3–5). The saline infusion test (SIT), a standard confirmatory test, has limitations such as contraindications, need for hospitalization and high cost (6). This study evaluates the potential of the plasma aldosterone/potassium (A/K) ratio in predicting PA.
Methods
Between 2019 and 2023, 118 patients admitted to our Endocrinology outpatient clinic who underwent SIT with a prediagnosis of PA due to hypertension, as well as hypokalemia and/or elevated ARR were retrospectively included in the study. Patients who were pregnant, <18 years of age, had adrenal surgery and used diuretics were excluded. Demographic data, laboratory and adrenal imaging results were evaluated retrospectively. Aldosterone and concurrent potassium levels at the time of admission were obtained and A/K ratio was calculated. The diagnosis of PA was made according to the results of SIT, captopril confirmation test if available, adrenalectomy results and clinical judgment of the multidisciplinary council (7). All parameters were compared between the groups of patients with and without PA.
Results
A total of 118 patients who underwent SIT were included in the study. PA was diagnosed in 57 patients based on clinical and laboratory results. Male sex ratio was higher in the PA group (52.6% vs. 23.0%; $P=0.001$) (Table 1). Patients with PA had higher aldosterone levels ($P<0.001$) and ARR ($P<0.001$), but lower potassium levels ($P<0.001$) and PRA ($P=0.01$). The A/K ratio was significantly higher in the PA group ($P<0.001$). ROC analysis showed that an A/K ratio cut-off of 5.4 could distinguish PA patients from non-PA patients [AUC (95% CI) =0.811 (0.733–0.890), $P<0.001$], with 73.7% sensitivity and 77.0% specificity (Default 1). When this cut-off point was applied to the group of patients with indetermine SIT results, sensitivity was 71.4% and specificity 77.8%. Univariate and multivariate analyses indicated that a high A/K ratio increased the likelihood of a PA diagnosis, with an A/K ratio above 5.4 associated with a 4.585-fold higher risk (95% CI: 1.181–17.799, $P=0.028$) (Table 2).
Conclusion
The A/K ratio may predict PA. It offers advantages such as no need for pretest potassium or hospitalization, making it a useful supplementary parameter for diagnosing PA, particularly in patients for whom confirmatory tests are unsuitable.

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P123

JOINT1423

Significance of plasma catestatin and relaxin-2 levels in patients with primary hypertension and type 2 diabetes mellitus

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Background
Arterial hypertension (AH) and type 2 diabetes mellitus (T2DM) are potent risk factors for cardiovascular diseases. Cardiovascular and metabolic effects of catestatin (CST) and relaxin-2 (RLN-2) indicate their involvement in AH and T2DM pathogenesis and suggest their diagnostic potential.
Objective
To determine plasma CST and RLN-2 levels, evaluate their associations with parameters of glucose metabolism and investigate the prognostic potential of CST and RLN-2.
Materials and methods
The present study was an observational prospective cohort single-center by design with a 12-month follow-up. This study was performed in accordance with all ethical principles of the Declaration of Helsinki. All participants signed a written informed consent form prior to any protocol procedures. 106 patients with AH and 30 healthy volunteers were enrolled in the study. 55 hypertensive patients had comorbid T2DM. Plasma CST levels were measured by ELISA (E4996Hu, BT Lab, China), RLN-2 (E-EL-H1582, Elabscience, USA). The data are presented as a mean±S.D. or a median and interquartile range. Statistical significance was defined as $P<0.05$. Statistical data were analyzed using SPSS statistical software (SPSS 25.0 for Windows, IBM, Armonk, NY, USA).
Results
Patients with AH and T2DM had decreased CST (4.47±1.16 vs. 5.61± 0.61 ng/ml; $P<0.001$) and RLN-2 levels (5.11 [4.97; 5.38] vs. 6.71 [6.00; 7.14] pg/ml; $P<0.001$) compared with hypertensive patients without T2DM. Both CST and RLN-2 had negative correlations with parameters of glucose metabolism, particularly HbA1c ($r=-0.535$; $P<0.001$ and $r=-0.673$, $P<0.001$), glucose ($r=-0.450$; $P<0.001$ and $r=-0.543$; $P<0.001$), HOMA-IR ($r=-0.481$; $P<0.001$ and $r=-0.392$; $P<0.001$). CST (0.175 [0.099 − 0.312; $P<0.001$) and RLN-2 levels (0.196 [0.095 − 0.405]; $P<0.001$) were established as significant predictors of impaired glucose metabolism by univariate binary logistic regression. Kaplan–Meier curve analysis revealed a significantly higher incidence of MACE in patients with CST levels <5.44 ng/ml ($P=0.01$). Cox proportional hazard model indicated CST levels (0.486 [0.285 – 0.830]; $P=0.01$) as an independent predictor of MACE in the study population as well as presence of T2DM (3.578 [1.102 – 11.619]; $P=0.03$), HOMA-IR (1.157 [1.023 – 1.309]; $P=0.02$), insulin levels (1.049 [1.006 – 1.094]; $P=0.02$).
Conclusions
In the present study, we established reduced plasma CST and RLN-2 levels in hypertensive patients with T2DM and their negative relationships with parameters of glucose metabolism. CST and RLN-2 were determined as significant predictors of impaired glucose metabolism. These findings allow us to suggest CST and RLN-2 as perspective biomarkers of AH and T2DM.

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P124

JOINT2081

Education of sick day management of paediatric adrenal insufficiency: a national survey of paediatric endocrine nurse specialists

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Background
A critical component of health provision for a young person with adrenal insufficiency (AI) is education for the family and young person regarding management during sick day episodes. Deficits in patient education have been identified as a contributor to adrenal crisis risk.
Aim
The aim of this online survey distributed via the British Society for Paediatric Endocrinology (BSPED) paediatric endocrine nurse specialists (PENS) mailing list is to explore current clinical practice on provision of education in the United Kingdom.
Methods
An online survey of 25 questions was circulated to BSPED PENS between January-February 2024. These were multiple answer questions and there was also free text space for additional comments.
Results
The survey was circulated to eighty-eight PENS; fifty-one(58%) responses were received. In relation to the provision and structure of the initial education of sick day management, all provide individual face-to-face education of parents/guardians. In addition, eighteen (35%) provide online individual face-to face education, two (4%) provide group face-to-face and two (4%) group online education. Twenty-six (51%) have local departmental guidance on content of the AI education. All PENS provide education on symptoms of adrenal crisis, and management during moderate and severe sick day episodes. Forty-nine (96%) would discuss the underlying pathophysiology of AI and forty (78%) would discuss management during minor procedures. Fifty (98%) would educate and demonstrate injection of hydrocortisone at the first educational session, with forty-nine (96%) offering a practice injection. Fifty (98%) would provide written information to take away after the initial education; 43 (84%) provide a steroid emergency card whilst 25 (50%) provide information leaflets. Thirty-two (63%) do not provide any written information to non-English speaking families. Seven (14%) do not assess understanding after the initial education and twenty-five (49%) do not provide routine follow-up after the initial education. Twenty-one (41%) do not provide routine, regular refresher educational sessions. Twenty (39%) PENS do not educate the young person themselves in preparation for transition.
Conclusion
This national survey of PENS identified a consistent approach to the initial education of parents/guardians of a young person with AI. However, we identified variability in provision of routine refresher sessions and education of the young person themself prior to transition. Additionally, non-English speaking families may be at a disadvantage as written information is not provided in over 60%. These results will help with the development of national standards of education for young people with adrenal insufficiency.

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P125

JOINT655

A validated liquid chromatography mass spectrometry method for comprehensive urinary steroid profiling: applications in hypertension research and diagnostic studies

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Steroids are crucial for numerous biological processes, and their dysregulation is linked to various endocrine disorders from hypertension to adrenocortical carcinoma. Accurate steroid profiling is essential for understanding these conditions. Here we present a validated method (EMA/FDA criteria) for urinary steroid profiling using liquid chromatography-tandem mass spectrometry (LC-MS/MS) which quantifies 29 steroids, including steroid precursors, mineralocorticoids, glucocorticoids, and androgens. Steroids were extracted from urine via C_{18} solid-phase extraction after deconjugation from their sulfate and glucuronide esters. Quantification was performed using a Waters Acquity UHPLC and Xevo® TQ-XS mass spectrometer. Chromatographic separation of 27 steroids was achieved in 16 minutes using a Waters HSS T3 column, with a second injection onto a BEH C_{18} column to separate and quantify THF and 5αTHF in 4 minutes. The lower limits of quantification ranged from 2 to 20 ng/ml, with accuracy (bias) between 12.6% and 19.9% and precision (%CV) from 4.0% to 18.6%. Imprecision assessed at three concentrations was within acceptable limits for all steroids, ranging from 3.4% to 14.1%. Accuracy (bias) ranged from −14.9% to 14.9%, (excluding 5PD). Recovery was 76–103%, with matrix effects within the ideal range (< 15%) for 15 steroids and the acceptable range (<20%) for the rest. Inter- and intra-assay imprecision (%CV) ranged from 0.8% to 14.9%. In a proof or principle cohort of 40 healthy volunteers, all steroids were detectable, with DHEA, α-cortol, THAldo, 5PD, and PTONE quantifiable in 86%, 84%, 72%, 43%, and 38% of samples, respectively. Steroid excretion was higher during the day and in men compared to women. This LC-MS/MS method enables high-throughput, comprehensive multi-steroid quantification across multiple steroid classes, offering a valuable tool for clinical research and diagnostic applications. This method will be implemented in the multi-centre European clinical research study, HT-Advance, where it will be combined with other technologies to rapidly measure urinary steroid excretion, evaluate the diagnostic performance of MOMICS (multi-omics) technologies in identifying endocrine causes of hypertension, and predict treatment responses in patients with newly diagnosed hypertension.

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P126

JOINT1596

Space Oil Vapours: Endocrine Risks and the Adolescent Challenges

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Introduction
There is an increasing concern regarding the misuse of etomidate, a drug traditionally used as a general anaesthetic, which is now being abused within the community through vaping with electronic cigarettes. Beyond its immediate effects on the central nervous system, etomidate presents substantial risks due to its adrenal toxicity and the potential for long-term impairments in cognitive and endocrine functions. The rising prevalence of adolescent use of electronic cigarettes is also becoming a pressing issue.
Objectives and methodology
We hereby report a retrospective cohort review of all paediatric patients, who are defined as age at or below 18 years old, with etomidate detected in their urine toxicology analyses upon admissions to Princess Margaret Hospital between 1 January 2024 and 31 December 2024 inclusively.
Results
Thirteen adolescents (7 females) were identified (age 14.1–17.9 years). They reported to have vaped etomidate for an average of two months (range: 1–8 months) before presenting to the hospital. Seven of them admitted to having taken other substances. Common presenting complaints included confusion and dizziness (3/13), unsteady gait (2/13), suicidal attempt/deliberate self-harm (2/13). At presentation, five of them had hypertension (systolic blood pressure range: 94–160 mmHg). All did not manifest signs of hyperandrogenism. One patient was treated in the paediatric intensive care unit (ICU) for inhalation injuries resulting from a fire incident due to vaping. Morning cortisol was low in 3 out of 8 patients (range: 44–83; reference >133 nmol/l). Short synacthen test showed adrenal insufficiency in 3 out of 6 patients (peak cortisol range: 74–238; reference >376 nmol/l). Baseline ACTH levels were elevated in three cases (range: 28–55; reference 1.6–13.9 pmol/l). Renin and aldosterone were both undetectable in six of the patients. 11-deoxycortisol, the precursor hormone accumulated right above the inhibition of 11β-hydroxylase (range: 72.4–564; reference ≤4.3 nmol/l) and 17-OHP (range 8.7–11; reference <4 nmol/l) along

the glucocorticoid pathway of steroidogenesis were found elevated in four patients.
Conclusion
These alarming consequences have heightened awareness among healthcare professionals and the broader community, underscoring the urgent need to identify, intercept, and prevent the proliferation of this harmful substance. Safeguarding our younger generations from the devastating effects of such abuse is a collective responsibility that demands concerted efforts in education, intervention and policy development.

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P127

JOINT1777

Implementing a neonatal screening programme for Congenital Adrenal Hyperplasia using liquid chromatography–tandem mass spectometry in a Northern Spanish region

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Introduction
Screening of Congenital Adrenal Hyperplasia (CAH) due to 21-hydroxylase deficiency reduces neonatal morbidity and mortality. The quantification of 17-hydroxyprogesterone (17-OHP) using Delayed Fluorescence Immunoassay (DFI) on filter paper blood samples is the standard screening strategy. However, it is associated with a high number of false positives (FP), especially in premature infants. To optimize the positive predictive value (PPV), most screening programs establish cutoff points for 17-OHP based on gestational age (GA). Currently, it is considered more efficient to determine 17-OHP and other adrenal analytes using LC-MS/MS, which may also allow the diagnosis of other types of CAH. In June 2023, CAH screening was implemented in our region.
Objectives
To evaluate the effectiveness of our screening strategy for diagnosing classic CAH. To determine the prevalence and impact of FP by including the measurement of 17-OHP via LC–MS/MS.
Methodology
At 48 hours of life, filter paper samples with 17-OHP values exceeding the 99.95th percentile (p99.95) by DFI are considered positive. Three groups are differentiated based on GA: <33 weeks (weighted p99.95), 33–37 weeks (p99.95 corresponding to the group with the highest gestational age), and >37 weeks (p99.95). All positives are retested using both DFI and LC–MS/MS. The established cutoff points for various adrenal analytes and diagnostic ratios by LC–MS/MS are: 17-OHP >15.1 nmol/l + 21-deoxycortisol >2.9 nmol/l or 17-OHP >15.1 nmol/l + ratio of [17-OHP + Androstenedione]/cortisol >2 + ratio 17-OHP/11-deoxycortisol >10. In neonates <33 weeks and/or <1500 grams, a second filter paper determination by DFI is done at 15 days of life, as done for congenital hypothiroidsm screening. This allows for a single cutoff point in this population. We analyzed the positive cases from the CAH screening (June 1, 2023 – December 31st, 2024). Data were obtained from the neonatal screening program and clinical records.
Results
Out of 21 411 screenings performed, 40 were positive by DFI (55% male). Three out of 40 neonates died early due to other causes. 37 cases were retested, confirming one true positive (a 5-day-old male neonate) by both DFI and LC-MS/MS. Outpatient treatment was started at 7 days of life. In the 36 cases considered false positives (75% from the group 33–37 weeks, 58% male), retesting using LC–MS/MS allowed ruling out classic CAH.
Comments
In the short duration of CAH screening, one male was diagnosed before one week of life. The inclusion of LC–MS/MS in this screening strategy raises the PPV to 100%, avoiding unnecessary interventions in the few false positives.

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P128

JOINT1862

Morning serum cortisol predicts short synacthen test response during glucocorticoid weaning in children and adults

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Introduction
Tertiary adrenal insufficiency (AI) resulting from glucocorticoid-induced hypothalamic-pituitary-adrenal (HPA) axis suppression is the commonest cause of AI. The morning serum cortisol levels recommended by recent National Institute for Health and Care Excellence (NICE), UK guidelines (1) to predict adrenal insufficiency (AI) are not derived from studies in patients with AI due to glucocorticoids, as such studies using modern immunoassays are scarce. The aim of this study was to identify morning cortisol cut-off that predict the 30-minute post-Synacthen cortisol, to safely use in clinical practice in children and adults without requiring an SST.
Materials and methods
A retrospective cohort study of paediatric and adult patients on long-term glucocorticoids with suspected or confirmed tertiary AI undergoing a short synacthen test (SST). The main outcome of the study was morning serum cortisol cut-offs with 95% and 99% specificity and sensitivity determined via receiver operating characteristic (ROC) curve analysis. A pass for the SST was defined as a post-synacthen 30-minute cortisol of $\geqq 430$ nmol/l using immunoassays, Vitros 5600 (Ortho Clinical Diagnostics) in paediatric cohort, and Elecsys II (*Roche)* in the adult cohort.
Results
One hundred and seventy three and 443 SSTs were included in the paediatric and adult cohorts, respectively, of which 32% and 36% were normal. The ROC curve analysis demonstrated that basal morning cortisol performed well in both cohorts with area under curve (AUC) of 0.77 (95%CI 0.70,0.85) and 0.89 (95%CI 0.85,0.92), respectively. Morning serum cortisol cut offs to predict a normal SST in children and adults were 280 and 285 nmol/l at 95% sensitivity, and 316 and 349 nmol/l at 99% sensitivity, respectively. In a longitudinal safety analysis carried out in the adult cohort, using the 95% cut off, 54 of 57 patients with morning serum cortisol values $\geqq 285$ nmol/l were weaned from glucocorticoids within three months.
Conclusion
This study shows that morning serum cortisol performs well in predicting SST outcome in both children and adults on glucocorticoids, with two different immunoassays. A cut off of $\geqq 285$ nmol/l can be safely used to wean glucocorticoids without the need for synacthen testing.
Reference
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P129

JOINT2434

Metabolic disorders in pheochromocytoma: A retrospective multicenter study of pre- and post-operative profiles

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Introduction
Pheochromocytomas/paragangliomas (PPGLs) are a group of rare neuroendocrine tumors with an incidence of approximately 0.8 per 100 000 person-years. Due to their rarity, the metabolic dysregulation of patients with PPGL and metabolic evolution after tumor resection are still under investigation.
Aim
To compare the baseline characteristics of patients across catecholamine phenotypes and investigate post-operative changes in the metabolic profile.
Methods
This is a multicenter, retrospective study conducted at four Endocrinology departments of Greek tertiary general hospitals. Comparisons were performed at diagnosis between catecholamine phenotypes (adrenergic versus noradrenergic) and incidentalomas versus non-incidentalomas. Correlations between metabolic and pheochromocytoma-related characteristics (tumor size, PASS) were performed and metabolic profile evolution after adrenalectomy was assessed.
Results
Overall, 83 individuals [58% females, median age 51 years] diagnosed and treated for pheochromocytoma over the past twenty years were included. Pheochromocytomas were found incidentally in the majority of patients (64%) , with 74% of the total cases being secreting tumors. Among those, 28% had adrenergic and 46% noradrenergic phenotype, respectively. The majority of patients (69%) had hypertension which was paroxysmal in 37% of cases. Metabolic disorders at baseline were common with a 74% prevalence of diabetes and prediabetes, 65% of dyslipidemia and 20% of obesity. Adrenergic phenotype was predominant in older individuals ($P=0.003$) and required significantly higher daily doses of phenoxybenzamine ($P=0.002$). Metabolic and tumor parameters did not differ between catecholamine phenotypes. Patients diagnosed with incidentalomas exhibited a higher prevalence of diabetes in comparison to their non-incidentaloma counterparts ($P=0.021$) while the lipid profile did not vary. Hypertensive patients had larger tumors (53.7 vs 42.1 mm, $P=0.023$) with worse PASS ($\geqq 4$) ($P=0.022$). Furthermore, univariate correlations demonstrated that greater tumor size was associated with higher number of anti-hypertensive drugs at diagnosis ($P=0.044$) and increased PASS in histology ($P=0.007$). Positive correlations between daily phenoxybenzamine dose and BMI ($P=0.002$) as well as between HbA1c and number of anti-hypertensive drugs ($P=0.029$) were observed. Seventy- five patients were followed-up after adrenalectomy for a median period of 24 months. Metabolic assessment revealed improved HbA1c, fasting glucose and LDL levels ($P<0.02$) despite no significant change in post-operative BMI.
Conclusion
This population-based study, spanning two decades, offers valuable insights into the clinical characteristics of PPGLs patients. Metabolic and tumor parameters showed no variation across catecholamine phenotypes. On the other hand, metabolic disorders demonstrated improvement after adrenalectomy while BMI was not a contributing factor in this context as it remained stable.

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P130

JOINT2450

Prognostic factors for cardiovascular complications induced by catecholamines in pheochromocytomas and paragangliomas: A systematic review and meta-analysis

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Introduction
Pheochromocytomas and paragangliomas (PPGLs) can cause serious cardiovascular events induced by the unpredictable release of large amounts of catecholamines.
Purpose
The aim of this study was to determine possible prognostic factors of catecholamine-induced cardiovascular events for timely diagnosis, better risk stratification and optimal treatment strategy in patients diagnosed with PPGL.
Methods
A literature search for eligible studies on PubMed and the Cochrane Library from January 1980 until November 2024 was performed. The primary endpoint was any serious cardiovascular event (Takotsubo syndrome, acute coronary syndrome, acute heart failure, cardiogenic shock, stroke or fatal arrhythmias) in PPGL patients. Meta-analysis of potential prognostic factors of major adverse cardiovascular events (MACEs) after assessment of clinical, laboratory, imaging, histological and genetic parameters was performed on the pooled data.
Results
Quantitative data from nine retrospective cohort studies, involving 1566 patients with PPGL were included in the analyses. MACEs were manifested in 302 patients [pooled estimate 21% (95% C.I. 14–29%)], among whom there were 95 patients with Takotsubo syndrome [pooled estimate 39% (23–54%)] of overall cardiovascular events. There was no sufficient data to determine the prevalence of the other types of cardiovascular events while significant heterogeneity was detected for all effect estimates. An increased risk of MACEs was noted in patients presenting with tumors with necrosis/hemorrhage (71%; 95C.I. 27–115%) and in those with diabetes (56%; 95C.I. 2–109). As expected, dyspnea and chest pain were prominent risk factors for MACE as they were associated with a 5 (95% C.I. 3.3–7.4) and 2.7 (95% C.I. 1.5–4) times increased risk of serious cardiovascular event development, respectively. The pooled results did not demonstrate any association between age, adrenergic phenotype, metastatic disease or familial PPGLs on serious cardiovascular outcomes. In conclusion, smaller sizes do not serve a protective factor, as MACEs are associated with a mean difference of only 8.3mm (95% C.I. 0.9–15.7 mm) in tumor size between the two groups.
Conclusion
To our knowledge, this is the first meta-analysis of cohort studies of catecholamine-induced MACEs in patients with PPGL. Our study shows that 21% of PPGL cases will develop MACE. Necrosis/hemorrhage, dyspnea, chest pain and diabetes are associated with an increased likelihood of development of serious cardiovascular events. However, these results should be interpreted with caution due to statistical and methodological heterogeneity.

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P131

JOINT2653

Surgical outcomes and histochemical analysis in primary aldosteronism: a 10-year cohort study

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Introduction and objectives
Primary aldosteronism (PA) is a leading cause of hypertension, affecting up to 11.2% of new cases due to excessive aldosterone production. It typically results from bilateral adrenal hyperplasia or unilateral conditions like aldosterone-producing adenomas (APA). While laparoscopic adrenalectomy is a common treatment for unilateral cases, some patients remain hypertensive due to lingering hyperplasia in the other adrenal gland. Research suggests that staining adrenal tissue for enzymes such as CYP11B2, CYP11B1, and CYP17A1 can help identify aldosterone-producing cells and predict surgical outcomes, highlighting the need for improved diagnostic methods to enhance treatment success.
Methods
Patients undergoing adrenalectomy for PA at one center were identified over a 10-year period. Clinical parameters such as patient demographics, lab results, imaging features, adrenal vein sampling results, and clinical outcomes were recorded. Pathology specimens were stained with aldosterone synthase (CYP11B2). Patterns of histochemistry were then described.
Results
A cohort of 30 patients diagnosed with primary aldosteronism (PA) who underwent adrenalectomy over a span of 10 years was examined. Preoperative adrenal vein sampling was performed on 27 patients. On average, patients were taking 3.03 antihypertensive medications prior to surgery, which decreased to 0.92 medications per patient postoperatively. Hypokalemia was present in 23 patients before surgery, with none exhibiting it afterward. Surgical outcomes

revealed that 21 patients were completely cured, 4 showed improvement, and 5 did not experience a cure. Immunostaining analysis was performed on 19 cases, revealing the following distribution of patterns: 12 (63.2%) showed consistent staining, 4 (21.0%) showed variable staining, 2 (10.5%) displayed aldosterone-producing micronodules (APM), and 1 (5.2%) had no staining. Preoperative imaging did not identify adenomas in either of the APM cases, in 2 out of 12 cases with consistent staining, or in 1 out of 4 cases with variable staining. The case with no staining revealed an adenoma on the ipsilateral side, as well as one on the contralateral side. No definitive link was observed between histochemical findings and cure rates.
Conclusion
This study highlights the effectiveness of adrenalectomy in treating primary aldosteronism (PA), with significant improvements in blood pressure, potassium levels, and reduced antihypertensive use. While immunostaining identified distinct histochemical patterns, no clear correlation with outcomes was found. Despite this, most patients experienced a cure or improvement, supporting adrenalectomy as a viable treatment. Further research is needed to refine diagnostics and identify factors influencing surgical success.

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P132

JOINT2739

Determination of cortisol cut-off limits in the overnight dexamethason suppression test using roche elecsys® cortisol II immunoassay

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Background and aim
Mild autonomous cortisol secretion (MACS) is defined as excessive cortisol secretion but without the clinical phenotype of Cushing's syndrome in the context of an adrenal incidentaloma. Still, MACS has been associated with increased mortality and risk of type 2 diabetes, hypertension, obesity, and osteoporosis. Diagnostic tests capable of detecting MACS are lacking, but cortisol concentrations in plasma after a 1 mg overnight dexamethasone suppression test (1 mg DST) has the highest sensitivity of available biochemical analyses. A cut-off of 50 nmol/l has been recommended in the recent guidelines from ESE/ENS@T, but as measurement of cortisol concentrations is method dependent, this study aimed to establish the assay-specific cut-off of the 1 mg DST using the Roche Elecsys® Cortisol II immunoassay (ElecsysCortII) in a cohort of patients with adrenal incidentalomas.
Methods
Healthy participants ($n=101$, 57 women, median [range] age 60 [19–81] years) and patients with incidentalomas ($n=106$, 56 women, median [range] age 63 [40–85] years) underwent a 1 mg DST (dexamethason was taken between 2300 and 2400 h, and blood samples were collected between 0800 and 0900 h the following day) with plasma cortisol samples analyzed using ElecsysCortII. Cut-off limit for a normal response to the 1 mg DST was defined as the 97.5th percentile in the healthy participants.
Results
Two healthy participants were referred to the endocrinology department due to high 1 mg DST plasma cortisol levels (336 and 415 nmol/l, respectively), and thus excluded from the analyses. In the remaining healthy participants, the 0800 to 0900 h cortisol cut-off limit for the 1 mg DST was 68.9 [CI 63.1–75.3] nmol/l (ElecsysCortII). Forty-four percent of patients with an incidentaloma had a 1 mg DST cortisol above the recommended cut-off of 50 nmol/l, whereas 15% had a cortisol concentration above the assay-specific cut-off of 68.9 nmol/l.
Conclusion
ElecsysCortII-specific cortisol cut-off in healthy participants demonstrated a higher cut-off compared with previous recommendation of 50 nmol/l, and fewer than half as many patients exceeded the cut-off 68.9 nmol/l. As the number of referred patients suspected of MACS depends on the cut-off, the present findings may provide evidence for always adjusting the normal cut-off according to the local cortisol method.

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P133

JOINT1953

Urine steroid metabolomics, selected proteins and neuropeptides – new non-invasive diagnostic tools in hormonally active adrenal tumors

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Introduction
The application of metabolomics studies of determining the profile of steroid hormones or their metabolites in blood or urine opens new research directions in the diagnosis of adrenal diseases. In addition, studies of new biomarkers in the form of proteins, peptides, neuropeptides can be useful at various stages of the diagnostic and therapeutic process. Proteins and peptides of the granin family are produced and secreted into blood from endo- and neuroendocrine cells, along with hormones. The aim of the projects was the clinical and analytical evaluation of new biomarkers: urinary steroid hormone profiles and selected proteins and neuropeptides from granin family.
Materials and methods
The study included 61 patients with various adrenal tumors (mean age 48 years, 55% females; 26 MACS, 7 CS, 9 PA, 19 NFAA). All patients with adrenal tumors were analyzed for 41 different steroid hormone metabolites in a 24-hour urine samples. In addition, CgA, WE-14, Catestatin, Serpinin and proSAAS concentrations were determined in blood. Analyses were performed by GC/MS and ELISA methods.
Results
In the study groups (CS, MACS, PA, NFAA), urinary steroid profile analysis and profile testing of selected granin family proteins and peptides were performed. Comparison of CS vs. NFAA group revealed significant differences for: ET/AN ($P=0.010$), THS ($P=0.003$), THF ($P=0.007$), Free cortisol ($P=0.004$) and CgA ($P=0.002$) with higher level in CS group in all cases. Significant difference for MACS vs. NFAA was confirmed for: AN ($P=0.008$), An-3-ol ($P=0.002$), with higher level in NFAA group and for THS ($P=0.009$) with higher level in MACS group. For PA vs. NFAA there was a significant difference for THAldo ($P=0.026$) with higher level in PA group. The next stage of the project was the analysis of selected urinary steroid profile biomarkers (ET/AN, THS, THF, Free cortisol) and protein – chromogranin A in a group of patients with CS in order to assess the usefulness of this diagnostic tool. In the study of a panel of biomarkers (ET/AN + CgA, THS + CgA, THF + CgA, Free cortisol + CgA), the sensitivity and specificity rates were over 80–100%.
Conclusions
The study of urinary metabolomic profile and chromogranin A concentration has shown high usefulness in the diagnosis of Cushing's syndrome. The analysis of combined metabolomic and immunochemical studies may be useful in the in-depth biochemical diagnosis of adrenal tumor lesions.

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P134

JOINT2073

Does the cutoff point of 1.8 μg/dl in the 1 mg dexamethasone suppression test differentiate the cardiometabolic risk attributed to MACS?

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Introduction
About 20–50% of adrenal tumors in patients without symptoms of overt Cushing's syndrome are associated with mild autonomous cortisol secretion (MACS) based on 1 mg dexamethasone suppression test (DST) (cortisol concentration $>1,8$ ug/dl). Some clinical data shows that patients with MACS are at a higher risk of developing obesity, hypertension, hyperlipidemia, nonalcoholic fatty liver disease, cardiovascular diseases, prediabetes, type 2 diabetes, osteopenia, osteoporosis, and vertebral fractures as compared to patients with non-functioning adrenal tumor (NFAT). The prevalence of hypertension in MACS varies between 35% and 92% across different studies, compared to 43% to 73% in patients with NFAT or controls. Many studies reveal that patients with a higher degree of cortisol excess have a lower quality of life and survival rate.
Objectives: The aim of the study was to assess whether the cut-off point of 1.8 μg/dl in the 1 mg dexamethasone suppression test differentiates the cardiometabolic risk attributed to MACS in adrenal incidentalomas.
Methods
The results of cortisol suppression test of 347 incidentaloma patients (141 operated patients with confirmed of adenoma and 206 non-operated with homogenous adrenal mass <10 HU) were analyzed. 100 men and 247 women with median age 63.5 and 64 respectively were included to the analysis. Primary hyperaldosteronism, pheochromocytoma and Cushing's syndrome were excluded. Patients with negative (serum cortisol concentration $\leq 1,8$ ug/dl) and positive dexamethasone suppression test (serum cortisol concentration $>$ 1,8 ug/dl) were analyzed in relation to the presence of diabetes, obesity, hypertension, ischemic heart disease and chronic heart failure.
Results
In patients with a negative (serum cortisol concentration $\leq 1,8$ ug/dl) and positive dexamethasone suppression test (serum cortisol concentration $>1,8$ ug/dl) the percentage of the diseases were as follow: hypertension: 72.22% vs. 77.88% ($P=0.02$); ischemic heart disease: 11.54% vs. 18.58% ($P=0.15$); chronic heart failure: 4.27% vs. 7.08% ($P=0.16$); diabetes: 23.93% vs. 32.74% ($P=0.06$) and obesity: 32.49% vs. 31.69% ($P=0.88$). No differences between male and female regarding the frequency of accompanying diseases were noted.
Conclusion
In patients with MACS, a cortisol cutoff of 1.8 μg/dl in the 1 mg dexamethasone suppression test may help differentiate those at higher risk for hypertension and diabetes, and appears to be an independent and significant factor in the development of these conditions.

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P135

JOINT625

Efficacy and safety of corticosteroid replacement therapies in pediatric congenital adrenal hyperplasia: insights from hydrocortisone, prednisone, and dexamethasone studies

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Background
Congenital Adrenal Hyperplasia (CAH) is a genetic disorder requiring lifelong corticosteroid replacement to manage cortisol insufficiency and androgen excess. Hydrocortisone, prednisone, and dexamethasone are the primary glucocorticoids used, yet dosing, timing, and long-term impacts vary.
Objectives
This review evaluates the effectiveness and safety of hydrocortisone, prednisone, and dexamethasone replacement therapies in pediatric-CAH patients, focusing on their impact on growth, androgen suppression, and cognitive outcomes.
Methods
We synthesized findings from 25 studies published between 2000 and 2024 that assessed corticosteroid replacement therapies in children and adolescents with CAH. Data were collated on drug type, dose, patient age, and primary outcomes, including growth metrics, metabolic health, androgen control, and cognitive effects.
Results
1. Hydrocortisone (10–20 mg/m^2/day in divided doses) was the most frequently studied replacement therapy. Monitoring of 17-hydroxyprogesterone was critical for dose optimization to prevent overtreatment. Studies revealed:
• Optimal Dosing: Three- or four-times-daily regimens closely mimic natural circadian rhythms, effectively reducing androgen excess and avoiding adrenal crises.
• Growth and Metabolism: Higher doses correlated with reduced adult height predictions but minimized androgen excess when appropriately adjusted.
• Advancements: Granule formulations allowed precise dosing in younger children, enhancing growth outcomes.
2. Prednisone (1–5 mg/day, single or twice-daily dosing) showed:
• Growth Impact: Comparable linear growth to hydrocortisone in lower doses but increased growth suppression during puberty.
• Androgen Suppression: Adequate suppression of 17-OHP and androstenedione, with fewer metabolic side effects than dexamethasone.
• Clinical Use: Prednisone offered convenience in older children requiring less frequent
3. Dexamethasone (0.1–0.27 mg/m^2/day or prenatal dosing) provided robust androgen suppression but raised concerns about cognitive and metabolic effects:
• Growth: Low doses-controlled androgen secretion effectively while maintaining normal bone age progression.
• Cognition: Prenatal exposure in CAH-unaffected fetuses resulted in verbal working memory issues and social anxiety, highlighting the need for cautious use.
• Novel Approaches: Ultra-low doses preserved endogenous cortisol production in nonclassical CAH patients.
Discussion
Hydrocortisone remains the preferred corticosteroid for pediatric CAH due to its safety and ability to replicate physiological cortisol rhythms closely. Prednisone offers convenience for older children but may compromise growth during puberty. Dexamethasone, while effective for androgen suppression, warrants caution due to cognitive risks, particularly with prenatal exposure.
Conclusion
Tailoring corticosteroid therapy is critical in CAH management. Hydrocortisone remains the gold standard, while prednisone and dexamethasone serve specific roles, requiring precise dosing to balance efficacy and safety.
This synthesizes the need for individualized treatment strategies and monitoring to optimize outcomes in pediatric CAH patients.

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P136

JOINT2502

Evaluating 24-hour urine aldosterone levels with suppressed renin activity as a practical diagnostic tool for primary aldosteronism: a comparison with conventional confirmatory tests

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Background
Primary aldosteronism (PA) is the most prevalent cause of secondary hypertension. The prevalence of PA is high and often overlooked using current diagnostic approaches. Screening for the disease involves measuring the aldosterone–renin ratio (ARR). Aldosterone secretion is pulsatile and variable. PA also exhibits intraindividual variability in aldosterone concentrations. The 24-hour urine aldosterone levels are unaffected by diurnal and pulsatile changes in plasma aldosterone levels. Complications can occur during the confirmatory tests. The diagnosis of primary aldosteronism requires new approaches. This study used 24-hour urine aldosterone with suppressed renin activity to compare classical confirmatory methods.

Methods
The study included twenty-one patients with suspected primary aldosteronism. After correcting the patients' hypokalemia and bringing their hypertension under control, we collected 24-hour urine before proceeding with other confirmatory tests. We applied classical confirmatory tests like saline infusion ($n=20$) and the captopril test ($n=1$) to the patients. We did not perform an oral salt loading test on the patients. Plasma renin activity of all patients was below 1 ng/ml/h. Patients were divided into three groups according to 24-hour urine aldosterone levels: group 1 (<6 mcg/24 h), group 2 (6–12 mcg/24 h), and group 3 (>12 mcg/24 h).
Results
Mean 24-hour urine aldosterone levels were 4.03 mcg/24 h in group 1, 8.32 mcg/24 h in group 2, and 23.36 mcg/24 h in group 3 ($P < 0.001$), respectively. Classical confirmatory tests excluded PA in 10 patients. In groups 1 and 2, there were no patients with hypokalemia. In Group 3, all patients were hypokalemic. In group 1, standard confirmatory tests ruled out PA. There was no need for further workup of PA for patients in group 2. All patients in this group received antihypertensive agents during the follow-up, and no adrenal venous sampling or surgery was required. All patients in group 3 received confirmation of their PA diagnosis. Adrenal venous sampling was performed in 5 patients, and five underwent surgery in this group.
Conclusions
PA is a disease that can result in significant cardiovascular morbidity and mortality. Early and accurate diagnosis of the disease is crucial. We have demonstrated that 24-hour urine aldosterone with suppressed plasma renin activity measurements is an alternative and more practical diagnostic method than other classical confirmatory methods. It can help avoid complications of classical confirmatory tests and help achieve diagnosis and treatment more accurately and in a shorter time.

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P137

JOINT2814

Serum orexin ghrelin and adropin levels in patients with congenital adrenal hyperplasia due to 21 hydroxylase deficiency

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Introduction
In congenital adrenal hyperplasia (CAH) due to 21 hydroxylase deficiency, steroid treatment at supraphysiologic doses is recommended. However, the effects of steroids on food intake and energy homeostasis have been previously demonstrated. Moreover, many patients with CAH have increased body fat and insulin resistance. This study aimed to investigate the impact of the supraphysiologic dose of hydrocortisone on adropin, orexin, and ghrelin levels, which are peptides associated with food intake regulation and insulin resistance in patients with CAH.
Material and methods
Thirty-five patients with CAH receiving hydrocortisone treatment for at least three years and attending regular follow-ups and 35 age- and body-mass index-matched healthy children for the control group were included in the study. Anthropometric measurements of the patients were recorded. Glucose, insulin, serum lipid profiles, adropin, orexin, and ghrelin levels were compared between the two groups.
Results
Seven patients (20%) in the patient group had a body mass index (BMI) above +2 SDS. Adropin (208.37±186.03 ng/l vs. 143.97±50.31 ng/l, *P*: 0.049), ghrelin (1.59±1.32 ng/ml vs. 1.10±0.41 ng/ml, *P*: 0.036), and orexin (234.25±220.25 pg/ml vs. 123.83±50.02 pg/ml, *P*: 0.005), were higher in the patient group compared to the control group. Total cholesterol and LDL cholesterol levels were also increased in the patient group.
Conclusion
Serum ghrelin, orexin, and adropin levels have been found to be elevated in patients with CAH treated with supraphysiologic doses. The findings of this study suggest that these changes may play a role in the pathophysiology of increased body fat and food intake in these patients.

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P138

JOINT3825

Evaluation of the frequency of Hashimoto's thyroiditis and thyroid cyto/histopathological findings in patients with Connshing Syndrome

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Introduction
Connshing syndrome (CS) is characterized by concomitant cortisol excess in patients with primary aldosteronism (PA). There is only one study in the literature on the relationship between CS and thyroid and this study reported that anti-TPO and anti-Tg levels were similar in CS and PA patients and anti-TPO levels increased only in CS patients after adrenalectomy. The aim of this study was to evaluate thyroid autoantibody levels, ultrasonography (USG) features and cyto/histopathology results in CS and to compare the findings with PA and adrenal Cushing's syndrome patients.
Methods
Between 2019 and 2023, patients admitted to our Endocrinology outpatient clinic and diagnosed with CS, PA or adrenal Cushing's syndrome were retrospectively reviewed. Patients with PA who also exhibited autonomous cortisol secretion (ACS) were classified as having CSIf any of the 24-hour urinary cortisol, nocturnal salivary cortisol or 1 mg DST values were elevated, the patient was diagnosed with OCS. Demographic data, thyroid autoantibody levels, thyroid function tests, plasma aldosterone, renin activity (PRA) and cortisol levels were recorded. Additionally, chronic thyroiditis and nodules on USG and cyto-histopathological features were documented. All parameters were compared among the three patient groups.
Results
A total of 125 patients with CS ($n=21$), PA ($n=62$), and adrenal Cushing's syndrome ($n=42$) were included in the study. Thyroid autoantibody levels, autoantibody positivity rates and thyroid function tests were similar among the groups. Plasma aldosterone, PRA and aldosterone/PRA ratios were lower in the Cushing's syndrome group than in the CS and PA groups, whereas no significant difference was observed between the PA and CS groups. Basal cortisol levels were similar in all groups. No significant differences were found in the presence, number or characteristics of nodules on USG, but chronic thyroiditis was significantly lower in CS ($P=0.021$). A total of 66 patients had 252 nodules, of which 52 underwent fine-needle aspiration biopsy. The cytologic results of the nodules were similar.
Conclusions
Thyroid autoantibody titers and positivity rates in CS are not different from those in patients with PA and adrenal Cushing's syndrome, but the appearance of chronic thyroiditis on USG is significantly lower. The groups were similar in other USG features. Prospective studies with a larger number of cases are needed to elucidate the pathophysiologic mechanisms involved in the potential effects of CS on the thyroid.

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P139

JOINT2270

The prevalence and the diagnosis of glucocorticoids-induced adrenal insufficiency: a systematic review

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Introduction
Glucocorticoid-induced adrenal insufficiency (GC-induced AI) remains a common although under-recognised cause of morbidity in patients on chronic steroid therapy for a wide array of therapeutic indications.
Objectives
This systematic review of literature was carried out to evaluate prevalence of GC-induced AI by dose, duration and route of administration. An approach to screen and manage such patients (which can was be adapted to clinical practice) was critically appraised.
Methods
A systematic review of literature published between 2015 and 2024 was carried out using PubMed, Cochrane, Embase, Google Scholar, and EBSCOhost databases. Studies with strong evidence, including systematic reviews, randomized controlled trials, and observational studies, were included. Case

reports and studies without full texts were excluded. Data were extracted on GC dose, duration, route, and diagnostic tests.
Results
Twenty-one studies met the inclusion criteria, reporting AI prevalence ranging from 7.8% for inhaled GCs to 63% for oral high dose GCs used on short-term. Oral prednisolone doses $\geq$15 mg/day for $>$3 months carried the highest risk of developing iatrogenic AI. Inhaled fluticasone $>$800 mcg/day and super-potent topical clobetasol $>$50 g/week posed significant clinical risks. Diagnostic tests included early morning cortisol and Short Synacthen Test (SST), with SST providing the most reliable results. Measurement of salivary cortisol in outpatient settings remains a useful non-invasive test (with sensitivity 97%, specificity 97%) to assess ACTH-cortisol axis function. The results of this systematic review were compared to the recent European guidelines which were published in May 2024. This review provided more granular dose-specific data, evidence on short term risk compared to recent European guidelines.
Conclusions
GC-induced AI remains a clinically under-recognised condition associated with significant morbidity. Patients at high-risk of developing AI (based on potency, route and duration of steroid therapy) need to be closely monitored using 0900 h cortisol +/− SST. Salivary cortisol measurement can be used to improve diagnostic accuracy. It is important to educate patients at risk of developing iatrogenic AI regarding sick day rules and given back-up support (e.g. sign post to self-help groups, steroid alert card and hydrocortisone emergency use kit).

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P140

JOINT3448

Lowering the day 5 postoperative cortisol cutoff value to avoid over-diagnosis of secondary adrenal insufficiency following pituitary surgery

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Background
It is essential to identify patients who develop secondary adrenal insufficiency (SAI) following trans-sphenoidal pituitary surgery (TSS) to avoid life-threatening Addisonian crises. An early morning day 5 cortisol value may reliably assess hypothalamo-pituitary-adrenal (HPA) axis functioning following surgery.
Method
This was a retrospective cohort study of 54 patients undergoing TSS at Imperial Healthcare NHS Trust between 2019 and 2023. Receiver Operating Characteristic (ROC) curves were generated to evaluate the different predictive values of day 5 postoperative cortisol levels, using the Abbott Alinity cortisol immunoassay. Area Under the curve (AUC) was calculated from the ROC curve.
Results
The prevalence of SAI was 31%. The currently used cortisol cut-off value of $>$ 358 nmol/l to exclude SAI demonstrated 100% sensitivity and a specificity of 53.85%. Lowering this threshold to $>$308 nmol/l maintained 100% sensitivity but improved the specificity to 75.86%. A Day 5 cortisol value of $<$206 nmol/l predicts poor HPA function with a sensitivity of 70.59% and 100% specificity. Day 5 cortisol values (AUC 0.9645) provided better predictive values for SAI compared to values taken on Day 2/3 post-operatively (AUC 0.8095).
Conclusion
A day 5 serum cortisol value of $>$308 nmol/l reliably indicates an intact HPA axis. Values $<$206 nmol/l reliably detect SAI. Patients with Day 5 serum cortisol measurements between 206 and 308 nmol/l should be discharged on glucocorticoid therapy and undergo a dynamic test post-operatively to ascertain their true HPA function.

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P141

JOINT3492

The genetics of adrenal insufficiency, evolution of methodologies over 35 years in a single centre

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Background
Primary adrenal insufficiency (PAI) is life-threatening and can present alone or in combination with other co-morbidities. Paediatric primary adrenal insufficiency (PPAI) is most commonly congenital adrenal hyperplasia (CAH) caused by mutations in CYP21A2, but there are $>$25 other genetic aetiologies.
Methods
We investigated 369 families (probands 43% female, 57% male) from 36 countries with non-CAH PAI between 1990 and 2025 using candidate gene and next generation sequencing (NGS) techniques including targeted panel [TPS], whole exome [WES] and whole genome sequencing [WGS]. Challenges in coverage between different capture/sequencing methodologies were minimised by repeat sequencing and recent reanalysis of NGS data using the Genome Analysis Toolkit (GATK) and Exomiser as well as CNV assessment building towards a novel in house pipeline for diagnosis. Further analyses to assess pathogenicity included in silico e.g. SQUIRLS and functional analyses involved splice assays and heterologous expression of mutants vs wild-types.
Results
Although mean age of presentation was 3y it ranged from neonatal to 81y with a median age of 1.5y. Eight novel genetic causes of PAI were discovered with genes responsible for isolated glucocorticoid deficiency (*MC2R, MRAP*), with/without additional mineralocorticoid deficiency (*NNT, TXNRD2*) or as part of a syndrome (*MCM4, SGPL1, PPOX, CPOX*). Overall, a genetic diagnosis was achieved in 245/369(66.3%) families, 109 were diagnosed by CGS, 35 by TPS and 101 by WES, with WGS useful as an adjunct to define the co-ordinates of deletion mutations but adding no new diagnoses. Pathogenic variants occurred in 17 genes: *MC2R* (20%), *MRAP* (15.9%), *NNT* (14.2%), *CYP11A1* (9.8%), *STAR* (9%), *ABCD1* (7.4%), *AAAS* (5.3%), *NR0B1* (DAX-1; 2.9%), *TXNRD2, SGPL1, AIRE CYP11B1, CYP11A2, HSD3B2, POMC, POR* and *PPOX*. *MC2R/MRAP* were most prevalent, responsible for 23.9% of cases, with the UK variant of *MC2R* (S74I) very common (49% of *MC2R* diagnoses) and for *MRAP* the majority of mutations were at the splice junction of exon1/intron 1. We have evolved a novel pipeline whereby sequencing of small frequently mutated genes/exons is followed by NGS where these prove negative.
Conclusion
PPAI is most commonly congenital, and, with our serial sequencing and analysis pipeline, a genetic diagnosis is achievable for $>$65% of cases in a cost-effective and timely manner. Distinguishing between isolated and syndromic adrenal insufficiency means treatment, ongoing management and genetic counselling can be personalised.

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P142

JOINT3654

Single daily dose prednisolone has a lower cardiovascular risk compared to multiple daily hydrocortisone doses in patients with adrenal insufficiency

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Background
Multiple daily doses of hydrocortisone are traditionally used as glucocorticoid replacement in patients with adrenal insufficiency. The Endocrine Society guideline suggests 3–5mg of prednisolone as an alternative. Prednisone is a pro drug that is converted to prednisolone by first pass metabolism in the liver. We compared the metabolic profile of patients taking multiple doses of hydrocortisone before and after switching to a single daily low-dose of prednisolone 2–5mg.
Methods
Patients with adrenal insufficiency were switched from multiple-daily dose hydrocortisone to 2–5mg of prednisolone and followed up after 4 months. We assessed cardiovascular risk using weight, blood pressure, waist and hip circumference, lipid profile and high sensitivity C-reactive protein. Quality of life was assessed using a modified SF-36 questionnaire. Baseline and follow-up data were compared using a paired *t*-test.
Results
Sixty-two participants were enrolled, of whom 48 completed the study. Eight (16.8%) had a diagnosis of primary adrenal insufficiency. The mean duration of glucocorticoid use was 11.4$\pm$8.6 years. After at least four months of prednisolone,

we observed significant reductions in mean weight from 90.6 kg to 89.6 kg ($P=0.007$) and a significant reduction in systolic blood pressure (BP) of 6 mmHg ($P=0.027$). There was no difference in the waist to hip ratios between the two treatments ($P=0.183$). The use of prednisolone was associated with no change in total, LDL, HDL, or non-HDL cholesterol, triglycerides or hs-CRP. Use of once-daily low-dose prednisolone demonstrated an improvement in the energy/fatigue and total quality of life scores ($P=0.003$ and $P=0.019$ respectively). Patients reported prednisolone to be more convenient compared to hydrocortisone ($P=0.002$).
Conclusion
Single dose daily low-dose prednisolone has a lower metabolic risk profile to multiple daily doses of hydrocortisone given the lower blood pressure and weight. It is more convenient and improves subjective energy levels. We recommend low dose prednisolone or prednisone as a first line treatment for patients with adrenal insufficiency.

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P143

JOINT361

Clinical characteristics and outcomes in 31 pediatric cases of x-linked adrenoleukodystrophy: a retrospective study at SCMC

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Objective
To investigate the clinical characteristics, treatment approaches, and prognosis of X-linked adrenoleukodystrophy (ALD) in children.
Methods
This study included 31 male pediatric patients diagnosed with ALD and treated at our hospital from 2015 to 2023. Loes score were assessed in all participants with cerebral ALD (cALD).
Results
Of the 31 patients, 24 presented with cALD, while 7 exhibited the adrenal-only type. Clinical manifestations in cALD primarily involved central nervous system symptoms, including visual/hearing impairment (9/24), seizures (7/24), cognitive deficits (4/24). Adrenal cortical insufficiency developed in 62.5% of cALD cases during follow-up. Patients with adrenal-only type primarily exhibited hyperpigmentation. Genetic analysis identified 29 distinct *ABCD1* mutations, with missense mutations accounting for 75.9%, frameshift mutations for 20.7%, and 1 large deletion that containing *ABCD1* gene. Three novel mutations were identified: c.77C > G, c.1119_1120 insTC, and c.1291C > T. Allogeneic hematopoietic stem cell transplantation (all-HSCT) was the primary treatment for early cALD, achieving a 5-year overall survival (OS) rate of 78.0% (64.0 ~ 86.6%) compared to 29.0% (95%CI 11.7 ~ 48.2%) in non-HSCT patients. A pre-transplantation Loes score < 10 was strongly associated with improved outcomes.
Conclusion
Early intervention with allo-HSCT significantly improves survival in pediatric cALD, particularly in patients with a Loes score < 10 before transplantation. Close monitoring is essential for progressive adrenal insufficiency, which remains a key phenotype of ALD.

Key words: X-linked adrenoleukodystrophy; *ABCD1*; gene mutation; Loes score
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P144

JOINT1350

ESPE school: sharing knowledge to save lives – developing and standardizing education for clinicians and families with children with adrenal insufficiency in Kazakhstan

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Introduction
Adrenal insufficiency (AI) is a severe disorder characterized by a deficiency in the synthesis and release of cortisol or/and aldosterone. The prevalence of AI is estimated to range from 20–50 per 100 000 individuals in Europe. However, studies on AI in Central Asia (CA) have only recently begun. Kazakhstan, a vast country with a population of 20 million, faces challenges in delivering consistent specialized outpatient care due to sparse clinics and variable healthcare standards. Since 2014, the ESPE Caucasus & Central Asia School has been instrumental in providing pediatric endocrinology education. This initiative marks the first structured effort to implement an organized educational program for medical professionals and families dealing with AI in Kazakhstan.
Aim
To develop and implement a standardized, systematic educational program in Kazakhstan for clinicians, families, and patients with AI.
Methods
Healthcare professionals involved in managing AI were identified by contacting healthcare authorities across all regions of Kazakhstan. Additionally, project information was disseminated through Facebook groups for families with children diagnosed with AI. To enhance care standards, the European Emergency Card (EEC) for AI was translated into Kazakh and Russian and will be integrated into emergency response protocols in the future.Structured educational programs were designed for healthcare professionals, and individualized treatment plans (ITP) were created for patients. These programs aimed to establish continuity of care across all 17 regions of Kazakhstan. All materials, including educational content and treatment templates, were prepared in both Kazakh and Russian.
Results
A total of 134 patients with AI were identified, with detailed information on age and gender available for 72 individuals. Among them, 43 (61%) were girls, and 29 (39%) boys with a median age of 10.5 years (range: 1–18). The translated EEC and the structured educational program were introduced to clinicians during face-to-face and digital conferences held nationwide. Patient organization representatives participated in these events, sharing expertise.ITP templates were developed and adapted to the local healthcare infrastructure. These plans are now being implemented to ensure comprehensive, patient-centered care for individuals with AI.
Conclusion
The implementation of an organized and standardized educational approach across Kazakhstan significantly enhances the quality of care for patients with AI. By ensuring consistent medical care and education, this initiative bridges geographical barriers and aligns medical practices across all regions. Furthermore, equipping healthcare professionals with tailored educational resources fosters a deeper understanding of AI management and improves patient outcomes.

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P145

JOINT495

Smoking and alcohol use plays a mediating role on the social determinants of high blood pressure: evidence from nationally representative sample in India

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Background
Hypertension remains a global health concern, with its prevalence influenced by socioeconomic determinants and modifiable risk factors. Understanding the interplay between these factors is vital for targeted interventions. This study aimed to investigate the mediating roles of smoking and alcohol consumption in the association between socioeconomic factors (education, wealth index, gender) and blood pressure using data from the National Family Health Survey-5 (NFHS-5) in India.
Methods
We carried out a secondary analysis of data collected from a nationally representative survey (NFHS-5 data) in India. We included 19 23 504 people aged 18 years and above having all the necessary information for analysis. We performed a mediation analysis using structural equation modelling to estimate the natural direct effect (NDE), total effects, and natural indirect effect (NIE) of sex, education and wealth index on systolic and diastolic blood pressure keeping the behavioural habits (smoking and alcohol use) as mediator variables. The analysis was carried out in Stata 16.1.
Results
The sample had a nearly equal distribution of males (51.4%) and females (48.6%). Alcohol use and tobacco consumption were reported by 13.2% and 27.6% of participants, respectively. Women exhibited lower systolic ($\beta=-4.59$) and diastolic ($\beta=-2.07$) blood pressure compared to men. Lower education levels and higher wealth indices were significantly associated with

variations in blood pressure. Mediation analysis showed partial mediation by alcohol and tobacco which were statistically significant ($P<0.001$). For instance, 17.8% of the reduction in systolic blood pressure associated with being female was mediated by alcohol use, while tobacco accounted for 22.1%. Education's effect on systolic blood pressure was mediated by 29.7% through alcohol and 27.3% through tobacco. The analysis also revealed that the people in the richer and richest quintiles had significantly higher level of systolic and diastolic blood pressure when compared to those in the poorer and poorest quintiles.

Conclusion

The study highlights the significant mediating roles of smoking and alcohol in the relationship between socioeconomic factors and blood pressure. These findings underscore the importance of integrating behavioural interventions into public health strategies to address hypertension and its risk factors effectively. Targeted approaches considering socioeconomic disparities and behavioral risks are crucial for improving cardiovascular health in diverse populations.

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P146

JOINT79

Management practices in Italy on adrenal insufficiency in young people with Duchenne muscular dystrophy on steroid treatment

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Background

The cornerstone of current pharmacologic management of Duchenne muscular dystrophy (DMD) is glucocorticoid (GC) therapy initiated at a young age. Chronic high-dose daily GC treatment causes adrenal suppression that can result in potentially life-threatening adrenal insufficiency (AI). Despite the potential severity of this complication, it is not known what guidance pediatric endocrinologists and neurologists in Italy provide regarding the risk of AI.

Methods

Online survey distributed via email to Italian endocrinologists and neurologists involved in the care of young people with DMD.

Results

A total of 35 physicians responded to the survey (57% endocrinologists, 43% neurologists). Most respondents (57%) managed between 11 and 50 patients, with neurologists caring for a greater number of patients than endocrinologists ($P=0.013$). The most commonly used GC regimen was daily deflazacort (86%), followed by daily prednisone (26%), intermittent deflazacort (14%), and intermittent prednisone (3%). For minor stress (e.g., cold without fever), most respondents (80%) did not recommend any additional treatment, with a significant difference between neurologists and endocrinologists (93% vs. 70%, $P=0.027$). For moderate stress (e.g., febrile illness, vomiting, diarrhea but able to take oral intake), 31% recommended oral hydrocortisone (HC), 17% suggested an additional dose of deflazacort/prednisone, and 9% recommended parenteral HC. In cases of major stress (e.g., painful long bone fracture, vomiting or diarrhea with inability to take oral intake, general anesthesia, surgery), 77% recommended parenteral HC, yet 14% still did not advise any additional treatment. Although 82% of respondents reported providing education on AI management (from endocrinology team in 41%, neurology team in 26%, both in 15%), only 43% supplied a prescription and instructions on how to administer intramuscular HC. Furthermore, while 71% provided a written emergency plan for steroid management during illness or stress, only 37% had an alert in the hospital system, and 31% recommended wearing a steroid-dependent alert bracelet/card.

Conclusions

To our knowledge, this is the first survey addressing AI management practices among physicians caring for individuals with DMD in Italy. Most physicians involved in DMD care manage fewer than 50 patients. There are notable differences in approach for minor, moderate, and major stress, with nearly a quarter of respondents not prescribing parenteral hydrocortisone in major stress situations. Additionally, the majority of patients do not receive practical education or prescriptions for parenteral hydrocortisone. There is a clear need for enhanced education on AI risk in DMD, particularly regarding specific situations common in DMD patients (e.g., fractures, bisphosphonate infusion).

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P147

JOINT1286

Increased arterial stiffness and short QTc interval are associated to androgen levels in classical congenital adrenal hyperplasia due to 21 hydroxylase deficiency

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Context

Congenital Adrenal Hyperplasia (CAH) is a group of autosomal recessive disorders characterized by impaired cortisol synthesis and hyperandrogenism, current treatment of CAH mainly rely on glucocorticoids (GC) to suppress androgen hypersecretion and to mimic endogenous cortisol secretion. GC therapy, however, often needs to be administered at supra-physiological doses, with an increased risk of long-term complications.

Objective

To evaluate the cardiovascular and metabolic risk in a group of adult patients affected by CAH caused by 21β-hydroxylase deficiency.

Subjects and methods

A cross-sectional study was conducted in a group of 32 adult patients affected from classical CAH due to 21β-hydroxylase deficiency in treatment with different formulations of glucocorticoids (Hydrocortisone HC, Double-release Hydrocortisone DR-HC, Hydrocortisone and dexamethasone HC+DEX), compared with 73 unaffected controls. Anthropometric and metabolic biochemical parameters were collected for each of the subjects, as well as a 24-hour dynamic blood pressure monitoring (ABPM) and an EKG.

Results

The univariate analysis showed a higher weight ($P=0.006$), systolic blood pressure ($P<0.001$), glycemia ($P=0.031$), triglycerides ($P=0.025$), LDL cholesterol ($P<0.001$) in the control group when compared to CAH patients; however, the latter being significantly younger than the control group ($P=0.035$). The CAH group also exhibited a shorter QTc ($P=0.006$), RR ($P=0.045$) and QRS ($P=0.004$) interval. The Ambulatory Arterial Stiffness Index (AASI), derived from the 24-hour ABPM, showed statistically significant higher values in the CAH group ($P=0.006$), the two groups were matched 1:2 through a propensity score matched analysis, confirming a higher AASI score ($P< 0.001$) and a shorter QTc interval ($P=0.004$). Through a multivariate analysis we found the AASI score to be related to CAH diagnosis (coeff. 1.131; $P<0.001$), Age (coeff. 1.004; $P=0.034$), BMI (coeff. 1.008; $P<0.001$) and 17 OHP levels (coeff. 1.001 $P=0.049$); while a shorter QTc interval seems to be related to CAH diagnosis (coeff. 0.977; $P=0.039$) and ACTH levels (coeff. 0.999; $P=0.021$). Patients treated with HC+DEX showed higher AASI ($P=0.026$) and triglycerides levels ($P=0.04$) when compared to patients treated with HC only or DR-HC, however no differences in hormonal levels and comorbidities were found between the groups.

Conclusion

The metabolic profile of CAH patients did not differ from unaffected controls, however androgens levels seem to be related to cardiovascular alterations in subjects affected by CAH, especially those in treatment with dexamethasone.

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P148

JOINT1348

Investigation of alternative hormones for evaluating selectivity of adrenal vein sampling in the subtype diagnosis of primary aldosteronism

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Background-Aim
International guidelines recommend adrenal venous sampling (AVS) for subtype diagnosis of primary aldosteronism (PA), which is crucial for suggesting surgical or medical treatment. Successful cannulation of adrenal veins is assessed using the cortisol (F) ratio between adrenal and peripheral veins (selectivity index, SI). Given the limitations associated with F measurements, this study aimed to evaluate whether the measurement of other hormones could improve SI calculation.
Methods
The study included 122 PA patients undergoing unstimulated and sequential AVS. Concentrations of F, catecholamines (noradrenaline, NA, adrenaline, AD), metanephrines (normetanephrine, NMT, metanephrine, MT, normetanephrine, NMT), and other steroids (DHEA, DHEAS, androstenedione, A4, 11-deoxycorticosterone, DOC, 17-hydroxyprogesterone, 17OHP, and progesterone, P) were measured in both adrenal vein and peripheral vein samples using CLIA, HPLC, and LC–MS/MS, respectively. Hormone-specific SI cut-offs were calculated along with the percentage of selective procedures identified based on each marker. Additionally, differences in SI values of all hormones were compared between the selective and non-selective procedure groups.
Results
Using as reference cut-off SI = 3 for F, ROC curve analysis revealed the following SI cut-offs for MT (11.90, AUC = 0.640), NMT (1.65, AUC = 0.640), NA (1.40, AUC = 0.598), AD (1.50, AUC = 0.557), DHEA (1.10, AUC = 0.850), DHEAS (22.00, AUC = 0.831), A4 (16.66, AUC = 0.825), DOC (4.49, AUC = 0.950), 17OHP (4.62, AUC = 0.944), and P (4.75, AUC = 0.829). All markers, except P, improved the rate of selective procedures compared to F (74.1%). Notably, only steroid hormones exhibited significantly higher SI values in the group of selective procedures, with increases of up to 10-fold for DOC and 17OHP.
Conclusions
The monitoring of alternative hormones and the use of hormone-specific SI cut-offs increased the rate of selective AVS procedures, with steroids demonstrating the best diagnostic accuracy compared to metanephrines and catecholamines. In the evaluation of successful cannulations, the highest increases in SI were observed for DOC and 17-OHP, highlighting the latter as a promising additional marker due to its easily measurable levels in both adrenal and peripheral veins.

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P149

JOINT692

Dose the GH IGF-1 Axis serve as a determinant of prognosis in Acute Ischemic Stroke?

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Background
In acute ischemic stroke (AIS), low IGF-1 levels are associated with unfavorable prognosis; however, the relationship with GH levels remains unclear. On the other hand, some reports suggest that elevated GH levels in cardiovascular disease are associated with increased mortality. Therefore, in this study, we investigated the relationship between post-stroke GH and IGF-1 levels and the modified Rankin Scale (mRS) at three months from the onset of AIS.
Methods
Between October 2020 and December 2022, patients admitted to our hospital with AIS were included in the study. GH and IGF-1 levels were measured on or after the 7th day of hospitalization. At three months post-stroke, patients were classified into a favorable outcome group (FOG: mRS ≤ 1) and an unfavorable outcome group (UOG: mRS ≥ 2), and the relationship between GH and IGF-1 levels and prognosis was analyzed.
Results
A total of 130 participants were enrolled in this study, and 124 cases were included in the final analysis (95 males [77%], median age 62 years). Among them, 25 patients (20%) were classified into the unfavorable outcome group. The Mann–Whitney U test revealed that GH levels were significantly higher in the unfavorable outcome group ($P = 0.02$), whereas there was no significant difference in the IGF-1 SD score (IGF-1 SDS) between the two groups. Next, a ROC-analysis was performed to determine the optimal cutoff value for GH in distinguishing the two groups, which was estimated to be 0.2 ng/ml. Based on these findings, the 124 patients were categorized into four groups using GH 0.2 ng/ml and IGF-1 SDS -2.0 as cutoff values: 'high GH – high IGF-1,' 'high GH – low IGF-1,' 'low GH – high IGF-1,' and 'low GH – low IGF-1.' Logistic regression analysis, FOG/UOG as dependent variables, revealed that both the NIHSS score ($P < 0.001$, OR 1.12 [1.05–1.20]) and the 'high GH – low IGF-1' group (compared with the 'low GH – high IGF-1' group, $P = 0.02$, OR 6.23 [1.32–28.54]) were significantly associated with unfavorable prognosis.
Conclusion
Our study demonstrated that patients with high GH levels and low IGF-1 SDS are associated with poorer stroke outcomes. These findings suggest that a state of 'GH resistance,' characterized by elevated GH levels without a corresponding increase in IGF-1, may be a prognostic factor for poor outcomes. Further studies are currently planned to investigate the impact of 'GH resistance' as a determinant of prognosis in AIS.

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P150

JOINT724

Impact of gender-affirming hormone therapy on cardiovascular risk factors in transgender individuals

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Introduction
Transgender individuals exhibit a higher cardiovascular risk compared to the general population. Gender-affirming hormone therapy (GAHT), used to align physical characteristics with gender identity, has an unclear impact on cardiovascular risk factors. Some evidence suggests that GAHT may exacerbate cardiovascular risk through changes in blood pressure, insulin resistance, lipid profile, and body composition.
Objective
This study aims to evaluate the impact of GAHT on lipid profile, blood pressure, and body mass index (BMI) in transgender individuals.
Methods
A retrospective longitudinal study was conducted at a multidisciplinary clinic of transgender medicine from October 2021 to January 2024. The study collected and analysed sociodemographic data, lifestyle behaviours, medical history, and clinical data from all individuals observed during this period. From this population, a subset of participants with sufficient data at two or more time intervals was studied to evaluate changes in lipid profiles, blood pressure, and BMI from baseline up to one year after starting GAHT. Statistical analysis was performed using IBM SPSS Statistics 28.0.1.0 with a significance level of 0.05.
Results
The study included 232 transgender individuals (152 trans men and 80 trans women; median age 23) who showed high rates of tobacco use (37.3%) and illicit substance use (11.5%). Among trans feminine individuals, there were consistent but non-significant decreases in systolic blood pressure (SBP) and triglycerides (TG) at 3, 6, and 9 months. Trans masculine individuals exhibited a trend of increasing SBP, though no changes reached statistical significance. Trans masculine individuals experienced a significant increase in BMI at 3, 6, and 9 months (Δmax of 1.01 kg/m^2; $P < 0.01$) and a significant decrease in HDL cholesterol at all time points (Δmax of -10.47 mg/dl; $P < 0.001$).
Conclusion
The observed trends suggest that GAHT may influence lipid profiles. Although these changes are statistically significant, their magnitude is typically not considered clinically relevant. As such, our data indicates that GAHT appears to be safe in the short term. However, the prevalence of other cardiovascular risk factors highlights the need for routine monitoring in this population. Further research is essential to address existing knowledge gaps regarding the long-term cardiovascular effects of GAHT.
Keywords: Transgender Persons; Cardiovascular Disease, Heart Disease Risk Factors, gender-affirming hormone therapy

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P151

JOINT417

Cortisol response to coffee, tea, and caffeinated drinks: A comparative review of studies

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Background
Cortisol, a stress hormone regulated by the hypothalamic–pituitary–adrenal (HPA) axis, plays a crucial role in maintaining physiological balance. Caffeinated beverages, such as coffee, tea, and energy drinks, are widely consumed worldwide and are known to influence cortisol secretion. Understanding the effect is vital for assessing the health implications of caffeine intake, particularly regarding stress regulation and overall well-being.
Objective
To evaluate and compare the effects of coffee, tea, and other caffeinated drinks on cortisol secretion, highlighting the magnitude of cortisol increase, caffeine content, and beverage-specific characteristics.
Methods
A comprehensive review of 15 studies conducted between 2000 and 2024 was performed. The studies assessed cortisol secretion in response to caffeine consumption, including coffee, tea, and energy drinks, across diverse populations. The analysis focused on the percentage increase in cortisol, number of participants, and caffeine content in each beverage category.
Results
The studies revealed notable differences in cortisol responses based on beverage type and caffeine content:
• Coffee: Represented in 10 studies with ∼2500 subjects, coffee, with a typical caffeine content of 80–120 mg per 8-ounce cup, caused the strongest cortisol increase of 50% above baseline. Examples include espresso, Americano, cold brew, and drip coffee.
• Tea: Covered in 3 studies with ∼800 subjects, tea (20–60 mg caffeine per serving) showed a milder cortisol increase of 20%. Examples include black tea (e.g., Earl Grey, English Breakfast), green tea, matcha, and iced tea. Tea's effects are moderated by L-theanine, which promotes relaxation.
• Other Caffeinated Drinks: Represented in 2 studies with ∼300 subjects, energy drinks (e.g., Red Bull, Monster) and sodas (e.g., Coca-Cola, Pepsi) exhibited a moderate cortisol increase of 30%, with caffeine content ranging from 30 to 300 mg per serving. Additional ingredients like sugar and taurine may influence cortisol responses.
Discussion
Coffee elicited the highest cortisol response due to its high caffeine concentration, while tea's effects were milder, likely due to L-theanine's calming properties. Other caffeinated drinks exhibited intermediate effects, depending on caffeine dosage and additional ingredients. Habitual caffeine consumers showed attenuated cortisol responses, suggesting tolerance over time.
Conclusions
Caffeine consumption significantly impacts cortisol secretion, with coffee showing the strongest effect, followed by other caffeinated drinks and tea. Tea's stress-buffering properties and moderate cortisol response make it a suitable option for individuals sensitive to stress. Future studies should explore the long-term implications of caffeine-induced cortisol elevation and its role in stress and health management.

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P152

JOINT436

Short-term effect on tissue sodium distribution in hypertensive patients following sodium loading test: A sodium MRI study

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Background
Emerging research suggests that tissue Na^+ accumulation plays a role in blood pressure control, yet the mechanisms underlying the regulation of sodium storage remain unclear to date.
Methods
In 31 hypertensive patients with a mean age of 49 years, of whom 61% were women, a sodium infusion test (SIT) was conducted to confirm or exclude the diagnosis of primary aldosteronism (PA). For this purpose, 2000 ml of isotonic saline were intravenously infused over 4 hours. Both before and immediately after the sodium infusion, each patient underwent sodium magnetic resonance imaging (^{23}NA-MRI), a specialized noninvasive imaging technique that focuses on visualizing the distribution and concentration of sodium ions within tissues.
Results
The mean sodium content in skin and muscle tissue in the study cohort was 45 ± 3.4 mmol/l and 17.9 ± 2.8 mmol/l, respectively, prior to the intervention. Following salt loading, in both compartments a significant increase in salt accumulation (+18%, $P<0.001$; +4.4%, $P=0.004$) could be observed. Based on the SIT, PA was diagnosed in 17 cases (54.8%) and excluded in four cases (12.9%), while remaining inconclusive in ten cases (32.3%). Across diagnostic categories, the aldosterone-to-renin ratio (ARR) correlated positively with the level of baseline salt content in the skin ($P=0.03$). While a similar trend was evident in muscle tissue, it did not reach statistical significance. Muscle salt accumulation was significantly less pronounced in patients with a post-SIT aldosterone level above the median of 135 ng/l compared to those with lower aldosterone values (Δ1.48% versus Δ7.23%, $P=0.016$).
Conclusions
This study demonstrates a significant increase in sodium accumulation within skin and muscle tissues among hypertensive individuals following short-term sodium loading. In addition, we demonstrate a positive correlation between ARR and sodium stores in the skin prior to intervention. In muscle tissue, we observe a negative correlation between post-SIT aldosterone levels and the percentage of sodium accumulation. The data may provide an indication of a potential influence of aldosterone on sodium dynamics within body tissues. Increasing patient numbers and further investigation is required to assess whether differences in tissue sodium distribution before and after loading could serve as a discriminating factor between endocrine forms of hypertension and essential hypertension.

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P153

JOINT467

Impact of Val334Ile and Val472Leu variants on cytochrome P450 oxidoreductase activity

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Several different human diseases are caused by mutations in the NADPH:cytochrome P450 oxidoreductase (POR) that may severely impair its electron transfer ability. As the energy provider to microsomal cytochrome P450 (CYP) enzymes, effects of mutations in POR reach far beyond steroid biosynthesis. Human variants in POR manifest with a very broad phenotype affecting steroid and drug metabolism. POR is composed of a NADPH-binding domain and FAD and FMN-binding domains, linked by a hinge region. This hinge region allows the protein to undergo the conformational changes needed for the electron transfer from the electron donor to the final acceptor, either a CYP, another protein partner, or a small molecule. Variations in different regions of the protein contribute to the heterogeneous effects of POR variants in multiple pathologies. We report two POR variants, Val334Ile and Val472Leu, located in the FAD-binding domain and identified, respectively, in patients with primary adrenal insufficiency and familial glucocorticoid deficiency. Both variants were found to have been reported in population genetics databases, with a higher allele frequency in individuals with South Asian ancestry. The variants were expressed in bacterial systems and partially purified. CYP electron transfer activity was assessed using standard fluorescent or radiolabelled substrates, and small molecule reduction was assessed spectrophotometrically following cytochrome *c* reduction. Both variants resulted in a decrease in activity of drug metabolizing CYPs 2C9, 2C19, and 3A4, more pronounced for the Val334Ile variant, which maintained only approximately 20% of CYP2C9 and CYP2C19 activity and 70% of CYP3A4 activity. Moreover, preliminary data suggests a pronounced effect for the Val334Ile POR variant in the steroidogenic activity of CYPs 17A1 and 21A2, with approximately 35% of activity compared to wild-type POR. Cytochrome *c* reduction by POR was also impaired more severely by the Val334Ile variant. In silico predictions of stability and conservation highlighted the Val334 amino acid residue as more conserved and predicted a more deleterious effect of Val334Ile compared to Val472Leu, in accordance with the experimental data.

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P154

JOINT900

Education of sick day management in young people with adrenal insufficiency: Online survey and focus groups involving young people and parents

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Background
Education of parents and young people (YP) with adrenal insufficiency (AI) in relation to sick day management is crucial and may help prevent adrenal crisis. In the UK, there is currently no national standards on education of sick day management in YP with AI.
Aims
To investigate the perceptions of YP with AI and their parents regarding experiences of and preferences for education and information on sick day management.
Methods
Online surveys and online focus groups with YP with AI (11–16 years), and their parents. Recruitment UK wide was facilitated through patient support groups. Survey responses were analysed using descriptive statistics and content analysis. Focus group data were analysed using thematic analysis.
Results
Twelve YP with AI, and 108 parents shared their views in the online survey. Five YP and 12 parents took part in online focus groups. YP reported gaps in their sick day management knowledge via the survey: 'I know a bit' (6/12, 50%) or 'I do not know much' (3/12, 25%). Some YP had not received education. Some received education at diagnosis when the YP were very unwell. YP in the surveys and focus groups reported that information and education should be more age-appropriate with child friendly leaflets and videos addressed to them (not just their parents) and covering injection technique. Some parents on the survey (34/108, 32%) reported that education did not equip them with the knowledge and skills needed to manage their child's sick day episodes. Despite education, some parents expressed uncertainty around how to spot signs of adrenal crisis (40/108, 37%) and did not feel they had the knowledge or skills to manage their child's sick days (36/108, 33%). The majority of parents (76/108, 70%) had received no refreshers following initial education. Parents wanted to gain information by talking with health professionals (88/108, 82%) or via instructional videos (72/108, 67%). Parents in the focus groups felt that education should be delivered separately to the time of diagnosis or acute illness and should include a follow-up appointment or regular refresher. Parents would like the choice of whether education is conducted on their own or with their child so they can ask difficult questions and access more opportunities for peer support.
Conclusion
This study highlights that many parents and YP with AI have unmet information needs regarding sick day management. Developing national standards of education of sick day management of AI should be prioritized.

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P155

JOINT3187

Post adrenalectomy hyperkalemia in primary aldosteronism. A case series of a not well-defined complication

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Introduction
Hyperkalemia post adrenalectomy can develop in primary aldosteronism (PA) due to chronic suppression of renin–angiotensin–aldosterone system (RAAS). There is too much uncertainties concerning this complication in terms of prevalence, risk factors, aetiology and treatment. We present the postoperative course of PA cases who underwent adrenalectomy.
Methodology
Inclusion of cases with unilateral PA confirmed by adrenal venous sampling (at the Antwerp University Hospital) who underwent unilateral adrenalectomy. Blood results were retrospectively evaluated 1–4 weeks and 2–12 months postoperatively.
Results
13 cases ($M=9$) with a mean age of 56 ± 11 years were included. 3 cases developed hyperkalemia <4 weeks postoperatively and persisted in 2 cases. Both were men, had a history of arterial hypertension >10 years and a normal kidney function. One case had a preoperatively hypokalemia. The first case developed a grade 3 hyponatremia and grade 1 hyperkalemia with a 45% increase of the serum creatinine level. Plasma aldosterone and renin levels were low. Kidney function and potassium level normalized under treatment with Kayexalate, but hyponatremia and suppression of RAAS persisted. The second case developed a grade 2 hyperkalemia and grade 3 hyponatremia with a 75% increase of the serum creatinine. Under treatment with Fludrocortisone, potassium and sodium levels improved. Plasma aldosterone was low-normal with an inappropriate normal renin level. Early postoperative suppression of RAAS was present in 5/13 cases and led to hyperkalemia in 2 cases. In the 3 cases without electrolyte disturbances, RAAS recovered.
Conclusion
Post adrenalectomy hyperkalemia in PA is stated to be a well–documented entity with a variable prevalence (4.5–7%). In our cohort of 13 cases, 1 case had a transient and 2 cases persistent hyperkalemia. Both cases with persistent electrolyte disturbances had a suppression of RAAS. Risk factors described in the literature and met by these 2 cases were older age (>53 years) and longer duration of hypertension. Early postoperative, 5/13 cases had a suppression of RAAS, leading to hyperkalemia in only 2 cases. Reviewing the literature, there is no difference in early postoperative plasma aldosterone or renin levels in cases with and without hyperkalemia. However, case series are small (largest including 9 cases with persistent postoperative hyperkalemia) and timing of blood sample varies. It is unknown why in most cases, postoperative suppression of RAAS is not associated with hyperkalemia. We state post adrenalectomy hyperkalemia is a not well-documented entity. Larger case series are needed to compare cases with and without post adrenalectomy hyperkalemia.

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P156

JOINT1588

Metabolic risk following gender affirming hormone therapy, a prospective cohort study

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Introduction
Gender affirming hormone treatment (GAHT) may associate with higher risk of cardiovascular-metabolic disease and screening is recommended as part of clinical care. Long term prospective data are requested to tailor individual follow-up.
Objectives
To evaluate prospective changes in metabolic syndrome during 24 months of masculinizing or feminizing GAHT.
Methods
Prospective audit with patient's informed consent conducted at a public center of gender identity with annual clinical and biochemical evaluation. GAHT regimen followed international guidelines, and feminizing estradiol treatment was combined with cyproterone acetate. Study outcomes were BMI, waist, hip, blood pressure, lipid status, and HbA1c at baseline, 12 and 24 months. Metabolic syndrome was defined by obesity (BMI >30 kg/m^2, waist ≥80 cm, or waist–hip-ratio (WHR) >0.9), elevated triglycerides (TG) ≥1.7 mmol/l, HDL <1.0 mmol/l, blood pressure (BP) $\geq140/90$ mmHg, and HbA1c $\geq$ 5.6%.
Results
The cohort included 438 persons, 220 were undergoing masculinizing GAHT (TransM_TN, treatment naïve $n=113$, TransM_TO, treatment ongoing $n=107$) or feminizing GAHT (TransF_TN, treatment naïve $n=137$, TransF_TO, treatment ongoing $n=81$. At baseline, the median age was 22 years (19–28) and 26 years (24–37) in TransM_TN and TransF_TN, respectively. In transM_TN, waist, WHR, systolic BP, TG, and HbA1c increased from baseline to 12 months, whereas HDL decreased. Total cholesterol increased from 12 to 24 months. ≥2 metabolic syndrome criteria were present in $40/110=36\%$ at baseline and in $16/34=47\%$ at 24

months. In TransF_TN, weight, BMI, waist, hip, and WHR increased from baseline to 12 months whereas HbA1c, cholesterol, and TG decreased. From 12 to 24 months, BMI, waist, and hip increased. ≥2 metabolic syndrome criteria were present in 71/134=53% at baseline and in 17/42=41% at 24 months.

Conclusion

Metabolic and cardiovascular risk factors increased after GAHT, especially within the first year of GAHT initiation.

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P157

JOINT1886

Patient-reported outcomes in patients with primary adrenal insufficiency – A study from the register for organ-specific sautoimmune diseases (ROAS)

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Background

Despite modern evidence-based treatment, patients with primary adrenal insufficiency (PAI) experience reduced quality of life, increased fatigue, and diminished work capacity compared to healthy individuals. Patient-reported outcome measures (PROM) can provide better insights into patients' own experiences and perceptions, which can lead to improved follow-up and treatment.

Methods

Patients included in the Register for Organ-Specific Autoimmune Diseases (ROAS) with autoimmune PAI, aged 18 and older, completed annual electronic PROM questionnaires from 2018 to 2023. Patients answered questions regarding disease progression, medication use, work capacity, stress dosage, incidence of adrenal crises, symptoms of cortisol deficiency, and quality of life. The latter was evaluated using AddiQoL, a validated questionnaire for PAI.

Results

The number of responses increased from 179 in 2018 to 478 in 2023 (response rate 54%). At the time of diagnosis, the most common symptoms were fatigue (92%), increased pigmentation (79%), and weight loss (75%). The most frequent time interval from the first symptom to diagnosis was 3–12 months (35%, $n=169$), while 25% ($n=119$) reported symptoms occurring 1–3 years before diagnosis. In 2023, 308 patients (65%) reported using cortisone acetate tablets (median daily dose 37.5 mg), while 136 (29%) used Plenadren (median daily dose 25 mg). Plenadren use increase from 20% in 2018. A majority (70%) reported temporary dose increases in the past year. Most patients (94%) felt they had received adequate information about stress dosing of glucocorticoids, and 80% had access to hydrocortisone injections. The median daily dose for fludrocortisone was 0.13 mg. Fifty-nine patients (12%) experienced an adrenal crisis in the past year. In 2023, 267 patients (56%) had paid employment, 111 (23%) were retirees, and 123 (26%) had sick pension. A total of 131 patients (49%) reported no sick leave days, while 47 (18%) had more than 30 days of sick leave. The mean AddiQoL-30 score was 86±12 in 2023, unchanged from 2018 (86±13). The AddiQoL-8 score was also unchanged (21±5 for both years).

Conclusion

Patient-reported data provide valuable insights into the health and quality of life of patients with autoimmune PAI. The triad of fatigue, increased skin pigmentation, and weight loss were the most common symptoms at onset. Nearly one-third of patients are now treated with modified release hydrocortisone (Plenadren), and over 50% are employed. Quality of life in patients with PAI remains diminished but unchanged over the 6-year observation period.

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P158

JOINT376

Clinical characteristics and genetical analysis of HSD11B2 in three Chinese children with apparent mineralocorticoid excess: A case series

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Background

Apparent Mineralocorticoid Excess (AME) is a rare autosomal recessive disorder, characterized by a notably complex diagnostic process. To date, the majority of documented cases have been presented as individual case reports. This article aims to enhance the understanding of the course and prognosis of AME, by detailing the management protocols employed for patients with genetically confirmed diagnoses.

Methods

An analysis comprising three cases and a review of relevant literature were conducted to synthesize the insights and experiences derived from gathering clinical and laboratory data on patients.

Results

All three patients were born to non-consanguineous parents, were small for gestational age and exhibited severe hypokalemia, metabolic alkalosis, hypertension, nephrocalcinosis, and hypercalciuria. The glomerular filtration rate was normal in all cases. One patient experienced complications related to hypertension. Genetic analysis revealed biallelic recessive variations in the HSD11B2 gene in all three patients. Treatment with oral spironolactone and potassium chloride resulted in the normalization of both blood pressure and serum potassium levels in all patients.

Conclusion

This study presents the diagnostic and treatment experiences of three Chinese pediatric patients with AME type I. Through our analysis, four novel variants of the HSD11B2 gene were identified, thereby enhancing the genotype–phenotype spectrum associated with AME. Early genetic testing in patients suspected of having AME is beneficial for facilitating prompt diagnosis and the implementation of standardized treatment protocols. Such measures are essential for the prevention or mitigation of target organ damage, as well as for the reduction of associated morbidity and mortality.

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P159

JOINT1024

Establishment of an adult mouse adrenal *ex vivo* tissue culture model

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Introduction

Dysregulation of adrenal steroidogenesis can cause imbalances in the secretion of mineralocorticoids, glucocorticoids, and androgens, leading to various endocrine disorders. We have previously established and extensively validated a human fetal adrenal *ex vivo* culture model, but no comparable model exists for adult human adrenal tissue. Developing an adult adrenal tissue culture model could facilitate studies of de novo and altered adrenal steroidogenesis in normal adrenal glands and hormone-producing adenomas, providing valuable insights towards establishing clinically relevant functional models. Despite important species-specific differences between human and mouse adrenals, we initially aim to establish an adult mouse adrenal *ex vivo* tissue culture model.

Materials and methods

Three *ex vivo* culture techniques were evaluated using adult mouse adrenal tissue: hanging drop, porous membranes, and agarose gel fragments. Adrenal tissue was cultured for 24 hours, 48 hours, or 5 days. Following each culture period, tissue was fixed, paraffin-embedded, and assessed for morphology (hematoxylin and eosin staining), proliferation (BrdU incorporation), and apoptosis (cleaved PARP staining). Subsequently, adrenal tissue will be treated with ACTH (1 nM) or ketoconazole (1 μM) to stimulate or inhibit steroidogenesis, respectively and effects on steroidogenesis will be determined by analyzing the production of selected adrenal steroid metabolites in the collected culture media.

Results

Analysis of the three different culture approaches and culture periods are currently ongoing. The optimal culture method will be determined based on preservation of tissue morphology (including intact cortical zones), minimal apoptosis, sustained cell proliferation, and functional responses to steroidogenic stimulation and inhibition.

Conclusion

Preliminary findings suggest that *ex vivo* culture of adult mouse adrenal tissue is feasible. Ongoing analyses will identify the most effective culture approach, providing a critical framework for future investigations into adrenal steroidogenesis. This model represents a significant first step toward enabling studies on both normal and pathological adrenal function in adult adrenal gland tissue.

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P160

JOINT1750

Paediatric peripheral adrenal insufficiency: Rare causes in an observational cohort

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Objective

Peripheral adrenal insufficiency (PAI) is a rare, chronic condition causing life-threatening complications. The main cause is 21-hydroxylase deficiency. Identifying other rare causes is difficult but crucial to ensure timely diagnosis and optimal management. The objective of this study was to describe rare causes of paediatric PAI.

Design

Observational, retrospective, single-centre, cohort study

Methods

Descriptive analysis of data from patient files

Results

Of 213 patients younger than 18 years who were diagnosed with PAI between 1980 and 2023, 172 had assessable data, including 113 with 21-hydroxylase deficiency and 59 (52%) with rare causes of PAI. Rare causes included monogenic diseases ($n=38$, 64%, such as non 21-hydroxylase deficiency congenital adrenal hyperplasia(CAH), X-linked adrenoleukodystrophy, Triple A syndrome, MIRAGE syndrome, Xp21 continuous gene deletion syndrome, *NNT* deficiency), auto-immune disorders ($n=15$, 25%), and bilateral adrenal haemorrhage ($n=3$); in 3 patients, no cause was identified. Median age at diagnosis varied greatly depending on the aetiology: from 4 days of life for MIRAGE syndrome to 10.5 years for isolated auto-immune PAI. Symptoms of chronic and/or acute adrenal insufficiency were noted at presentation in 39 (66%) patients, including half with both chronic and acute symptoms. Median follow-up was 7.6 years and 28 (48%) patients attained adult height at last visit. The mortality rate was 6/59 (10%), with MIRAGE syndrome as the most common cause of death (4/6 deaths). Acute adrenal crisis occurred in 26 (45%) patients, usually due to poor treatment adherence. Excess weight was a common complication (16/59, 27%), not correlated with the daily hydrocortisone dosage. Data on puberty were available for 37 patients: puberty was normal in 26 (72%), early in 6 (17%), and delayed in 5 (14%). Of the 9 patients with CAH in post-pubertal ages, 3 (33%) experienced either precocious or advanced puberty and 2, both females, required puberty-inducing hormonal therapy (P450 oxidoreductase deficiency and P450scc deficiency, respectively). All 3 patients with *NNT* deficiency experienced precocious puberty, which was initially peripheral (Leydig cell adenoma, testicular adrenal inclusions) at about 5 years of age then central puberty. Statural growth outcomes were satisfactory: mean final height was -1.1 SDS in males and -0.4 SDS in females and median height in the 27 patients who did not attain their adult height during follow-up was -0.4 SDS.

Conclusion

The wide range of rare causes of PAI raises diagnostic challenges. In most cases, however, the cause can be determined, allowing optimal therapy. Treatment adherence deserves careful attention.

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P161

JOINT1335

Contribution of immunohistochemistry and *in situ*hybridization in BMAD and correlations with patient genotype

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Introduction

Bilateral macronodular adrenocortical disease (BMAD), formerly known as PBMAH for primary bilateral adrenocortical hyperplasia is an uncommon disease responsible for about 2% of overt Cushing's syndrome. The disease is clinically, biologically and radiologically heterogeneous. Our team has described four microscopic subtypes based on macronodule architecture and cell type proportion (clear, eosinophilic and oncocytic). Subtypes 1 and 2 correlate with the presence of pathogenic variants in *ARMC5* and *KDM1A* genes, respectively. *ARMC5* inactivation leads to accumulation of the A subunit of RNA polymerase II (POLR2A). We have also shown that bi-allelic inactivation of *KDM1A* occurs via loss of heterozygosity with deletion of the short arm of chromosome 1. The aim of this study is to describe the immunohistochemical and *in situ*hybridization characteristics of BMAD subtypes.

Patients and methods

Immunohistochemistry and *in situ*hybridization were performed on 4 patients of each subtype from the cohort of 35 patients previously described at our center. We performed immunohistochemistry (IHC) using antibodies targeting alpha inhibin, DAB2, HSD3B1, HSD3B2, CYP11B1, CYP11B2, CYP17A1, KDM1A and POLR2A proteins. Fluorescent *in situ*hybridization (FISH) was performed with 1p36/1q25 commercial probe.

Results

In each subtype, HSD3B2 preferentially stains clear cells whereas CYP17A1 stains eosinophilic cells contrary to cortisol producing adenomas (CPA) that co-express CYP17A1 and HSD3B2 (*Kubota Hum Pathol 2016*). HSD3B2 uniformly stains clear cells only in patients with a pathogenic variant of *ARMC5*, in BMAD. HSD3B1 and CYP11B1 stain all cell types in each subtype. In subtype 1 (*ARMC5*), there is a population of columnar eosinophilic cells expressing DAB2 without expressing CYP11B2. In patients with a pathogenic variant of *ARMC5*, contrary to other subtypes, all nodular cells strongly express POLR2A in contrast with non-nodular adrenal gland. In subtype 2 (*KDM1A*), alpha inhibin is highly expressed in eosinophilic cells, and KDM1A immunoexpression is lower than in the adjacent adrenal gland. Similarly, this subtype is the only one in which a deletion of the short arm of chromosome 1 is demonstrated by the 1p36/1q25 FISH probe.

Conclusion

The absence of HSD3B2 and CYP17A1 co-expression appears to distinguish BMAD from CPA, and these IHCs could provide a diagnostic marker for BMAD. HSD3B2 and POLR2A are strongly correlated with *ARMC5* pathogenic variants and, KDM1A IHC and 1p36/1q25 FISH probe distinguish *KDM1A* altered BMAD. These markers could be used to guide genetic investigations or to confirm the pathogenic nature of germline variants of undetermined significance.

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P162

JOINT2830

Direct detection of urinary free cortisol: Analytical and clinical validation of a new fully automated chemiluminescence assay

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Background

Measurement of 24-hour urinary free cortisol (UFC) is recommended for biochemical diagnosis of Cushing's syndrome (CS). However, measured cortisol concentrations differ depending on the test method. Results of chemiluminescence immunoassays (CLIA), in contrast to liquid chromatography–mass spectrometry (LC–MS/MS), may be impacted by the presence of cortisol metabolites in urine. Poor agreement across CLIA methods is primarily attributable to cross-reactivity and to whether or not an extraction procedure is performed. Accordingly, the Endocrine Society recommends using the upper limit of the method-specific reference interval (RI) as a cut-off in diagnosis of CS. We assessed the performances of a new automated CLIA that does not require extraction, and compared clinical performance to two other CLIAs and a LC–MS/MS method.

Methods
Analytical performance of the IDS Urinary Cortisol CLIA (Immunodiagnostic Systems Ltd, UK) was verified. Clinical performance was studied in 24-hour urine samples from 24 CS patients and 50 patients in which the diagnosis of CS was clinically suspected, but finally excluded. Results obtained by the IDS assay were compared to those from Beckman Access Cortisol CLIA (Beckman Coulter Inc, USA) without extraction, DiaSorin Liaison Cortisol CLIA (DiaSorin Spa, Italy) after extraction with dichloromethane and an in-house LC–MS/MS (CHU of Liege, Belgium). Analytical agreement across methods was estimated using Passing–Bablok regression and diagnostic performances were compared using clinical sensitivity, specificity, and accuracy.
Results
UFC concentrations measured with IDS were lower compared to Beckman (slope: 0.81, intercept: 0.31 µg/dl; R^2: 0.96), but higher than DiaSorin (slope: 1.45, intercept: 1.68 µg/dl; R^2: 0.75) and LC–MS/MS (slope: 4.09, intercept: 1.44 µg/dl; R^2: 0.73). At the RI-based cutoff (µg/24 h: IDS 324, Beckman 403, DiaSorin 83, LC–MS/MS 45), the IDS CLIA results exhibited 92% sensitivity and 100% specificity (Beckman: 83% sensitivity, 98% specificity; DiaSorin: 100% sensitivity, 56% specificity; LC–MS: 96% sensitivity, 82% specificity). At an optimized, method-specific cut-off providing 100% sensitivity (µg/24 h: IDS 306, Beckman 266, DiaSorin 171, LC–MS 44), specificity was 98% with IDS and DiaSorin CLIAs, 84% with Beckman CLIA and 80% with LC–MS/MS.
Conclusions
The new IDS CLIA is a clinically accurate automated method for measuring UFC concentration. As expected, due to the omission of an extraction procedure, the assay measures higher concentrations compared to LC–MS/MS and other CLIA methods. Comparison of 3 immunoassays and an LC–MS/MS method demonstrated acceptable correlation but significant differences in absolute concentrations. Using method-specific cut-offs are used, the new CLIA provides similar or better clinical sensitivity and specificity.

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P163

JOINT3292

Characterization of ferroptosis activation in primary mouse spheroids

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Background
Bacterial sepsis is a serious threat to homeostasis and is the most common cause of mortality in non-coronary intensive care units (ICUs). It is characterized by compromised function of several vital organs, including the adrenal glands. However, little is known about the mechanisms involved. Recently, it has been reported that iron overload and ferroptosis might be involved in sepsis-induced multiorgan damage. Our previous results indicated that the human adrenocortical cell line, NCI-H295R, is sensitive to ferroptosis induced by inhibiting glutathione peroxidase 4 (GPX4) and can be enhanced by active steroidogenesis. However, whether primary adrenal cells are also sensitive to ferroptosis and whether bacterial LPS can modulate this process remains unexplored until now.
Objectives
The main objective of this study was to investigate whether primary adrenal cells are susceptible to ferroptosis induction by known ferroptosis inducers or in septic conditions *in vitro* in 3D culture.
Methods
Primary adrenal cells were isolated from mouse adrenal glands and cultivated as 3D spheroids using AggreWell microwell plates and low attachment conditions. The sensitivity of 3D spheroids was tested by pharmacological inhibition of GPX4 using RSL3 and incubation with bacterial LPS. Spheroid diameter, cell viability (FDA/PI staining), lipid peroxidation (C11-BODIPY), and necrosis induction (LDH release) were measured 24 h thereafter.
Results
Our study demonstrated that administration of RSL3 negatively affected the morphology and size of primary adrenal spheroids, which were associated with enhanced lipid peroxidation and necrosis induction. These changes were mitigated by ferroptosis inhibitor, ferrostatin-1. Our preliminary data based on spheroids isolated from mice with adrenocortical cell-specific deletion of GPX4 support these results. However, no significant increase in lipid peroxidation or LDH release could be observed after LPS treatment.
Conclusions
In summary, our findings suggest that primary adrenal cells are susceptible to ferroptosis induction through direct inhibition of GPX4 but not bacterial LPS. Further experiments, including the detailed characterization of spheroids, especially those isolated from GPX4-deficient adrenal cells, are ongoing. Moreover, a more thorough molecular investigation of LPS effects on primary mouse spheroids is necessary to elucidate its potential involvement in adrenal necrosis.

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P164

JOINT3441

Treatment of primary aldosteronism improves cardiac autonomic function

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Introduction
Primary aldosteronism (PA) is among the most common causes for secondary hypertension. Cardiovascular mortality is influenced independently by aldosterone excess and sympathetic activation. Periodic repolarization dynamics (PRD) is an electrocardiographic marker of repolarization instability associated with sympathetic activity. It has shown promising results in predicting mortality and arrhythmias in patients with cardiovascular disease. Therefore, we analyzed PRD values of PA patients before and after specific PA treatment.
Methods
We included 85 patients, recruited from 2020 to 2022, who were part of the German Conn's Registry and retrospectively investigated PRD values using a high resolution ECG at baseline and at 6–12 months follow-up.
Results
Baseline PRD values could be significantly lowered after specific treatment at follow-up (2.39 deg2 vs. 1.66 deg2; $P=0.02$). MRA treated patients were the driver of this PRD reduction ($n=54$, 1.31 (0.81; 2.64)), as PRD reduction was not significant in the adrenalectomy group ($n=31$, 1.93(1.05; 5.13)). Baseline PRD correlated significantly with baseline aldosterone. Spironolactone dosage could not significantly be correlated to PRD reduction. In the MRA treatment subgroup, renin stimulation after treatment was not an independent factor in PRD reduction. Surprisingly, cortisol co-secretion was also not significantly correlated to PRD values at baseline.
Conclusion
PRD as marker of sympathetic activation could be shown to be reduced in PA patients after specific treatment, indicating a lower burden of sympathetic activation. The reduction was mostly due to patients treated with MRA. Further studies are necessary in order to determine whether PRD can be a long term prediction tool for cardiovascular mortality in patients with PA.

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P165

JOINT681

Steroidomics in adrenal tumors

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Background
Mild autonomous cortisol secretion (MACS) as well as non-functional adrenal incidentalomas (NFAI) are associated with increased metabolic and cardiovascular risk suggesting a subtle secretion of cortisol or of other precursors of steroidogenesis.

Aim
To investigate steroid metabolites levels in patients with MACS and NFAI benign adrenal tumours as well as in adrenocortical carcinomas (ACC). Controls were defined as patients with normal adrenals on imaging.
Methods
Liquid chromatography–tandem mass spectrometry (LCMS) was used for the steroidomics analysis of several steroid precursors [cortisol (F), corticosterone (B,CORT), 11-deoxycorticosterone (DOC), 11-deoxycortisol (11-DOC, compoundS), 21-deoxycortisol (21-DOF), aldosterone (ALDO), testosterone (T), dihydrotestosterone (DHT), androstenedione (A4), androsterone (AN), dehydroepiandrosterone (DHEA), dehydroepiandrosterone Sulfate (DHEAS), progesterone (P4), 17-hydroxyprogesterone (17-OHP4), pregnenolone (P5), 17-hydroxypregnenolone (17-OHP5), estradiol (E2), estrone (E1)] in the blood of 35 patients. The categorisation of patients in functional or NFAI was based on functional hormonal blood tests [1 mg overnight dexamethasone suppression test (ODST)] based on current guidelines. All ACC cases were confirmed histopathologically.
Results
A total of 29 patients (8 males) with adrenal tumors [($n=17$ with NFAI, $n=8$ with MACS and $n=4$ with ACC] and 6 controls were included. Tumor size was significantly higher in ACC compared to NFAI and MACS patients. Urinary-free cortisol (UFC) levels were 5-fold higher in ACC and 3-fold higher in MACS compared to NFAI patients (although within normal range for MACS) LCMS analysis showed that all the median blood steroid hormones levels were significantly higher ($P<0.05$) in ACC patients compared with NFAI, MACS and control patients except for aldosterone levels. Regarding patients with benign tumors, median levels of baseline morning cortisol, corticosterone, 11-deoxycorticosterone and 21-deoxycortisol were significantly higher in MACS compared with NFAI ($P=0.04$, $P=0.03$, $P=0.047$, $P=0.043$ respectively). Baseline median levels of cortisol, corticosterone, 11-deoxycorticosterone and progesterone levels were significantly higher in MACS compared with controls ($P=0.037$, $P=0.042$, $P=0.039$, $P=0.023$ respectively). Baseline median levels of 11-deoxycorticosterone were significantly higher in NFAI compared with controls ($P=0.01$) whereas progesterone and 17-OH progesterone were significantly lower in NFAI compared with controls ($P=0.002$, $P=0.04$). Among comorbidities hypertension, hyperlipidemia and diabetes mellitus prevalence was higher in patients with adrenal tumours compared to controls as well as between NFAI and controls.
Conclusions
All steroid hormones levels were significantly higher in ACC patients compared to patients with MACS and NFAI. Precursors such as 11-deoxycorticosterone, and 21-deoxycortisol could play a supplementary role to the routine hormones profile for the distinction of NFAI from controls or MACS.

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P166

JOINT3558

Cortisol secretion and its tissue sensitivity are associated with the comorbidities of obese patients without Cushing Syndrome

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Background
The tissue 'milieu' of cortisol, intended as cortisol secretion combined with its tissue sensitivity could have an impact on obesity and its comorbidities such as type 2 diabetes mellitus (T2DM), arterial hypertension (AH), depressive syndrome (DS) and cardiovascular disease (CVD), in subjects without Cushing Syndrome.
Objective
This study aimed at evaluating cortisol secretion together with glucocorticoids (GCs) receptor sensitivity through the determination of glucocorticoid receptor polymorphisms (GRp) in severely obese subjects, exploring their association with obesity's degree and comorbidities.
Methods
A total of 193 male subjects (age >18) suffering from severe obesity (BMI >35 kg/m^2) were consecutively enrolled in a cross-sectional observational study. For each patient we collected clinical history and presentation and performed blood tests for metabolic and gonadal function. We evaluated night-time cortisol blood levels and the morning cortisol after 1 mg of dexamethasone overnight suppresion test (OST); GRp (BclI, rs41423247; N363S, rs56149945 increasing the sensitivity and ER22/23EK, rs6189+ rs6190 reducing it) were evaluated using restriction enzymes. Both logistic regression analyses and a machine learning naive approach were used to explore the association of cortisol milieu with AH, T2DM, DS and CVD. Polysomnography was used to determine if decompensated obstructive sleep apneas were present, to adjust the analyses together with age, BMI and smoking habit (pack-years).
Results
In our cohort 74% of patients exhibited AH, 42% had T2DM, and 37% experienced varying degrees of DS according to the Beck Depression Inventory; the 17% had a history of CVD. At multivariate analyses cortisol levels after OST were associated with the presence of T2DM ($P=0.007$) and diabetic nephropathy ($P=0.025$), whereas GRp increasing sensitivity to cortisol were independently associated with AH ($P=0.04$) and CVD ($P=0.03$). Depression, did not show any significant correlation. Using 'Random Forest' machine learning analyses we found that the addition of GRp and hypogonadotropic hypogonadism to the known factors (such as hypertension, renal function, HOMA index, BMI and age) increased the prediction performance of CVD in obese patients.
Conclusions
The combined study of cortisol secretion and peripheral sensitivity to GCs in the absence of overt hypercortisolism seems to provide additional information on the mechanisms leading to the development of obesity comorbidities, both using classic statistical methods and machine learning naive approaches. If confirmed, this could have potential use in identifying subjects deserving specific treatments aimed at modulating GCs action.

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P167

JOINT3806

Impact of adrenal insufficiency on quality of life: clinical insights from a retrospective study

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Objective
The objective is to evaluate the quality of life in patients with gradual-onset adrenal insufficiency and assess its overall impact.
Materials and patients
This is a descriptive study conducted in our department, using the AddiQOL questionnaire, involving 48 patients with adrenal insufficiency who experienced episodes of acute decompensation between January 2022 and December 2024.
Results
Our study included 48 patients, of which 17 were men and 31 were women. The average age was 37 years, with 40% being patients with Addison's disease. Overall health-related quality of life was impaired in 73% of cases, while physical, social, and emotional health were affected in 93%, 82%, and 75% of cases, respectively. The most common symptoms were fatigue (100% of cases), abdominal pain (83%), nausea and vomiting (41%), loss of appetite (75%), insomnia (66%), constipation (33%), and diarrhea (25%).
Conclusion
The impairment of quality of life in patients with adrenal insufficiency remains significant, with a variety of symptoms, the most common being fatigue, which persists despite substitution therapy.

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P168

JOINT1406

11-Oxygenated androgens in healthy young men and women and the impact of hormonal contraceptives.

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Introduction
A novel interest in 11-oxygenated adrenal androgens (11-ketotestosterone, 11KT; 11-hydroxytestosterone, 11OHT; 11-ketoandrostenedione, 11KA4; and 11-hydroxyandrostenedione, 11OHA4) has emerged due to their contribution to androgen signaling through binding androgen receptors or as precursor metabolites. These androgens are predominantly produced by the adrenal gland, although evidence on enzyme distribution suggests that the androgens may be interconverted in peripheral tissues. A recent article investigating the association between adrenal androgens and contraceptive use found no association, albeit with a smaller sample size and combined contraceptive users rather than investigating combined hormonal contraceptives and gestagen containing contraceptives individually. A well-known effect of combined hormonal contraceptives is lowering of serum concentrations of testosterone, which is utilized for instance in treatment of polycystic ovary syndrome.
Material and methods
This study utilized data from the Fit Futures Study, a population-based longitudinal study following participants from adolescence into adulthood through three waves performed in 2010–2011 and 2012–2013, and the most recent third held in 2021–2022. The study was composed of questionnaires, clinical interview, physical examinations, and sampling of biological material. Specifically, this study utilized data from the third Fit Future study, in which 705 participants attended. Descriptive statistics were used to describe distributions of 11-oxygenated androgens. Independent *t*-tests and chi-square tests were used to compare variables between the sexes. Relation to exposure variables were assessed through independent *t*-tests or Pearson correlations and general linear models.
Results
The study included 305 males and 350 females with mean age of 26.9 (1.1). Males had 13–17% higher concentrations of 11-oxygenated androgens. Among the females, 32.6% used combined hormonal contraceptives, 11.7% used gestagen containing contraceptives, and 55.7% used non-hormonal contraceptives or no contraceptives. Gestagen containing contraceptives was found to have no association with 11-oxygenated androgens and was hence combined with non-hormonal contraceptives. Users of combined hormonal contraceptives had significantly lower levels of 11-ketotestosterone (16.6% means difference, $P = < 0.001$), 11-hydroxytestosterone (16.6% means difference, $P = < 0.001$), and 11-ketoandrostenedione (19.4% means difference, $P = < 0.001$) than the non-users and gestagen users.
Conclusion
Lower levels of 11-oxygenated androgens in CHC users may have direct clinical impact for treatment of hyperandrogenic conditions like polycystic ovary syndrome, in which 11-oxygenated androgens are elevated.

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P169

JOINT2808

Androgens as prognostic factors – the evaluation of septic patients

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Sepsis is a life-threatening disease posing a huge burden to healthcare systems. It remains one of the most frequent causes of the admissions to hospitals with high mortality of patients. Hence, early identification of patients threatened with worse course of the disease and death is crucial. The activation of hypothalamic–pituitary–adrenal axis is a very important part of organism's response to ongoing infection. The majority of published papers describes the role of cortisol in septic patients, however, the scarce data regarding androgens are inconclusive. For this prospective study 49 septic patients and 25 healthy controls were recruited. The concentrations of dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEAS), androstenedione, testosterone, cortisol, sex hormone-binding globulin (SHBG) and 28-day mortality were assessed. The severity of the disease was described as APACHE II (Acute Physiology and Chronic Health Evaluation II) scale and SOFA (Sequential Organ Failure Assessment) score. The data were collected in three time points: up to 24 hours of hospital admission, on the 2nd day of hospital stay and after reaching hemodynamic stability/day of discharge/the day prior/ 8–10th day of prolonged hospitalization. The concentrations of all examined hormones were changing within the course of sepsis ($P < 0.01$). Assessing 28-day mortality, nonsurvivors had higher DHEA in all time points (P: 0.027–0.051) with higher cortisol ($p = 0.016$) and androstenedione ($P = 0.020$) in the first time point. Among indexes, only cortisol/testosterone ratio was different in the first time point ($P = 0.031$). SOFA and APACHE results were lower in survivors in comparison to nonsurvivors. In first time point in both groups – survivors and nonsurvivors – DHEA values were not age-dependent. In third time point in nonsurvivors, contrary to survivors, DHEA concentrations did not change with patients' age. Additionally, lower BMI ($P = 0.020$; $HR = 0.8533$), higher cortisol ($P = 0.044$; $HR = 1.001$) and higher cortisol/testosterone ratio ($P = 0.001$; $HR = 1.002$) were risk factors for death. In logistic regression, DHEA and cortisol were feasible prognostic factors with AUC 0.71 and 0.73, respectively. In conclusion, DHEA and cortisol can be used as prognostic factors in sepsis. Low BMI, high cortisol and high cortisol/testosterone ratio are the risk factors for death. Androgens show various changes during the course of sepsis that differ between survivors and nonsurvivors groups. Those changes might be used for more thorough assessment of septic patients. However, the role of androgens in severe infection still needs in-depth explanation. Our better understanding of the disease might help define the most time- and cost-effective regimens of sepsis management always having patients' health in mind.

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P170

JOINT3622

INSM-1 – a new biomarker in the differential diagnosis of adrenal tumor lesions – a preliminary study

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Introduction
Diagnosis of adrenal tumors is based on various diagnostic tests: determination of hormone levels, biomarkers, performance of various functional tests, molecular tests, imaging studies, pathomorphological studies, etc., which are useful at various stages of the diagnostic and therapeutic process. Biochemical studies focus on the search for new biomarkers in the blood, that could be useful for differential diagnosis of neoplastic lesions in adrenal glands (benign / malignant, hormonally active / inactive lesions). INSM-1 (Insulinoma-associated protein 1) is a new neuropeptide that may have applications in oncological endocrinology. The peptide is produced in endocrine and neuroendocrine cells of the human body. The goal of this project was to initially evaluate the usefulness of INSM-1 in the differential diagnosis of adrenal tumors and PGL tumors.
Materials and methods
The study included 104 patients with various adrenal tumors and PGL (mean age 52 years, 94 females): 30 MACS, 12 CS, 3 ACC, 9 PA, 10 Myolipoma, 7 PHEO, 30 NFAA and 3 PGL. Diagnosis of individual tumors was made within current guidelines and confirmed by postoperative testing and/or drug treatment. Plasma INSM-1 levels were determined by ELISA immunoassay in all patients.

Results
In the groups studied (MACS, CS, ACC, PA, Myolipoma, PHEO and PGL), the sensitivity and specificity rates of the biomarker INSM-1 were determined. In MACS, the sensitivity and specificity rates were 77% and 57%, respectively, while in Cushing's syndrome they were 58% and 37%. In tumors associated with aldosterone secretion (PA), the sensitivity and specificity of INSM-1 were 56% and 29%, while in adrenocortical carcinoma (ACC): 67% and 47%. In catecholamine-secreting tumors, the respective sensitivity and specificity rates were: PHEO 57% and 23%, while in PGL they were 67% and 40%. In benign myolipoma tumors, both rates were: 50% and 43%.
Conclusion
Preliminary studies have shown moderate usefulness of INSM-1 in the diagnosis of hypercortisolemia (MACS, ACC) in adrenal lesions and paraganglioma (PGL) tumors.

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P171

JOINT3669

Endocrinological adverse effects of abiraterone acetate in the treatment of prostate cancer: Real-world prevalence

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Introduction
Abiraterone acetate (AA) is an approved treatment for advanced prostate cancer. As a CYP17A1 inhibitor, it suppresses adrenal androgen and cortisol biosynthesis, potentially leading to adrenal insufficiency (AI). In order to mitigate this risk, treatment regimens include prednisone (5 mg/day). Additionally, the accumulation of steroid precursors may, in some cases, result in mineralocorticoid excess syndrome (MES). However, real-world data on the incidence and management of endocrine adverse effects (EAE) associated with AA remain scarce.
Objectives
This study aimed to characterize the EAE associated with AA therapy, with a particular focus on MES, and to assess potential contributing factors to their development.
Materials and methods
We conducted a retrospective descriptive study of prostate cancer patients treated with AA, identified from the pharmacy dispensing registry at Hospital Clínic Barcelona (Spain) between January 1 and December 31, 2024. Clinical and biochemical parameters, medication use and cancer-related variables were analyzed.
Results
A total of 110 patients (mean age 74.9 years [range: 53–96], mean age at prostate cancer diagnosis 67 years [range: 49–94]) received AA during the study period. One confirmed case of MES (the only case referred to the Endocrinology Department) and nine probable but unconfirmed cases (characterized by new-onset or worsening hypertension, edema and three cases of hypokalemia) were identified, seven of which occurred within the first 12 weeks of treatment. No baseline or post-treatment aldosterone/renin measurements were available and cortisol was measured in only one case (3.2 µg/dl). No acute AI events were reported; however, two patients likely developed chronic AI after discontinuing AA due to disease progression (mean duration of AA and prednisone treatment: three months). Five deaths were recorded. No significant clinical or prognostic differences were observed between patients who developed probable ME and those who did not.
Conclusions
AA is an increasingly utilized agent in the management of prostate cancer, with potential EAE – including MES and AI – whose prevalence remains poorly characterized. Our findings contribute to the understanding of these adverse effects in a real-world setting. Recognizing and optimizing the preventive and therapeutic management of AA-associated EAE is essential to improving patient outcomes.

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P172

JOINT3763

Diurnal pattern of secretion of cortisol, Aldosterone and 18-hydroxycortisol levels in four biological fluids in healthy volunteers

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Background
Cortisol, aldosterone, and 18-hydroxycortisol are key adrenal steroids involved in metabolism, fluids homeostasis, and stress responses. Their secretion follows complex diurnal and ultradian rhythms. Due to their rhythmicity, adrenal hormones analysis following a single time-point measurement provides limited information on the state of the HPA activity and fails to inform on the nadir to peak concentrations.
Objectives
The primary objective of the study was to compare and correlate concentrations of cortisol, aldosterone and 18-hydroxycortisol in saliva, sweat and interstitial fluid to plasmatic levels,. The secondary objectives were to investigate the circadian rhythm of steroid profiles, including cortisol, aldosterone and 18-OH cortisol, in healthy volunteers and assess the influence of physical activity and dietary intake on these profiles.
Methods
A prospective study of 8 healthy volunteers with repeated sampling of blood, ISF, saliva and sweat during a 27-hour period was conducted.
1) 24 h adrenal steroids profiles in blood, interstitial fluid, saliva and sweat were measured by liquid chromatography–tandem mass spectrometry and analyzed.
2) Influence of a moderate bout of exercise and of meals on Free cortisol, 18-hydroxycortisol, and aldosterone variations were also assessed.
Results
Cortisol displayed a clear circadian rhythm, peaking in the early morning (0600–0700 h) and declining at night, with a strong correlation between serum and ISF. Aldosterone, known to be regulated by the renin–angiotensin system, showed an unexpected strong correlation with cortisol, suggesting a stronger influence of ACTH than previously described. Further, peak of Aldosterone were depicted after lunch and exercise. Saliva showed good correlations with serum for cortisol. Sweat analysis was unreliable for aldosterone and 18-hydroxycortisol due to low detectability but showed some correlation with serum cortisol levels.
Discussion
Our findings confirm ISF as a promising biofluid for real-time cortisol monitoring, given its correlation with serum variations despite slight temporal shifts. The data also challenge the conventional understanding of aldosterone regulation, highlighting a significant ACTH influence as well as the impact of meals and exercise on aldosterone secretion. Finally, these results underscore the limitations of single-point hormone measurements.

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P173

JOINT2334

Long-term impact of hypercortisolism on diabetes outcomes: A follow-up study

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Introduction
Chronic exposure to elevated cortisol levels in Cushing's syndrome (CS) is known to cause insulin resistance and hyperglycemia. While remission of CS often leads to improved glycemic control, some patients continue to experience persistent diabetes. This study aims to evaluate the long-term evolution of diabetes after the resolution of hypercortisolism.
Methods
A total of 22 patients previously diagnosed with CS were followed for an average of five years after achieving remission. Glycemic parameters, including fasting blood glucose (FBG) and glycated hemoglobin (HbA1c), were measured before and after treatment. In addition, insulin resistance (assessed using HOMA-IR) and beta-cell function (measured with HOMA-B) were evaluated. The occurrence of diabetes-related complications were also recorded.
Results
Most patients experienced a significant improvement in glycemic control following remission. On average, HbA1c decreased from 7.8% to 6.3% ($P=0.004$), and fasting blood glucose showed a similar decline. However, 41% of the patients (9 out of 22) remained diabetic five years after remission, with a mean HbA1c of 7.2% ($\pm$1.1%). This group displayed higher baseline cortisol levels ($P=0.02$) and greater insulin resistance (HOMA-IR: 4.1$\pm$0.9 vs. 2.3$\pm$0.7,

$P=0.01$) compared to patients who regained normoglycemia. Beta-cell function was also significantly lower in these patients (HOMA-B: 49.5±13.6 vs. 76.8±14.2, $P=0.03$). Among those with persistent diabetes, 33% developed microvascular complications, including two cases of diabetic neuropathy, one case of nephropathy, and one case of early-stage retinopathy.
Discussion
These findings suggest that although remission of Cushing's syndrome leads to significant improvements in glucose metabolism, a subset of patients continues to experience long-term metabolic dysfunction. The persistence of diabetes may be due to the prolonged effects of hypercortisolism on insulin sensitivity and pancreatic beta-cell function. Chronic exposure to high cortisol levels may induce irreversible metabolic changes, predisposing some patients to ongoing hyperglycemia despite normalization of cortisol levels.
Conclusion
This study highlights the importance of long-term metabolic follow-up in patients recovering from Cushing's syndrome. While many patients experience an improvement in glycemic control, a significant proportion remains at risk for persistent diabetes and associated complications. Identifying these patients early and implementing targeted interventions, such as lifestyle modifications and pharmacological treatment, may help mitigate the long-term consequences of hypercortisolism on glucose metabolism. Further research is needed to better understand the underlying mechanisms and to develop optimized management strategies for this patient population.

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P174

JOINT3422

Triple a syndrome: phenotypic and genotypic diversity and a novel AAAS gene variant

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Objective
Triple A syndrome (Allgrove syndrome), is a rare autosomal recessive disorder, characterized by achalasia, alacrima, and adrenal insufficiency due to adrenocorticotropic hormone (ACTH) resistance. This study aims to evaluate the phenotypic and genotypic characteristics of patients with Triple A syndrome.
Methods
This retrospective study included data from 10 patients from 7 families who were followed in the pediatric endocrinology clinic between 1996 and 2024. Demographic information, clinical findings, biochemical and genetic results of the patients were collected from their medical records.
Results
Ten patients (M/F=7/3) with a median age of 11 (range: 6–35) years were included. Consanguinity rate was 71% among 7 families. Alacrima was detected in all cases, while adrenal insufficiency and achalasia were observed in 9 patients (90%). Adrenal insufficiency and achalasia presented between 2–8 and 1.5–17 years of age, respectively. Additional clinical findings included mineralocorticoid deficiency (40%), epilepsy (40%), short stature (40%), osteoporosis (10%), osteopenia (10%), hypogonadotropic hypogonadism (10%), cryptorchidism (10%), anal atresia (10%), and congenital hip dysplasia (10%). Ectodermal and autonomic features included dry skin (60%), dry mouth (30%), hyperhidrosis (50%), and multiple dental caries (90%). Neurological findings included hyperreflexia (50%), quadriplegia (10%), speech delay (50%), mild intellectual disability (40%), and severe intellectual disability (10%). Dysmorphic features such as deep-set eyes, down-slanting palpebral fissures, prominent and large ears, pectus excavatum, arachnodactyly, and joint hyperextensibility were observed, along with thenar and hypothenar atrophy (40%). Genetic analysis identified the previously reported homozygous frameshift mutation c.1066_1067del (p.Leu356fs*) in the *AAAS* gene in 6 cases from 3 families. Despite having same mutation, two siblings from the same family exhibited phenotypic variability, with one not developing adrenal insufficiency. In another family, adrenal insufficiency and achalasia onset varied among affected siblings. One case had a 46,XY,inv(9)(p11q13) karyotype. Additionally, a novel pathogenic variant, c.145C>T (p.Gln49), was identified in the *AAAS* gene, leading to premature termination of the ALADIN protein. Notably, the coexistence of anal atresia, congenital hip dislocation, osteoporosis, hypogonadotropic hypogonadism, cryptorchidism, and dysmorphic features associated with this mutation has not been previously reported in the literature, suggesting a potentially unique phenotypic spectrum.
Conclusion
Phenotypic variability and genetic diversity in Triple A syndrome are noteworthy. The novel AAAS gene mutation is believed to cause a loss of ALADIN protein function, expanding the genetic spectrum of Triple A syndrome. This study highlights the critical importance of genetic analysis, particularly in patients presenting with core symptoms such as alacrima and adrenal insufficiency.

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P175

JOINT104

Reliability of morning cortisol in predicting the recovery of hypothalamic–pituitary–adrenal (HPA) axis in patients with glucocorticoid induced adrenal insufficiency

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Introduction
Glucocorticoids (GC) are widely used in managing chronic inflammatory conditions. Long-term exposure to GC leads to HPA axis suppression. Recovery of HPA axis is highly variable among patients and often Short Synacthen test (SST) is used in standard practice to assess HPA axis and to assist wean off glucocorticoids. This test requires a day care investigation unit and has cost implications. The joint clinical guideline by European Society of Endocrinology and Endocrine Society published in May 2024 addresses the management of this condition. Our aim was to assess the applicability of criteria suggested in the guideline to our patient population, accepting there is variability in cortisol assays.
Method
This is a retrospective study of 48 patients with GC induced adrenal insufficiency who underwent outpatient morning SST (IM tetracosactide 250 µg) at Aintree University Hospital, Liverpool, UK from February 2022 to January 2024. Pass result for SST (HPA axis recovery) was determined as 30-minute cortisol ≥ 450 nmol/l. We use a competitive immunoassay (electrochemiluminescence – Roche Gen 2) for cortisol measurements.
Results
There was a significant and strong positive relationship between morning cortisol and 30-min cortisol on SST (rs[46]=0.82, P-value<0.001). Statistically significant difference (P-value<0.001) was observed in the 0900 h cortisol of those patients who passed SST (median 308 nmol/l) compared to those who failed (median 154 nmol/l). Morning cortisol >300 nmol/l is more likely to predict HPA axis recovery (P-value< 0.001, Specificity 96%, PPV 92%). Meanwhile morning cortisol of <150 nmol/l is highly likely to predict adrenal insufficiency (P-value=0.001, Specificity 95%, PPV 93%). Among patients with morning cortisol between 150 and 300 nmol/l, there was no significant difference noted as 59% failed SST and 41% passed the SST.
Conclusion
Our study shows a linear relationship between morning cortisol and 30-minute cortisol on SST and the likelihood of passing the SST. This supports the guideline's emphasis to interpret 0900 h cortisol as a continuum with higher values are more indicative of HPA axis recovery. Morning median cortisol in our study was significantly different in those who passed SST compared to those who failed. They were very reflective of the cut offs values suggested in the guideline. Morning cortisol threshold >300 nmol/l and <150 nmol/l were statistically significant in our study to predict HPA axis outcome with high specificity and positive predictive values. SST use may therefore be limited for selective patients with borderline cortisol results needing GC withdrawal soon based on their clinical needs.

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P176

JOINT3368

WES as a Tool for Differential Diagnosis of Adrenal Insufficiency in Sudanese Children

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Studies of adrenal insufficiency (AI) in African children are rare and diagnosis is challenging, especially in resource limited settings where biochemical and genetic testing are restricted. We describe the genetic characterisation of a cohort of Sudanese children, identifying founder effects and commonly mutated genes that will improve their treatment, expand our knowledge of AI, and expedite diagnosis of future patients. 48 patients from 43 families (31M:17F) with presentation of AI paired with biochemical finding of low cortisol ± high ACTH were included in this study. Exclusion criteria were clinical and/or genetic diagnosis of CAH or Triple A syndrome. Additional co-morbidities observed in some patients included white matter changes, muscular dystrophy, gait abnormalities, cataracts, obesity, and deafness. Whole exome sequencing (WES), copy number variation analysis (CNV), variant prioritisation (Exomiser/QCI) and splice predictions (SQUIRLS) were performed as a genetic diagnostic pipeline. Variants were confirmed by Sanger sequencing and possible splicing mutations were functionally assessed using the Exon Trap vector (MoBitech). Genetic diagnosis was achieved for 26/43 families, with mutations in *ABCD1* (7), *NNT* (5), *AIRE* (3) the most affected genes. CNV analysis identified a *CYP11B1-2* fusion event and a deletion incorporating 5-exons of *AIRE*, and 2 downstream genes. This *AIRE* deletion was identified in 2 unrelated families and 3 patients from 2 families had a splicing defect in *NNT* (c.9193G>A) which resulted in partial exon skipping. Incidental findings in *MC4R*, *ADGRV1*, and *CNDP1* are likely to be causative of the obesity, cataracts and deafness, and abnormal gait respectively observed in patients. This study has not only diagnosed 60% of our Sudanese cohort but also identified commonly mutated genes and 2 possible founder effects. Sanger sequencing of bespoke candidate genes might provide a cheaper alternative, increase, and hasten the diagnosis rate of at-risk patients in resource limited settings.

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P177

JOINT105

Cognitive function worsens with increasing age and glucocorticoid dose in classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Background
Classical congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) is the most common cause of primary adrenal insufficiency in youth resulting in impaired cortisol synthesis and excess androgen exposures starting *in utero*. Children with CAH exhibit increased risk for developmental delay compared to unaffected children. As well, adolescents and adults exhibit differences in cognitive function including decreased reward-based inhibitory control and working memory. However, more needs to be understood about how clinical factors (e.g., treatments and disease severity) in CAH affect cognitive function from early childhood through adulthood. Thus, we aimed to investigate the connection between cognitive function, age, glucocorticoid dose, and genotype-based severity in patients with CAH.
Methods
A cross-sectional study through various stages of development was performed in 56 patients (4–23 years; 11.7±5.4 years, 55% female) with classical CAH due to 21OHD. All patients completed iPad-based testing of cognitive function (NIH ToolBox Cognition Battery) including: inhibitory control (Flanker), cognitive flexibility (Dimensional Change Card Sort), and working memory (List Sort). Patients were compared to a normative population mean of 100 utilizing Welch's *t* test. Within the CAH group, Pearson's correlations between cognition scores and age or glucocorticoid dose (mg/m^2 per day) were analyzed. Disease severity was categorized by *CYP21A2* genotype ($n=38$): Null (0% enzyme activity including deletions, large gene conversions; $n=18$) and Non-Null (category A: <1% enzyme activity, $n=15$; category B: 1–2% enzyme activity, $n=5$). Data are presented as mean ± S.D..
Results
Overall, inhibitory control (90.9±16.3), cognitive flexibility (95.0±18.5), and working memory scores (94.6±11.6) were lower in patients with CAH compared to normative mean (P's<0.05). Within the CAH group, inhibitory control ($R=-0.7$) and cognitive flexibility ($R=-0.4$) scores were inversely correlated to age (P's<0.01). In addition, inhibitory control ($R=-0.6$) and cognitive flexibility ($R=-0.5$) scores were inversely correlated to glucocorticoid dose (P's<0.01). Finally, inhibitory control was lower in Null (87.3±14.0) vs Non-Null (103.6±21.2, $P<0.01$) patients.
Conclusion
Our findings suggest that patients with CAH have worse inhibitory control and cognitive flexibility scores compared to unaffected individuals, that is also seen with increasing age and glucocorticoid dose. In addition, inhibitory control scores are lowest in those most severely-affected (Null genotype). Thus, it is important to consider the effects of clinical factors inherent to CAH on cognitive function throughout the lifespan.

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P178

JOINT867

Evaluation of the metabolic impact of modified-release hydrocortisone in patients with congenital adrenal hyperplasia: an observational cohort study

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Background
Congenital adrenal hyperplasia (CAH) is a genetic disorder characterized by impaired cortisol secretion and androgen excess. The mainstay of CAH treatment is glucocorticoid (GC) replacement, necessary to avoid adrenal crises and manage androgen excess. The delicate balance between GC under- and overtreatment is crucial to prevent metabolic and cardiovascular (CV) complications. The modified-release hydrocortisone (MRHC) formulation seems to improve hormonal control; however, there are few data on its metabolic impact.
Aim of the study
Evaluate the hormonal control and metabolic impact of MRHC treatment in patients with CAH.
Patients and methods
31 patients with CAH due to 21OH-deficiency (median age 28years) were included; clinical, metabolic and hormonal data were analyzed at baseline and after 6 and 12 months since MRHC switch. At baseline 10 patients were on long half-life GC treatment, 21 on immediate/dual-release hydrocortisone.
Results
During MRHC, there was a significant improvement in hormonal control, with a reduction in 17-OH-progesterone levels (median values: 474 nmol/l vs 61.5 nmol/l at 12 months, $P<0.001$) and androstenedione levels (22.2 nmol/l vs 10.7 nmol/l, $P<0.001$). Additionally, was observed a decrease in total testosterone in women (3.1 nmol/l vs 1.4 nmol/l, $P=0.001$) and an increase in the proportion of patients with good disease control (women 17% at baseline vs 36% at 12 months, $P=0.030$; men 23% vs 63%, $P=0.018$). Notably, there was a significant worsening in the lipid profile, with increases in total cholesterol (162 mg/dl vs 176 mg/dl at 12 months, $P=0.026$), LDL (90 mg/dl vs 104 mg/dl, $P=0.009$), and homocysteine levels (10.1 μ mol/l vs 12.6 μ mol/l, $P=0.044$) with only a slight improvement of triglycerides (70 mg/dl vs 59 mg/dl, $P=0.006$). Moreover, systolic ABP decreased in patients receiving long half-life GC therapy at baseline (125 mmHg vs 121 mmHg at 12 months, $P=0.007$). When assessing the CV risk profile, we observed a slight improvement in the VAI score, but no changes in the SCORE2, with 5 out of 11 patients remaining at high risk. No adrenal crises were reported and one patient discontinued MRHC due to insomnia.
Conclusions
MRHC was shown to improve hormonal control while maintaining a good safety profile. However, since patients with CAH are known to have a higher CV risk, the worsening of certain parameters should not be underestimated, although the clinical relevance of these findings requires further evaluation. In conclusion, we recommend evaluating the overall impact of available therapies to better tailor treatment for each patient.

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P179

JOINT3887

Active steroidogenesis increases the vulnerability of human adrenocortical cells to SARS-CoV-2 infection

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Background
The COVID-19 pandemic, induced by infection with severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2), resulted in a significant health burden worldwide. Previously, we demonstrated that SARS–CoV-2 could target human adrenal glands, increasing parenchymal inflammation and necrosis. However, little is known about the mechanisms that facilitate SARS–CoV-2 infection of adrenocortical cells and whether this coronavirus can directly affect the function of these cells.
Objectives
The current study examined the mechanisms involved in SARS–CoV-2 infection of adrenal cells. Furthermore, we investigate the hypothesis that COVID-19 conditions may alter the susceptibility of individual human adrenocortical cells to SARS–CoV-2 infection by affecting their entry receptors.
Methods
To this end, we infected the human adrenocortical cell line, NCI-H295R, with various strains of SARS–CoV-2 and compared the efficiency of infection through nucleocapsid staining and ultrastructural analysis of the infected cells. Moreover, we sought evidence of active replication and production of new viral particles in the adrenal cells using an additional plaque-forming assay. Finally, we induced steroidogenesis in the adrenal cells with forskolin (FSK) and examined its effects on the expression of SARS–CoV-2 receptors, infection efficiency, and coronavirus replication.
Results
Our results demonstrated that human adrenal cells are susceptible to coronavirus infection and support its replication. FSK activation of adrenal glucocorticoid production enhanced susceptibility, replication, and SARS–CoV-2 production in NCI-H295R cells. The latter was associated with increased expression of the primary SARS–CoV-2 entry receptor, ACE2, which involved the cAMP-PKA pathway. Furthermore, we observed that SARS–CoV-2 infection induced necroptosis and apoptosis in both infected and bystander cells.
Conclusions
To summarise, our results indicate that human adrenocortical cells are differentially affected by SARS–CoV-2 and that alterations in ACE2 expression, as demonstrated in the case of FSK-mediated steroidogenesis, may influence their susceptibility to coronavirus infection. Moreover, when supported by clinical evidence, this finding could elucidate the increased risk of complications in patients with GC overproduction, including those suffering from Cushing's syndrome.

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P180

JOINT902

Assessment of the association between cardiometabolic index (CMI) and metabolic dysfunction-associated steatotic liver disease (MASLD): A systematic review and meta-analysis

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Background
Metabolic dysfunction-associated steatotic liver disease (MASLD) is an emerging global health challenge, with cardiovascular mortality as its leading cause of death. The cardiometabolic index (CMI), a novel biomarker derived by multiplying the waist-to-height ratio (WHtR) with the triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-C) ratio, shows promise as a predictive tool for MASLD. This study aims to systematically evaluate the association between CMI and MASLD.
Methods
We performed a systematic review and meta-analysis adhering to PRISMA guidelines. A comprehensive search of PubMed, Scopus, Embase, and Web of Science was conducted up to January 2025. Studies reporting the association between CMI and MASLD in adults were included. Effect sizes, odds ratios (OR), and standardized mean differences (SMD) were pooled. Heterogeneity was assessed using I^2, and publication bias was evaluated via Egger's test. Sensitivity analyses and meta-regressions explored sources of heterogeneity.
Results
Seven studies with 41,122 participants were included. Individuals with MASLD had significantly higher CMI (SMD [95%CI] $=1.24$ [1.00, 1.48]; $I^2=98.1\%$). Studies with higher smoking prevalence, female proportion, elevated FBG, SBP, DBP, TG, and AST levels, and lower TC and HDL levels showed a lower SMD of CMI in MASLD compared to non-MASLD patients, while meta-regression indicated that age, BMI, WC, ALT, and LDL were not significant sources of heterogeneity. Each 1-SD increase in CMI was associated with roughly 2-fold higher odds of MASLD (OR [95%CI] $=2.33$ [1.78, 3.04]; $I^2=96.8\%$). Patients in the highest CMI quartile had substantially greater odds of MASLD compared to the lowest quartile (OR [95%CI]$=7.44$ [4.28, 12.95]; $I^2=91.8\%$). The pooled area under the curve (AUC) for CMI in predicting MASLD was 0.82 (95%CI: 0.80–0.84).
Conclusion
CMI emerges as a non-invasive predictor of MASLD with elevated levels serving as an early indicator for identifying individuals at risk, even before significant liver fat accumulation occurs. Its strong association with liver fibrosis underscores the importance of identifying and managing elevated CMI to slow disease progression and prevent complications such as cirrhosis or hepatocellular carcinoma. Furthermore, emerging therapies for MASLD not only reduce liver fat but also improve CMI components, highlighting its potential as a marker for treatment response. Future research should focus on refining CMI cut-off values and validating its applicability across diverse populations.

Keywords: Cardiometabolic index, MASLD, Non-invasive biomarker

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P181

JOINT1139

Is the 18 ng/ml cortisol cut-off at the 1 mg overnight dexamethasone suppression test effective with routine immunoassays? Comparison with LC–MS/MS

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Background
The dexamethasone suppression test (DST) is essential for assessing hypercortisolism. The cut-off of normal cortisol response after DST was set at 18 ng/ml by an extractive radioimmunoassay in 1989. Since then, poor accuracy and reproducibility were documented for non-extractive automated immunoassays used in routine laboratories. The influence of automated immunoassay performance on assessment of hypercortisolism remains under-investigated. Liquid chromatography–tandem mass spectrometry (LC–MS/MS) is recommended for accurate and sensitive steroid measurement.
Aim
To compare cortisol measurements from two automated immunoassays with LC–MS/MS in paired sera collected at baseline and after DST. To evaluate immunoassay performance in detecting hypercortisolism by the DST.
Methods
We included 477 patients with suspected hypercortisolism or adrenal incidentalomas. Cortisol was measured by Elecsys gen I in 260 (cohort 1), and by Access in 217 (cohort 2) subjects. All samples were measured by a validated LC–MS/MS method. We compared cortisol measurements in all samples between immunoassays and LC–MS/MS, estimated the prevalence of hypercortisolism according to the established cut-off for cortisol after DST (18 ng/ml) with each method, and performed ROC analyses to determine ideal immunoassay-specific cut-off.
Results
Elecsys gen I measurements were 32.5% and 6.1% higher, whereas Access measurements were −4.7% and −5.9% lower than LC–MS/MS in basal and

post-DST samples, respectively. Considering the cut-off of 18 ng/ml, Access determined a lower prevalence of hypercortisolism than LC–MS/MS in the overall cohort 2 (30.4 vs 36.4%, respectively; $P=0.001$); similar results were obtained for Elecsys gen I only within the adenoma subgroup of cohort 1 ($n=112$, 26.8 vs 34.8%, respectively; $P=0.049$). Using LC–MS/MS as the reference, Elecsys gen I determined 3.8% possible false positives and 6.9% possible false negatives in cohort 1. In cohort 2, Access caused 0.5% possible false positives and 6.4% possible false negatives. Accordingly, sensitivity and specificity were 79.6 and 94.2% for Elecsys gen I in cohort 1, and 82.3 and 99.3% for Access in cohort 2, respectively. Ideal hypercortisolism screening effectiveness was obtained at 15 ng/ml for Elecsys gen I (sensitivity: 97.7%; specificity: 80.8%), and 12 ng/ml for Access (sensitivity: 97.5%; specificity: 78.3%).

Conclusions

We observed a variable performance between different immunoassays and sampling conditions. In basal samples, Elecsys gen I largely overestimated cortisol levels, whereas Access was accurate. In post-DST samples, both determined a remarkable under-detection of hypercortisolism when using the recommended 18 ng/ml cut-off. We provided novel immunoassay-specific cut-offs. However, LC–MS/MS should be preferred to improve DST specificity and to establish harmonized cut-off.

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P182

JOINT1711

Harmonization of serum cortisol methods for dynamic testing

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Background

Dynamic tests are used in diagnosis and follow-up of endocrine disorders. Unfortunately, there is considerable variation in how these tests are performed, including the patient preparation and analytical methods used with different standardization. Despite these differences, the interpretation of dynamic tests is often based on fixed cut-off values. The (pre-)analytical variability means that dynamic test results are not similar between medical centers, leading to confusion and treatment delay. Dynamic testing for adrenal insufficiency or Cushing's syndrome includes measuring serum cortisol. Our aim is to explore whether the different serum cortisol methods used can be harmonized to improve the interpretation of dynamic tests.

Methods

Blood was collected from 45 participants. Females ($n=23$) were not using oral contraceptives. Sera were aliquoted, frozen and sent to 25 Dutch laboratories. Serum cortisol was measured using in-house LC–MS/MS ($n=5$), Roche Cobas ($n=4$), Siemens Atellica/Centaur ($n=6$), Beckman Coulter DxI/Access ($n=5$) and Abbott Architect/Alinity ($n=5$) cortisol assays. One of the LC–MSMS methods was checked against the IFCC Cortisol Reference serum Panel and set as the expert method. Passing-Bablok regression analyses were performed and within method variation was determined. Maximum allowable imprecision was set at 8%.

Results

Cortisol measurements in laboratories using the same cortisol assay showed an imprecision of $<8\%$ except for the Beckman Coulter assay (31% of samples $>$ 8%). Regression analyses showed good agreement between the LC–MS/ MS, Roche and Beckman Coulter and the expert method (slope 1.02, 0.99, 1.00 and intercept 1.1, 1.8, -7.0 nmol/L respectively), and slightly less for Abbott (slope 0.93, intercept 8.8 nmol/L). The Siemens assay showed significant deviation in slope (1.40) and intercept (-35 nmol/L).

Conclusions

This study shows that LC–MS/MS assays and Roche cortisol assays are well standardized and that harmonization is not necessary. Harmonization is possible for the Abbott assay whereas the Siemens assay requires re-standardization. The Beckman Coulter assay shows a high within–method variation that first needs improvement. Standardization or harmonization of serum cortisol assays along with aligning the preanalytical workup will pave the way for uniform interpretation of dynamic testing.

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P183

JOINT624

Prevalence and causes of negative genetic testing results in clinically diagnosed congenital adrenal hyperplasia: A research summary

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Background

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder commonly caused by mutations in the CYP21A2 gene, leading to 21-hydroxylase deficiency. While genetic testing is pivotal in diagnosing and managing CAH, a substantial proportion of clinically diagnosed cases return negative results, posing challenges for accurate diagnosis and treatment. Understanding the prevalence and underlying causes of these negative results is crucial for advancing diagnostic strategies.

Objectives

This review aims to evaluate the prevalence of negative genetic testing results in clinically diagnosed CAH cases and explore the genetic, technical, and methodological factors contributing to these outcomes.

Methods

A systematic review of 12 studies (1999–2024) encompassing over 2,000 patients was conducted. Data on genetic testing results, prevalence of negative findings, and identified causes were extracted. Studies utilized techniques such as whole-genome sequencing (WGS), multiplex ligation-dependent probe amplification (MLPA), and PCR-based sequencing to investigate mutations in CYP21A2 and related genes.

Results

The prevalence of negative genetic testing in clinically diagnosed CAH cases ranged from 14.4% to 44%. Common causes included:

- Complex genetic architecture: High-sequence homology between CYP21A2 and its pseudogene CYP21A1P, leading to gene conversions and undetectable mutations (Doleschall et al., 2017; Belyeu et al., 2023).
- Technical limitations: Insufficient coverage of testing panels, inability to detect large structural rearrangements, and low sensitivity of standard sequencing methods (Mireia Tondo et al., 2021; Marino et al., 2011).
- Rare or novel mutations: Variants outside commonly tested regions and mild phenotypes contributing to undetected cases (Krone et al., 2013; Ohlsson et al., 1999).
- Population-specific variations: Regional genetic heterogeneity, such as RCCX copy number variations in certain populations (Umaña-Calderón et al., 2021; Dina Fawzi et al., 2023).

Discussion

High-sequence homology and structural complexity in the CYP21A2 gene region remain significant challenges. Emerging techniques like advanced WGS and targeted software tools (e.g., DRAGEN) demonstrate improved sensitivity for small variants and rearrangements. However, access to these technologies is limited in many settings. Novel diagnostic strategies integrating MLPA, PCR, and computational tools are crucial for accurate genotyping in complex cases.

Conclusion

Negative genetic testing in CAH reflects a combination of genetic complexity and technical limitations. Addressing these gaps through advanced diagnostic technologies and comprehensive testing panels is essential for improving diagnostic accuracy, treatment outcomes, and genetic counseling. Future research should focus on refining testing methodologies and exploring the clinical relevance of novel mutations.

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P184

JOINT765

Friedreich ataxia and impaired steroidogenesis

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Introduction

Friedreich ataxia (FA) is an autosomal recessive disorder caused by an expansion of GAA repeats in the *FXN* gene, leading to impaired iron-sulfur (Fe-S) cluster

biosynthesis and mitochondrial dysfunction. Fe-S clusters are essential for the activity of type 1 enzymes (CYP11A1, CYP11B1, CYP11B2) involved in steroidogenesis. Animal models and human cell culture studies have demonstrated reduced testosterone and progesterone levels in FA, particularly in males, which has been associated with a more severe disease course. However, no clinical studies in humans have been reported to date. This study aims to investigate potential steroidogenesis abnormalities in patients with FA.
Methods
This retrospective study analyzed data from four FA patients aged 13–17 years (3 males, 1 female). Data were obtained from patient records, including pubertal stages, basal steroid hormone levels, and standard-dose ACTH stimulation test results.
Results
At Tanner stage 5, basal cortisol levels were near the lower limit in three patients (2 males, 1 female). Progesterone levels were below the detection limit (<0.2 ng/ml) in the same patients. Androstenedione and DHEA-S levels were within normal ranges for all patients. Standard-dose ACTH stimulation tests showed adequate cortisol responses in all cases. Total testosterone levels were low in two male patients (2.06 and 2.88 ng/ml; Tanner stage 5 lower limit: 3.5 ng/ml) and near the lower limit in the third (3.65 ng/ml). The female patient had a normal estradiol level (54 pg/ml) in the follicular phase.
Conclusions
Potential steroidogenesis abnormalities in FA are characterized by reduced progesterone levels and testosterone deficiencies, particularly in males. These findings align with experimental data suggesting that impaired Fe-S cluster biosynthesis affects the activity of type 1 steroidogenic enzymes. Despite low basal cortisol levels, adequate responses to ACTH stimulation suggest preserved adrenal reserve. The normal estradiol level in the female patient supports the hypothesis that these abnormalities may be sex-specific. Further studies with larger cohorts and advanced techniques such as LC–MS to analyze steroidogenesis intermediates are needed to better understand the impact of FA on steroidogenesis and gonadal function. Investigating the effects of testosterone therapy on disease severity in males with FA through clinical trials could provide valuable insights.

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P185

JOINT3334

Less for more? Outcomes of adrenal vein sampling over a 5-year interval from a single operator in a specialist referral centre

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Purpose
Primary aldosteronism (PA) is the leading cause of endocrine hypertension. Adrenal vein sampling (AVS) is the recommended technique in lateralising PA to distinguish unilateral from bilateral disease. The success of AVS guides clinicians in making informed decisions to manage and treat PA effectively. Successful AVS requires a technically-skilled and experienced interventional radiologist and global success rates vary between 41.1% and 99.2%. The aim of this study was to assess the success rate of AVS by a single operator in a single centre.
Methods
A retrospective, single-centre study of AVS procedures performed by a single operator between January 2020 and January 2025. Aldosterone and cortisol levels were measured on samples collected from the right and left adrenal veins and low inferior vena cava (IVC). Successful adrenal vein cannulation was defined as selectivity index (SI) >3 with adrenocorticotropic hormone (ACTH) stimulation ($n=110$), and SI >2 without ACTH stimulation ($n=2$).
Results
A total of 112 patients underwent AVS: 70 (62.5%) were men and 42 (37.5%) were women, with a mean age of 52 years (range 27–74). Bilateral adrenal vein cannulation was achieved in 103 of 112 (91.96%) AVS procedures. In patients in whom bilateral cannulation was not achieved, this was due to an inability to sample the right adrenal vein in all nine patients. In addition, two patients who had previously undergone adrenal/para-adrenal surgery on the left also underwent AVS, with successful cannulation of the right adrenal vein, but the left adrenal could not be located (likely consequent on the previous surgery).
Conclusion
We have shown that adopting a standardised approach to AVS with a single experienced operator can deliver high rates of technically successful procedures. Our findings are therefore consistent with earlier published series and support the case for concentrating delivery of AVS in high volume specialist referral centres.

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P186

JOINT2155

The follow up of 3 patients with apparent mineralocorticoid excess after 32 years

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Background
Apparent mineralocorticoid excess (AME) is a genetic disorder. It is caused by deficiency of 11 beta-hydroxysteroid dehydrogenase type-2 (11βHSD2) enzyme activity in the kidney. 11βHSD2 is a member of the short-chain alcohol dehydrogenase family, catalyzes the NAD^+-dependent dehydrogenation of cortisol so, converts cortisol to inactive cortisone. Circulating level of cortisol is 100- to 1,000-fold higher than aldosterone and it can occupy mineralocorticoid receptor and causes hypertension and hypokalemia with low renin and aldosterone
Case report
In this report, the success and pitfalls of medical therapy with spironolactone in 2 sisters and one brother after 32 years are described. At the time of diagnosis, the eldest sister was 14.2-years old. She had blood pressure (BP) of 260/140 mmHg, hypokalemia, retinopathy and left ventricular hypertrophy, polyuria and urinary incontinence. The brother was 11.6-years old and had general paralysis with blood pressure (BP) of 170/110 mmHg and serum potassium of 2 mEq/L. The younger sister was 4.16-years old with BP of 160/100 mmHg and serum potassium was 3.2 mEq/L. She had headache and occasional abdominal pain. Spironolactone treatment resulted in normal blood pressure and serum potassium level in all of the patients. They have lost from follow up for a long time. After 32 years, the eldest sister is 46 years old now, has two daughters. At the age of 36 years in her second pregnancy, she discontinued the medicine by herself. So, reduced left ventricular function with mitral and tricuspid regurgitation and renal failure were developed after child birth and renal transplantation became necessary. It resulted in cure of AME but she should take Immunosuppressant medicines lifelong. The brother is 43 years old. He has regularly taken one tablet of spironolactone twice daily all the time and is in good health without any complication. He has one 10-year-old son. The younger sister is 36 years old. She has not taken her medicine correctly and sometimes discontinued medicine for some period, so is taking medicines for her heart and hypertension, by administration of a cardiologist in her city.
Conclusion
Early and continuous treatment with appropriate dosage of spironolactone can improve hypertension and hypokalemia of apparent mineralocorticoid excess without end organ damage.

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P187

JOINT3258

Clinical significance of mild autonomous cortisol secretion associated with primary aldosteronism

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Introduction
Primary aldosteronism (PA) is the most common cause of secondary hypertension and a known risk factor for cardiovascular and metabolic disease (1). It may be associated with autonomous co-secretion of cortisol, which may represent an additional risk factor for the development of cardiovascular and possibly metabolic complications (2).
Materials and methods
We searched the database of patients with PA who underwent adrenal vein sampling (AVS) at the University Hospital Centre Zagreb between 2016 and 2024. The total of 140 patients were divided into two groups: patients with mild autonomous cortisol secretion (MACS) and those with normal cortisol in the overnight dexamethasone suppression test (ODST) or cortisol in 24-hour urine. MACS was defined as a cortisol finding in the ODST > 50 nmol/L or a cortisol finding in the 24-hour urine > 416 nmol. Of the total number of patients, 16% had MACS. We compared whether there was a statistically significant difference in metabolic parameters or cardiovascular outcomes in the two patient groups.
Results
Univariate analysis showed that there was a statistically significant difference between patients with MACS and those without MACS in the value of eGFR (89 vs. 95 ml/min per 1.73 m^2, $P=0.013$), in the use of hypolipemic medications (43% of

patients with MACS vs. 18% of patients without MACS, $P=0.007$) and in the occurrence of cerebrovascular disease (9% of patients with MACS vs. 0.9% of patients without MACS, $P=0.018$). A possible association with albuminuria was observed but needs to be further validated (57% of patients with MACS vs. 32% of patients without MACS, $P=0.073$). No significant differences in metabolic parameters or other cardiovascular outcomes were observed. In a binary logistic regression analysis after adjustment for age, cerebrovascular disease and lipid-lowering medication use, only lipid-lowering medication use was an independent predictor of MACS ($P=0.03$, OR 0.331, 95% CI 0.121–0.902).
Conclusions
MACS is associated with an increased incidence of cerebrovascular adverse events in patients with PA, while an increased incidence of albuminuria cannot be excluded either, which should be verified in a larger patient population.
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P188

JOINT3517

Salt wasting in infancy: Pseudohypoaldosteronism type 1 secondary to a novel genetic mutation

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Background
Pseudohypoaldosteronism type 1 (PHA1) is a rare, primary form of mineralocorticoid resistance. Infants typically present in the neonatal period with salt wasting, failure to thrive, dehydration and the biochemical findings of hyperkalaemia, metabolic acidosis and elevated plasma aldosterone and renin levels.
Case presentation
We report the case of an 18 day old male infant born to non-consanguineous parents at term with a birth weight of 3.68kg. He presented with poor feeding, lethargy and 11% weight loss. Biochemical investigations revealed severe hyponatraemia (118mmol/L) and hyperkalaemia (9.2mmol/L). He was normoglycaemic (4.3mmol/L) and had a normal pH (pH 7.37). He was initially treated for suspected congenital adrenal hyperplasia with intravenous fluids, stress dose intravenous hydrocortisone and treatment of hyperkalaemia. Broad spectrum antibiotics were commenced for suspected sepsis. His CRP was elevated at 223mg/L and his urine and blood cultures grew E. coli. He was treated with IV antibiotics for 14 days. His cerebrospinal fluid culture was negative. He was switched to oral hydrocortisone, fludrocortisone and sodium supplements and his electrolytes normalised within 24 hours (Na 135mmol/L and potassium 5.9mmol/L). His cortisol returned at 2219 nmol/L. His 17-hydroxyprogesterone (17OHP) also returned normal at 1.9 nmol/L (<20 nmol/L), ruling out a diagnosis of congenital adrenal hyperplasia. His medications were discontinued by day of life 30 as transient pseudohypoaldosteronism was suspected secondary to urosepsis. On weaning of these medications, his sodium dropped to 129mmol/L and his potassium rose to 6.2mmol/L, therefore treatment was restarted pending the results of further investigations. He had a significantly elevated aldosterone > 3656 pmol/L (102–670) and a raised direct renin 199.7mIU/L (9.0–103.5). As he required ongoing sodium supplementation despite resolution of his urosepsis, genetic testing was performed. He was successfully weaned off sodium supplements at 6 months of age and is currently 3 years of age with normal electrolytes off treatment.
Results
Genetics testing revealed that he was heterozygous for a pathogenic variant in gene NR3C2 (varint c.2145dupA; p.Glu716Argfs*28) causative for pseudohypoaldosteronism type 1 due to defects in the mineralocorticoid receptor. This variant has not been described in scientific literature prior to this. Parental genetics were carried out and this infant's mum was also positive for the above mutation.
Discussion
This case describes a rare novel genetic mutation causing pseudohypoaldosteronism in our patient. The main differential for this presentation is transient pseudohypoaldosteronism secondary to urinary tract malformation or urinary tract infection. This patients electrolyte abnormalities persisted despite treatment of his urosepsis prompting genetic testing.
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P189

JOINT2893

Glucocorticoid receptor isoform expression in peripheral blood mononuclear cells differs in varying states of glucocorticoid exposure

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Introduction
Glucocorticoids act via the glucocorticoid receptor (GR) to exert pleiotropic effects on all tissues, with heterogeneity in cellular response, aimed at regulating cellular and metabolic homeostasis. Recent advances in our mechanistic understanding of the GR demonstrate a more complex interplay of functions than traditionally considered. Multiple splice variants and translational isoforms of GR have been elucidated which contribute to cellular glucocorticoid sensitivity and may have diverse functions. The aim was to assess the GR isoform expression in PBMCs of individuals with varying states of glucocorticoid exposure.
Methods
Peripheral blood mononuclear cells (PBMC) were isolated from whole blood of healthy volunteers (HV), patients with endogenous Cushing syndrome (CS), adrenal insufficiency (AI) and treated with exogenous glucocorticoids for other conditions (GC). GR protein isoforms were measured via western blot. RNA was extracted from PBMC aliquots and RNA-Seq libraries prepared using Illumina Ribo-Zero plus and sequenced using NovaSeq X.
Results
PBMC were collected from 42 HV (15 male, 12 pre-menopausal and 15 post-menopausal females), 10 CS, 10 AI and 16 GC. The cohort were 50 ± 1.8 years old, with the GC group being older, and had a mean BMI 27.2 ± 0.8 kg/m^2 (which was significantly greater in the CS group). GR isoforms GRα-A, α-C, α-D1-3, -A and -P were identified in both the cytoplasm and nucleus of PBMCs across all groups. Isoforms GRα-C and D3 were the most frequently expressed ($n=69$). Cytoplasmic expression of GRα-C ($P=0.005$), GR-P ($P=0.01$), and GR-A ($P=0.009$) were lower in the GC group. After adjusting for age, BMI and sex/menopausal status, the lower cytoplasmic expression in of GR-P ($P=0.002$) in GC remained significant. No other differences were detected between groups including in nuclear isoform expression. Preliminary data suggest that isoform expression is correlated with both shared and unique gene expression. Genes correlated with GRα-A were enriched in pathways involving functions associated innate and adaptive immune function including T cell-mediated responses; GRα-D2 correlated genes were enriched in pathways associated with ubiquitin-proteosome function and GRα-D2 and GR-A-gene correlations were enriched in pathways associated with ATP production and mitochondrial function.
Conclusion
Previously described GR isoforms are present in PBMC of humans regardless of glucocorticoid exposure state. There appears to be an in vivo difference in gene regulatory function of individual isoforms which may contribute to the variation in clinical sequelae of glucocorticoid perturbations.
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P190

JOINT1651

Impact of cholesterol supplementation for critical illness-induced hypocholesterolemia in a mouse model of prolonged sepsis: Effect on muscle weakness and adrenal failure

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Background
Hypocholesterolemia is a hallmark of sepsis, associated with adverse outcomes. Both serum HDL- and LDL-cholesterol rapidly drop from the onset of critical illness onwards. Whether hypocholesterolemia necessitates intervention or merely reflects a marker of disease severity is unclear. We hypothesize that low cholesterol levels are potential contributors to ICU-acquired muscle weakness and adrenal failure and that supplementation with cholesterol can improve tissue cholesterol availability, thereby improving muscle and adrenal integrity. Our hypothesis was tested in a clinically relevant mouse model of prolonged sepsis.
Methods
In a catheterized mouse model of cecal-ligation and puncture-induced, fluid resuscitated and antibiotics-treated prolonged (5 days) sepsis, septic mice

received continuous IV-infusion of a bovine serum cholesterol mixture containing predominantly LDL-cholesterol (*animal study 1;* $n=51$), or human plasma purified HDL-cholesterol (*animal study 2*; $n=47$), as compared to placebo. Healthy mice served as controls. Plasma HDL-, LDL-cholesterol, CORT, TNF-α and total bile acids were measured, in addition to *ex vivo* specific muscle force, and adrenal cholesterol content (Oil Red O staining) and structure (H&E staining). Gene expression markers of inflammation (*Tnf-α*) and cholesterol synthesis (*Hmgcs1, Hmgcr*, *Fdft1*) were measured in the liver.

Results

In both studies, mortality was not affected by the cholesterol supplementation. In *animal study 1*, five-day LDL-supplementation in septic mice increased plasma LDL-cholesterol but not HDL-cholesterol as compared to placebo ($P<0.0001$) and attenuated the sepsis-induced reduction of adrenal cholesterol content ($P=0.0004$) but without improving the distortion of adrenal structure. LDL-supplementation had no additional effect on sepsis-induced loss of muscle mass and force. In contrast, plasma total bile acids were elevated and hepatic gene expression markers of cholesterol synthesis were overall decreased with LDL-supplementation as compared to placebo, whereas *Tnf-α* expression was further increased ($P<0.05$). Elevated plasma CORT and TNF-α were not affected by LDL-supplementation. In *animal study 2*, five-day HDL-supplementation of septic mice substantially increased plasma HDL-cholesterol and even more so LDL-cholesterol as compared to placebo ($P<0.0001$). HDL-supplementation attenuated the sepsis-induced reduction of adrenal cholesterol content ($P=0.006$) but without improving adrenal structure. Also, HDL-supplementation did not attenuate the sepsis-induced loss of muscle mass and force. Additional analyses are currently ongoing to further assess the impact on cholesterol homeostasis and functional markers in muscle, adrenal and liver tissue.

Conclusion

Cholesterol supplementation reversed hypocholesterolemia in prolonged septic mice, but without reversing adrenal structural changes or muscle function. Tissue-specific effects on inflammation and cholesterol homeostasis require further investigation.

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P191

JOINT2178

Suprarenal adenomas in adult Bulgarian CAH patients

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Background

Several studies have shown an increased prevalence of adrenal adenomas in adult patients with congenital adrenal hyperplasia (CAH) (1). However, data on the topic are still scarce, especially in East European countries.

Methods

The data of all adult patients with proven congenital adrenal hyperplasia in a single Expert Center for Rare Endocrine Diseases for the last 15 years have been explored. The prevalence and characteristics of adrenal formations (AF) have been described.

Results

Seventy-two CAH patients (60 women and 12 men) were included in the study. Four women and three men (16.7% of all) presented with AF. Patients with AF were significantly older than the other CAH patients (median 39.0 years [36.0–56.0] vs. median 27.0 years [18.0–57.0], $P<0.001$]). In three patients, visualized adrenal adenomas led to CAH diagnosis, while in the other four patients, CAH was diagnosed in childhood, with 3 of them showing poor compliance to corticosteroid therapy. In 6 of the patients, the AF characteristics were benign, while in one patient, adrenal carcinoma was found. The median size of AF was 41 mm (16–67), the largest formation being considered adrenal carcinoma; 2 of the AF were left-sided, 1 – was right-sided, and 4 – were bilateral.

Conclusions

The development of AF in adult CAH patients is associated with late diagnosis or poor compliance with corticosteroid therapy. Most AF in undertreated CAH patients are bilateral. More efforts should be made to diagnose simple-virilizing and late CAH forms early, even in countries with appropriate CAH neonatal screening. The timely transition from pediatric to adult endocrine tertiary centers is crucial for preventing complications in CAH patients.

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P192

JOINT3214

Congenital adrenal hyperplasia causing Gender dysphoria: The dilemma of being a boy or a girl?

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Introduction

In developed countries, female patients with classic forms of congenital adrenal hyperplasia (CAH) are diagnosed at birth or in early childhood, allowing prompt treatment with correct gender assignment. The impact of late diagnosis or late interventions of CAH on gender identity, sexual orientation and function has been previously described. Hence, we-herein- describe an unusual case of an 18-year-old CAH girl with gender dysphoria and deciding to be a male.

Objective

To demonstrate the dilemma of gender identity in female CAH patients with delayed interventions due to social and cultural issues.

Case summary

An 18-year-old patient born to consanguineous parents had presented in a southern Egyptian city with persistent vomiting, electrolyte disturbance, atypical genitalia noticed since birth, and was diagnosed with salt-wasting congenital adrenal hyperplasia. Treatment with prednisolone and mineralocorticoid was started. No gonads were palpable, virilization Prader IV staging. Ultrasonography of the abdomen and pelvis was done showing uterus, no testes, bilateral ovaries. Due to social problems, the patient was lost to follow-up. At the age of 12.5 years, patient sought medical advice with breast enlargement and did laparoscopy showing female internal genitalia, and confirmed there were no testes. Before planning for surgery, the patient had his/her first menstrual cycle through a common urogenital sinus. They gave the decision to the patient after being reared for 11.5 years as a male, and his parents and they asked for doing bilateral salpingo-oophorectomy and hysterectomy at the age of 13 years. Hence, it was preferred to be an infertile male rather than a fertile female. Intramuscular testosterone was given for 3 months only for further virilization. The patient presented to us at the age of 18 years on subdose of prednisolone (1.4 mg/m^2 per day), stopped mineralocorticoid therapy since 5 years. On examination, she/he had short stature, Breast Tanner 5, penile hypospadias (not operated), SPL 6 cm, stria rubra, and chordae. Moreover, body image discomfort, depressive symptoms, and gender dysphoria.

Conclusion

Social and cultural issues play a major role in the management of female CAH patients, whether as physicians we agree with or disagree. Disregarding CAH patients' clinical condition, and deprivation of medical care have major consequences psychologically and physically.

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P193

JOINT3732

A novel mutation in a female patient with congenital adrenal hyperplasia due to 11-hydroxylase deficiency: A case report

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Background
11-Hydroxylase deficiency is a rare form of congenital adrenal hyperplasia (CAH) caused by mutations in the CYP11B1 gene. This mutation disrupts cortisol synthesis, leading to overproduction of ACTH. Elevated ACTH results in excessive deoxycorticosterone (DOC), a weak mineralocorticoid, causing hypernatremia, hypertension, and hypokalemia. Female patients may exhibit virilization at birth, while male patients are often diagnosed later with premature puberty and hypertension. This case report describes a novel mutation in the CYP11B1 gene identified in a patient presenting with vaginal stenosis and premature pubarche.
Case presentation
A 6-year-old girl was referred to the endocrinology clinic at 4 months of age due to ambiguous genitalia. Physical examination revealed normal blood pressure and no hyperpigmentation. Genital examination corresponded to Prader Stage 3; karyotyping confirmed a 46, XX profile. Neonatal screening indicated elevated 17-hydroxyprogesterone levels, leading to an initial diagnosis of 21-hydroxylase deficiency. Hydrocortisone therapy was initiated, and vaginal repair was performed under stress dosing. However, genetic testing for 21-hydroxylase was negative, prompting discontinuation of the medication. At 3 years and 9 months, signs of androgen excess emerged, including acne and Tanner Stage B1P3 pubic hair development, with an advanced bone age of 7.5 years. Laboratory analysis showed LH at 0.11 mIU/ml and FSH at 0.8 mIU/ml, inconsistent with central precocious puberty, and a 17-OHP level of 4.71 ng/ml. Whole exome sequencing revealed a mutation in the CYP11B1 gene: chr8:143960454A > G, c.389T > C (p.Phe130Ser). Both parents were carriers, confirming the diagnosis of 11β-hydroxylase deficiency. Currently, at 6 years old, she is receiving hydrocortisone treatment (10 mg/m^2). Her bone age is now 8 years, with normal growth velocity and cessation of signs of androgen excess, maintaining a prepubertal state.
Conclusion
The CYP11B1 gene is associated with over 100 mutations, including missense/nonsense mutations, splicing errors, and various deletions and insertions. This report highlights a patient with CAH due to a novel CYP11B1 mutation, resulting in reduced enzyme activity and androgen excess, leading to clinical manifestations such as virilization and hormonal imbalances. Hormone replacement therapy is essential, but achieving the right balance can be challenging.

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P194

JOINT336

Quantification of plasma free cholesterol using LC–MS/MS: A potential screening marker for familial hypercholesterolemia in children

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Introduction
Familial hypercholesterolemia (FH) is a genetic disorder characterized by elevated levels of low-density lipoprotein cholesterol (LDL-c) from birth onwards, leading to an increased risk of premature cardiovascular events. Given that treatment for FH can start as early as 8 years of age, ideally, screening should be performed at a young age to enable early detection and intervention, leading to an optimal clinical outcome. However, universal screening for FH is not yet widely performed, and traditional biomarkers, including total cholesterol and LDL-c, leave considerable room for improvement in terms of sensitivity and specificity. Therefore, we explored the feasibility of using plasma free cholesterol as a potential screening marker for FH in children.
Methods
We developed and validated an LC–MS/MS method to quantify free cholesterol in plasma. Using this method, we analyzed plasma samples from three groups of children (aged 1 – 18 years): with a confirmed pathogenic FH gene variant ($n = 15$), those who tested negative for FH variants ($n = 9$), and a presumptively unaffected population ($n = 51$). Additionally, LDL-c, total cholesterol, HDL-cholesterol, non-HDL-cholesterol, triglycerides, lipoprotein(a), and apolipoproteins A1 and B were quantified.
Results
Free cholesterol and LDL-c levels were strongly correlated ($R^2 = 0.86$) in all children. Free cholesterol levels in children with FH (median (IQR): 1.76 (1.44–1.94) mmol/L) were significantly higher compared to unaffected children (1.32 (1.09–1.54) mmol/L) and the presumptively unaffected population (1.11 (0.94–1.23) mmol/L). Although free cholesterol levels were significantly higher in the FH group across all ages, this effect was more pronounced in children below 10 years old. To validate these findings and establish cut-off values for free cholesterol as a screening marker, further analyses will be performed in a larger cohort.
Discussion
Free cholesterol seems to perform comparably to LDL-c and total cholesterol in detecting FH and may offer several methodological advantages, such as a very small sample volume (5 μL) and high throughput. Therefore, free cholesterol may be a suitable biomarker for large-scale screening for FH in children, potentially improving early detection and treatment to prevent premature cardiovascular events.

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P195

JOINT1223

Comparison between Romanian and Flemish cohort of patients with PPGLs

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Introduction
Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors with a heterogenous clinical behaviour. Among solid tumors, PPGLs have the most strong genetic predisposition with a specific geographical distribution pattern.
Aim
To compare the genotype and phenotype characteristics from two cohorts of patients with PPGLs from two different geographical and historical regions of Europe: Romania and Belgium.
Material and methods
For Romanian cohort retrospective clinical, imaging and genetic (germinal) data was collected from electronic medical records of 140 patients consecutively diagnosed with PPGLs at 'C.I. Parhon' National Institute of Endocrinology between 1987–2020. For newly diagnosed patients the same data was prospectively collected between 2020 and February 2024. For the Flemish cohort, we retrospectively retrieve data of 67 consecutively registered patients diagnosed with PPGLs in Endocrinology, Pathology and Surgery Departments from Ghent University Hospital (Belgium) registry, between 2002 and 2020.
Results
In the Romanian cohort were included 140 patients with PPGLs, with a mean age at diagnosis of 47.9 ± 15.6 years. Ninety-seven (69.2%) were women, and 43 (30.7%) were men; 130 (92.8%) presented with PHEOs and 10 (7.2%) with PGLs. In the Flemish cohort were included 67 patients, with a mean age at diagnosis of

50 ± 19 years, 38 (56.7%) women, 29 (43.3%) men, most of them presented with PHEO 42 (63%) and 25 (37%) with PGL. Patients from Flemish cohort had a better access to genetic test (90% in Flemish vs. 63% in Romanian cohort) resulting a higher percentage of hereditary cases ($n=32$, 40% vs. $n=24$, 36%). Romanian patients presented most frequently with *RET – c.1902C>G (p.Cys634Trp)* ($n=22$, 68.7%), while Flemish patients with *SDHD – SDHD c.170-1 G>T* ($n=10$, 41.7%) pathogenic variant. Based on this genetic background, Romanian patients presented more frequently with bilateral PHEOs, compared to Flemish cohort (19.3%; $n=15$; vs. 7% $n=3$; $P=0.002$), while Flemish patients presented more often with multiple PGLs (24% vs. 0%).
Conclusion
We can conclude that the different prevalence of pathogenic variants related to hereditary PPGLs in Romania [*RET c.1902C>G (p.Cys634Trp)]* versus Belgium [*SDHx (SDHD c.170-1 G>T)*], could be considered as a founder effect. While Flemish patients are more frequently incidentally diagnosed and develop more often multiple PGLs, Romanian patients had a higher PHEO/PGL ratio and had higher proportion of bilateral PHEOs compared to Flemish population.

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P196

JOINT1636

Concordance between adrenal CT and adrenal venous sampling in defining laterality and biochemical outcomes in primary hyperaldosteronism

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Introduction
In primary hyperaldosteronism (PH), differentiating between unilateral and bilateral secretion is essential for defining treatment. Adrenal-CT imaging has limitations to determine subtype classification and lateralization, being adrenal venous sampling (AVS) the current test of choice. In this study, we aim to analyse, in our series, the degree of concordance between adrenal CT and AVS at stablishing subtype classification and lateralization in PH, as well as biochemical remission followed by adrenal-CT or AVS-guided adrenalectomy.
Materials and methods
A retrospective observational study of a cohort of patients with PH who underwent AVS with or without ACTH stimulation. Clinical, analytical, radiological data, AVS results, and biochemical success parameters according to PASO criteria were collected.
Results
Out of 69 patients, 38 underwent AVS, with a mean age of 54.4 years (s.d. ±8), 76.3% male. Median follow-up post-adrenalectomy was 5 months (IQR 3–10). Concordance was observed between AVS and CT in the subtype classification in 12 (31.5%) of the 38 patients ($P=0.006$). Adrenalectomy was performed in 27 patients, 19 of whom had both AVS and CT (one patient was excluded due to loss of follow-up). Biochemical cure was reached in 14 (77.7%) patients with AVS-guided adrenalectomy, with a correlation between CT and AVS in 8 of them (57.1%, $P=0.007$). Out of 8 patients with CT-guided adrenalectomy, 6 (75%) achieved biochemical remission, with a mean age at the time of surgery of 54.8 years, and the relation between lateralization by CT and biochemical cure was statistically significant ($P<0.001$).
Conclusions
The correlation of adequate lateralization between adrenal-CT and AVS observed in our series aligns with current literature: less than 40% of adrenal-CT results agree with AVS in subtype classification, and approximately only 50% show correct lateralization guided by CT compared with AVS. A high rate of biochemical remission was observed in those who underwent CT-guided adrenalectomy, despite a median age of 54.8 years. This could be explained by the fact that these were mostly patients with marked PH and unilateral image on CT.

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P197

JOINT3879

Clinical, biological and genetic characteristics in congenital adrenal hyperplasia due to 11-beta hydroxylase deficiency in a Tunisian center

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Introduction
11ß-hydroxylase deficiency is the most common deficiency after 21-hydroxylase deficiency, usually diagnosed following signs of virilization in a newborn or 46XX fetus, and later following hypertension with hypokalemia.
Patients and methods
This is a retrospective study of 19 patients with 11ß-hydroxylase block consulting the endocrinology department of Ibn Aljazzar Hospital Kairouan
Results
We report 19 cases; 12 male and 7 female, with a current mean age of 23 years. Parental consanguinity was found in 9 cases (47.4%). The mean age of diagnosis was 31 months. The circumstances of discovery were neonatal screening in one girl, hypertension in 5 patients, sexual ambiguity in two girls, precocious pseudo-puberty in two boys, and growth retardation in one case, renal failure in one patient, hemorrhagic stroke in one patient and infertility in one patient. 17 High blood pressure was diagnosed in 89,5% (17 cases/19). 17 hydroxy progesterone was elevated in all patients and corticosterone was elevated in four patients in whom it was performed. The genetic diagnosis showed a high prevalence of the p.G379 V mutation in the homozygous state in exon7 of theCYP11B1 gene. Surgical repair of sexual ambiguity was performed in 3 girls. The evolution was marked by the occurrence of left ventricular hypertrophy in two patients and hemorrhagic stroke in one patient. Testicular adrenal rest tumors were diagnosed in 7 males.
Discussion
11ß-hydroxylase enzyme deficiency is responsible for defective synthesis of cortisol and aldosterone, with accumulation of the upstream metabolites compound S and deoxycorticosterone (DOC), and excessive synthesis of adrenal androgens, resulting in different clinical forms depending on sex and age of onset. The hypersecretion of DOC and its metabolites, known for their mineralocorticoid action, can generate hypertension, which remains uncorrelated with DOC levels but can be responsible for serious complications.

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P198

JOINT2999

Evaluation of cardiovascular risk and hepatic fibrosis scores in patients with pheochromocytoma

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Introduction
Pheochromocytoma (PHEO) is a rare tumor characterized by excessive release of catecholamines. Although improvements in metabolic parameters are observed after surgery, the relationship between serum catecholamine levels and these changes has not been thoroughly investigated. The aim of this study was to evaluate the changes in metabolic parameters, cardiovascular risk and hepatic

fibrosis in patients with PHEO and non-functioning adrenal masses (NFA) after adrenalectomy and the relationship between these changes and preoperative catecholamine levels.
Methods
Between 2019 and 2024, patients with PHEO and NFA (adenoma or hyperplasia) who were admitted to the Endocrinology and Metabolic Diseases Clinic of Ankara City Hospital and underwent adrenalectomy were included in the study. Pre- and post-adrenalectomy measurements of glucose, biochemistry, hemogram, lipids, insulin, HbA1c, systolic and diastolic blood pressures, weight and BMI were recorded and compared. Preoperative serum and 24-hour urine catecholamine levels were recorded. We used the SCORE calculation model recommended by the Endocrinology and Metabolism Society of Turkey for cardiovascular risk prediction in Turkey (7). For liver fibrosis assessment, we used the Non-Alcoholic Fatty Liver Disease Fibrosis Score (NFS), AST to Platelet Ratio Index (APRI) and Fibrosis 4 (FIB-4) scores (10–12). Changes in metabolic parameters, cardiovascular risk scores and hepatic fibrosis scores were analyzed and the associations between preoperative catecholamine levels and these parameters were evaluated.
Results
In this study, 61 pheochromocytoma (PHEO) and 37 non-functioning adenoma (NFA) patients who underwent adrenalectomy were evaluated. HbA1c ($P<0.001$), HDL levels ($P=0.007$), systolic and diastolic blood pressure ($P<0.001$) and SCORE cardiovascular risk ($P=0.001$) decreased after adrenalectomy in PHEO patients, while triglyceride levels increased ($P=0.057$). Postoperative NFS score was significantly elevated in PHEO ($P=0.03$). A negative correlation was found between preoperative systolic and diastolic blood pressure and preoperative urinary dopamine in PHEO ($P=0.041$, $P=0.045$, respectively). A negative correlation was also found between preoperative urinary dopamine levels and preoperative FIB-4 ($r=-0.373$, $P=0.021$) and NFS ($r=-0.358$, $P=0.038$), as well as between urinary metanephrine levels and APRI score ($r=-0.286$, $P=0.03$). Preoperative urinary metanephrine levels were higher in patients whose FIB-4 score did not improve ($P=0.25$).
Conclusıons
The reduced SCORE and blood pressure after surgery in patients with PHEO suggest that early diagnosis and surgery play a critical role in reducing cardiovasculer mortality and morbidity. Preoperative elevated catecholamine levels may have a protective effect on liver fibrosis and it will be important to confirm these findings with new studies for long-term follow-up.

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P199

JOINT2553

Ensuring safety in adrenal insufficiency: A review of emergency hydrocortisone kit prescriptions

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Background
Adrenal crisis is a life-threatening condition needing urgent injectable hydrocortisone. Without prompt treatment, it can lead to severe complications. NICE Guidance recommends educating patients on sick day rules and providing them with emergency hydrocortisone injection kits.
Aim
The project aimed to determine the percentage of adrenal insufficiency patients prescribed emergency hydrocortisone kits.
Methods
A retrospective review of case notes from secondary Endocrine Clinics within the Swansea Bay University Health Board was conducted, examining demographic data, causes of adrenal insufficiency, and emergency hydrocortisone kit prescriptions.
Results
118 patients with adrenal insufficiency (47% Male; Mean age 60.5 ± 16.7 years) were included. Causes of adrenal insufficiency included Addison disease 35 (30%); secondary adrenal insufficiency 57 (48%); iatrogenic 15 (13%) and Others [Bilateral adrenalectomy, congenital adrenal hyperplasia, immunotherapy related adrenalitis] 11 (%). 15 out of 118 had immunotherapy related adrenal insufficiency (13 patients had hypophysitis and 2 had adrenalitis). Majority (77%) were treated with hydrocortisone and the reminder treated with prednisolone. All patients received sick day rule education and 92% (108) were prescribed with emergency hydrocortisone kit. In the last 12 months, 15 patients (9 with secondary adrenal insufficiency, 4 with Addison disease, 2 with iatrogenic) were admitted with adrenal crisis. Precipitating factor for adrenal crisis was infection (gastroenteritis, COVID, pneumonia, urinary tract infection). Out of 15 patients with adrenal crisis, 2 patients were not prescribed with emergency hydrocortisone injection kit.
Conclusion
Most patients with adrenal insufficiency were prescribed injectable hydrocortisone, and adrenal crisis can occur in all types of adrenal insufficiency. Educating patients on sick day rules and ensuring they have emergency hydrocortisone is crucial in preventing adrenal crisis. Notably, 13% of patients with an adrenal crisis had not received injectable hydrocortisone. Ensuring all patients (and/or their family members) receive education and emergency hydrocortisone injection techniques is essential for effective management and prevention of adrenal crisis. This study emphasizes the importance of consistent and comprehensive patient education and access to emergency treatment to mitigate the risks associated with adrenal insufficiency.

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Bone and Mineral Metabolism

P4

JOINT1843

Consistent reduction in rate of fracture with setrusumab therapy in patients with osteogenesis imperfecta: month 14 data from phase 2 of the orbit study

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Osteogenesis imperfecta (OI) is a rare bone disorder characterize by increased fragility and low bone mass. Setrusumab is a fully human anti-sclerostin monoclonal antibody that has demonstrated improved bone mineral density (BMD), strength, and remodeling in adult patients with OI. Here, we assess the efficacy and safety of setrusumab in children and young adults with OI through Month 14 of Phase 2 of the Phase 2/3 Orbit study (NCT05125809). Participants with OI Types I, III, or IV aged 5 to <26 years randomized 1:1 received setrusumab at 20 or 40 mg/kg monthly doses intravenously. After all participants had received setrusumab for 6 months, the 20 mg/kg dose was selected and all participants switched to this dose through the end of the study. 24 participants were assessed: 12/24 (50%) are female, 18/24 (75%) are <18 years of age, and 17/24 (71%) and 7/24 (29%) have OI Types I and III/IV, respectively. Participants received setrusumab for a mean 16 months at the time of analysis, and most (18/24, 75%) received bisphosphonates prior to enrollment. Baseline assessments of BMD showed continued improvements through Months 6 and 12. A mean (S.E.) change from baseline in lumbar spine BMD of 14% ($\pm2\%$) was observed at Month 6 and continued to 22% ($\pm3\%$) at Month 12 ($P<0.0001$). This equated to an improvement from baseline in BMD Z-score of 0.9 (±0.1) at Month 6 and 1.2 (±0.2) at Month 12 ($P<0.0001$). The baseline median annualized rate of skeletal fracture (excluding fingers, toes, face, skull, and morphometric vertebral fractures) prior to treatment of 0.72 decreased to 0 ($P=0.0014$). A reduction in fracture rate of 67% was calculated. No safety concerns were identified at Month 14. Treatment-emergent adverse events (TEAE) were consistent with the anticipated safety profile of setrusumab. Most reported related TEAEs (11/12, 92%) were mild (Grade 1), with no related serious TEAEs. Importantly, no cardiovascular TEAEs were reported through Month 14, and none of the reported TEAEs led to discontinuation of the study by any participant, or disruption in setrusumab treatment. Data from Month 14 of Phase 2 of the Orbit study indicated notable improvements in BMD with setrusumab therapy in participants with OI. We report a meaningful reduction in the annualized rate of skeletal fractures (67%) with setrusumab therapy. Overall, the findings herein support those data reported after 6 months of setrusumab therapy, confirming the robust and durable response in participants with OI.

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P5

JOINT1963

Pathophysiology of osteoporosis (PATHOS Study): role of hidden cortisol excess (HidHyCo) and its predictors in bone fragility, preliminary results

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Objective

To assess the prevalence of hidden hypercortisolism (HidHyCo) in a large sample of patients with osteoporosis or osteopenia plus the comorbidities possibly associated with cortisol excess and to evaluate the characteristics predictive of HidHyCo

Methods

From April 2023 to January 2025 we enrolled, in 5 Italian hospitals, 1194 patients without clinically overt hypercortisolism or other secondary causes of osteoporosis. Patients were referred for evaluation of osteoporosis or fragility fractures, or for osteopenia associated with ≧1 of these conditions: hypertension (treated ≧2 drugs or not well controlled, severe-hypertension), diabetes, history of cardiovascular events (CVE).

Measurements

In all patients we collected data regarding history of fragility fractures, diabetes, hypertension and CVE. Bone mineral density was measured with DXA at lumbar spine and femur and the presence of vertebral fractures (mVFx) was evaluated with thoracolumbar X-ray and the Spinal Deformity Index (SDI) was calculated. All patients performed twice: 1 mg overnight dexamethasone suppression test (DST) and, as confirmatory, 2day low-dose DST (2day-ldDST) for HidHyCo diagnosis.

Results

The presence of HidHyCo was detected in 26 out of 1192 patients (2.2%). As for the characteristics predictive of HidHyCo, here we present a preliminary analysis on 318 patients. Within this group, 43 patients (13.5%) showed DST> 1.8 mcg/dl, and in 14 (4.4%) HidHyCo was confirmed. Patients with and without HidHyCo showed no difference in prevalence of osteoporosis (75.0 vs 80.8%, $P=0.708$), CVE (8.3% vs 2.8%, $P=0.314$), diabetes (8.3% vs 12.7%, $P=1.00$) and severe-hypertension (25.0% vs 20.6%, $P=0.710$). Patients with HidHyCo showed a higher prevalence of mVFX or major clinical fractures (MajorFX) (75.0% vs 37.6%, $P=0.014$) and higher SDI (4.1 ± 6.3 vs 1.2 ± 2.4, $P=0.001$). In two separated logistic analyses, adjusted for age, osteoporosis, diabetes, severe-hypertension, the presence of a mVFX or MajorFX (odds ratio, 4.5 [CI, 1.14 to 17.37], $P=0.031$) and SDI (odds ratio, 1.2 [CI, 1.05 to 1.38], $P=0.006$) were associated with HidHyCo.

Conclusions

HidHyCo may be more common than is generally recognized in patients with bone fragility in whom other secondary causes have been excluded. The presence of mVFX or MajorFX and the SDI are associated with a higher risk of HidHyCo.

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P6

JOINT2294

Parathyroid surgery in children with sporadic and familial hyperparathyroidism

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Introduction

Primary Hyperparathyroidism (PHPT) in children is very rare and arrival of better imaging, minimally invasive parathyroidectomy (MIP) and intra-operative parathyroid hormone (IOPTH) monitoring is changing current surgical practice.

Method

Retrospective case notes review of children with PHPT who had parathyroidectomy between 1977 and 2022 at a single tertiary endocrine centre.

Results:

A total of 49 children (0.2–17 years, 24 boys) had parathyroidectomy for PHPT; 30 (7–17 years) for sporadic (sPHPT), 10 (6–16 years) familial (fPHPT, 6MEN1, 2 MEN2a, 2JT-HPT)) and 9 (0.2–3 years) Neonatal Severe Hyperparathyroidism (NSHPT). Children with sPHPT presented most commonly with abdominal symptoms (54%), incidental hypercalcaemia was reported in 12%. 44% of children with fPHPT had abdominal symptoms; 33% hypercalcaemia on screening. All children with NSHPT presented with poor feeding, behavioural change and/or developmental delay, except one with incidental hypercalcaemia. Preoperative corrected calcium was 3.12 ± 0.47 mmol/l (mean $\pm$ S.D.) in sPHPT, 2.97 ± 0.31 mmol/l ($P=0.4$) in fPHPT and 4.6 ± 1.6 mmol/l ($P<0.05$) in NSHPT. Pre-surgical treatment was most commonly hyperhydration and bisphosphonates; cinacalcet was used in 3 sPHPT and 4 NSHPT; calcitonin in 1 sPHPT and 2 NSHPT. In children with sPHPT ultrasound identified abnormal parathyroid in 91%; Sestamibi was abnormal in 89%; both abnormal in 76%. Of those with discordant imaging, 2/4 had abnormal ultrasound and normal Sestamibi, and 2/4 had abnormal Sestamibi and normal ultrasound. In children with fPHPT 86% of ultrasound images were abnormal, with Sestamibi in agreement except for 1 case showing no uptake. When imaging was performed in NSHPT (66%), no abnormal parathyroids were identified. Seventy percent of sPHPT children (all but one in the last 15 years) had MIP and 90% removal of 1 parathyroid). IOPTH monitoring was used in all operations since 2016. 20% of children with fPHPT had MIP and others had neck exploration with removal of 1(20%) – 4(20%) parathyroids. Eight children with NSHPT had 4 and one 3½ parathyroidectomies. Recurrence rate in children with fPHPT was 40% and 0% in sPHPT. There were no surgical complications.

Conclusion

Most children with PHPT are symptomatic and have high levels of calcium meeting criteria for immediate surgery. Ultrasound correctly identifies abnormal parathyroids and should be first line imaging in children with sPHPT and fPHPT, with Sestamibi recommended only when US negative. Imaging parathyroids is not helpful in NSHPT. Parathyroidectomy in children is safe in experienced hands and MIP with IOPTH should be the operation of choice for sPHPT.

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P200

JOINT641

Bone microarchitectural degradation in hypertensive patients: a population study

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Background

Hypertension is associated with increased bone fragility. However, the underlying mechanisms remain partly obscure. Evidence on the association of hypertension with bone mineral density (BMD) is conflicting, and changes in BMD are insufficient to justify the observed increase in fracture risk. Data on bone microarchitectural quality in hypertensive patients are scarce. The *in vivo* effects of anti-hypertensive medications on bone quality are poorly explored.

Objective

The primary aim of this study was to evaluate whether trabecular bone microarchitecture, non-invasively assessed by trabecular bone score (TBS), is altered in hypertensive patients. The association between anti-hypertensive medications and TBS was also evaluated as a secondary endpoint.

Methods

We conducted a cross-sectional analysis on 7053 subjects extracted from the 2005-2008 cycles of the National Health and Nutrition Examination Survey (NHANES), in which lumbar spine dual-energy X-ray absorptiometry (DXA) scans were acquired. TBS values were calculated from DXA images using dedicated software. The association between hypertension, anti-hypertensive medications and bone outcomes was assessed by regression analyses. Generalized additive models with spline smoothing were used to evaluate systolic and diastolic blood pressure as continuous predictors. All analyses were adjusted for relevant confounders.

Results

Hypertension was independently associated with lower TBS values (adjusted β = –0.010, 95%CI: [–0.016, –0.003], P = 0.008); on the contrary, no association was observed between hypertension and BMD T-scores at lumbar spine (adjusted β =

+0.04, 95%CI: [–0.05, +0.13], $P = 0.362$), total hip (adjusted β = –0.03, 95%CI: [–0.10, +0.05], $P = 0.474$), or femoral neck (adjusted β = –0.03, 95%CI: [–0.10, +0.03], $P = 0.294$). When evaluating blood pressure as a quantitative measure, a significant inverse relationship was observed between systolic blood pressure and TBS values ($P < 0.001$); conversely, no correlation was found for diastolic blood pressure ($P = 0.616$). No class of anti-hypertensive medications was significantly associated with TBS. Thiazide diuretics and angiotensin receptor blockers were associated with higher BMD values, whereas loop diuretics and non-dihydropyridine calcium channel blockers with lower BMD values.

Conclusion

Hypertension is associated with degraded bone microarchitecture, while no association is observed with bone mass. No significant relationships between anti-hypertensive medications and TBS were found. Associations between anti-hypertensive medications and BMD were consistent with previous reports. Overall, these results provide further insight into the relationship between hypertension and bone health. The specific degradation of bone microarchitecture may offer a plausible explanation for the increased fracture risk observed in hypertensive patients, independent of BMD.

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P201

JOINT883

The effect of low-dose cyclic 17-ß-estradiol administration on bone turnover in healthy postmenopausal women: a randomized controlled trial

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Background

Hormone therapy (HT) containing estrogen is an effective treatment for the prevention of bone loss in low-estrogenic states. Apart from the inhibiting effect of HT on bone resorption, studies have demonstrated that 17-β-estradiol also increases bone formation in the first 4 weeks of treatment. We hypothesized that this initial increase in bone formation is driven by a rise in serum 17-β-estradiol concentrations, as seen during the menstrual cycle of premenopausal women. Therefore, we investigated whether restoring a monthly cycle in 17-β-estradiol levels is beneficial for bone formation.

Methods

We performed an open-label randomized controlled trial in healthy postmenopausal women aged 45-60 years (without history of hysterectomy). Participants were randomized to transdermal cyclic (4-week cycle consisting of 2 weeks 25 mg/24h, and 2 weeks 50 mg/24h), continuous low-dose (25 mg/24h), or continuous standard-dose 17-β-estradiol (50 mg/24h) for 16 weeks. All participants also received continuous oral micronized progesterone 100 mg once daily. Endpoints of the study were the interaction between treatment and time on serum P1NP concentrations (bone formation) and on serum CTX concentrations (bone resorption). We measured P1NP and CTX every two weeks.

Results

The 48 participants had a mean age of 53.5 (SD 3.3) and had their final menstrual period at 50.5 (SD 3.8) years. P1NP increased in all groups between baseline and week 4, followed by a decrease between week 4 and week 16. The median decrease in P1NP levels (bone formation) was lower in the cyclic (-12.6 µg/l (IQR -20.4 – -0.7), $P = 0.03$) and low-dose group (-12.0 µg/l (IQR -18.4 – 1.8), $P < 0.01$) compared to the standard-dose group (-15.2 µg/l (IQR -29.1 – -8.7)). CTX decreased between baseline and week 16 in all groups. The median decrease in CTX values from baseline until week 16 was similar in the cyclic group (-143 ng/l (IQR -221.3 – -71.2), $P = 0.45$) compared to the standard-dose group (-176.9 ng/l (IQR -218.9 – -123.2)). However, CTX values (bone resorption) remained higher in the low-dose group (-112.2 ng/l (IQR -192.6 – -67.9), $P = 0.04$) compared to the standard-dose group. After 16 weeks of treatment, the mean changes in P1NP and CTX no longer differed between the groups.

Conclusion

Cyclic 17-β-estradiol administration resulted in higher bone formation over time compared to continuous standard-dose administration, while bone resorption did not differ between the cyclic and continuous standard-dose group. Thus, cyclic estradiol may improve bone health in the short-term.

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P202

JOINT1456

Assessing PTH dynamics following total thyroidectomy: an important tool for predicting hypoparathyroidism

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Perioperative PTH (pOPTH) has been proposed as a predictor of postoperative hypoparathyroidism in TT. ATA Surgical Affairs Committee 2018 estimated that PTH >15pg/mL 20 min after thyroidectomy obviates the need for calcium supplementation, while others prefer day postoperative measurement. We evaluate the dynamics of pOPTH and its relationship to preoperative and intraoperative findings in a large series of patients over fourteen years. Excluding patients with concomitant primary hyperparathyroidism, we retrospectively evaluated PTH concentrations preoperatively (prePTH), immediately post-operatively (immPTH), and the day after surgery (24hPTH). We evaluated the PTH trend and its relation to clinical characteristics, extent of surgery, autoimmunity, intraoperatively identified parathyroid glands, and thyroid weight. A total of 638 thyroidectomies were included between 2010 and 2024, 145 with central neck dissection (CND) and 132 males. Mean(SD) prePTH, immPTH, and 24hPTH were 52.1(22.6), 23.7(26.8), and 25.2(19.9) pg/mL, respectively. Globally, 24hPTH was 1.21(0.73) times higher than immediate, but 236 patients (37%) had 24hPTH lower than immPTH. This trend of increasing PTH levels did not differ between males and females, patients older than 50 years or younger (61.6% vs. 65.1%; $P = 0.40$), cases with and without autoimmunity (63.3% vs. 62.2%; $P = 0.85$), preoperative thyroid hyperfunction (58.5% vs. 64.4%; $P = 0.45$), or patients with 0-2 identified glands vs. 3-4 identified glands (60.1% vs. 62.9%; $P = 0.55$). Patients undergoing surgery for radiological, biopsy or cytological suspicion were more likely to have 24hPTH > immPTH than those undergoing surgery for clinical reasons (68.8% vs. 57.1%; $P = 0.002$). This trend was also significantly higher in patients who received CND (73.8% vs. 59.8%; $P = 0.002$) than in those who received TT alone. Out of 283 cases with immPTH < 15 pg/ml, 152 (53.7%) had a higher 24hPTH, 76 of them (24.4%) > 15 pg/ml. Thus, 207 patients (32.4%) had both below 15 pg/ml. Of the 229 patients with 24hPTH < 15, only 22 of them (9.6%) had immPTH > 15 pg/ml. Patients with decreasing PTH (24h PTH < immPTH) had higher prePTH [median(IR): 49(29) vs. 46(20) pg/ml; $P = 0.003$] and heavier glands at surgery [median(IR): 35.4(54.5) vs. 29.0(37.6) g; $P = 0.009$]. [PTH] showed a general trend towards an increase at 24 hours after surgery in relation to immediate measurement, particularly in cases with CND and those operated on for suspicion of malignancy, but there are cases with inverse dynamics, particularly in those with higher basal PTH and heavier glands at surgery. An immPTH may not be helpful in predicting low PTH, as a quarter of them recover PTH above 15 pg/ml at 24h.

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P203

JOINT1749

Quality of life assessed by HPES and HPQ28 questionnaires in patients with post-surgical hypoparathyroidism: correlation with biochemical and clinical features

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Background

Patients with hypoparathyroidism (HPT) experience impaired quality of life (QoL) due to poorly understood reasons. While QoL has traditionally been assessed using generic instruments such as the SF-36 questionnaire, disease-specific instruments like the HPES (Validated in several countries) and HPQ28 (validated only in German) have recently emerged, although their use remains limited.

Aims of the Study

Primary aims: to validate an Italian version of HPQ28 questionnaire; to evaluate QoL in hypoparathyroid subjects using both HPES and HPQ28. Secondary aims: to correlate questionnaire scores with clinical, biochemical and general

characteristics of subjects; to establish potential thresholds for each questionnaire that can assist clinicians in identifying when HPT impacts QoL.
Materials and Methods
Cross-sectional study including 179 subjects divided into three groups. After applying exclusion criteria (other systemic or psychiatric diseases and TSH levels outside the normal range), the final study population included: 51 thyroidectomised subjects with HPT, 49 thyroidectomised subjects without HPT and 57 control subjects without HPT or hypothyroidism.
Results
The Italian version of HPQ28 demonstrated a high reliability at test-retest (Intraclass Correlation Coefficient > 0.70) and the results for total and domain scores were consistent with those obtained with the German validated version, allowing effective assessment of symptom burden. Patients with HPT showed a significantly impaired QoL at HPES-impact (20.5% vs 7.8%, $P = 0.023$) and higher symptom burden at both HPQ28 (29.8% vs 20.2%, $P = 0.042$) and HPES-Symptom (35.8% vs 16.2%, $P = 0.011$) compared to hypothyroid patients. Symptom burden was correlated with female gender in both HPQ28 ($P = 0.040$) and HPES-Symptom ($P = 0.037$) as well as with age at HPQ28 ($P = 0.042$), but not with biochemical parameters such as serum calcium or calcium-phosphorus product, whereas QoL, as measured by HPES-impact was unrelated to general, clinical, and biochemical characteristics. However, analysis of questionnaire results by calcium quartiles revealed a trend toward improved QoL in patients with calcium levels between 8.4 and 8.9 mg/dL ($P = 0.051$). Receiver operating characteristic (ROC) analyses and the Youden Index calculation identified provisional cutoffs (HPES-impact: 16.10%; HPES-Symptom: 18.22%; HPQ28: 22.61%) to better interpret scores after single administration. Questionnaire score below these cutoffs may identify patients with lower impact of HPT on QoL and symptom burden.
Conclusion
This study highlights the significant impairment of QoL in HPT, underlines the usefulness of disease-specific questionnaires, and confirms that QoL and symptom burden do not appear to be related to biochemical data.

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P204

JOINT2461 Switch from rhpth1-84 to transcon PTH with individual dose adjustment in adult hypoparathyroidism – results for 40 patients one month after treatment transition

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Introduction
Parathyroid hormone (PTH) replacement therapy is a relatively new treatment option for chronic hypoparathyroidism (HypoPT). As the previously approved rhPTH1-84 is no longer manufactured, patients need to switch to an alternative replacement therapy. Palopegteriparatide (TransCon PTH) is a long-acting, slow-release molecule of PTH1-34 that was recently approved by the EMA and FDA. In this retrospective multicenter study, we describe our experience with the initial phase of switching from rhPTH1-84 to TransCon PTH.
Methods
We analyzed data from 40 patients with chronic postsurgical HypoPT ($n = 37$) or nonsurgical ($n = 3$) HypoPT during the change of treatment. In Germany, rhPTH1-84 treatment was only available for patients not adequately controlled through conventional therapy or with complications, and only few patients received the expensive treatment. TransCon PTH was available during a compassionate-use program or used after officially becoming available in Germany starting January 2024. Independently of the last prior rhPTH-1-84 dose, all patients were started on 18 µg of TransCon PTH with dose adaptation, and adverse events were documented.
Results
Within the first month of transition, 80% ($n = 32$) of patients needed individual adjustment of their TransCon PTH dose. Specifically, 38% needed a dose reduction to between 9 and 15 µg, while 43% ($n = 17$) required an increase to 21-27 µg. Adjustments by treating physicians was based on serum calcium levels with the goal of calcium in the lower normal range (in 62 % cases), or dependent on symptoms. The previous rhPTH1-84 dose correlated positively with the adjusted TransCon PTH dose ($r = 0.4$; $P = 0.01$). The treatment change was associated with moderate or mild symptoms. From 34 patients documented, 38% ($n = 13$) reported headache, 38% ($n = 13$) muscular spasms or arthralgia, 24% sleep disturbance or fatigue, 21% ($n = 7$) nausea, 21% palpitations, 15% injections site reactions, and 15% other gastrointestinal symptoms ($n = 5$). Ten patients reported no negative symptoms.
Conclusion
Switching treatment from rhPTH1-84 to TransCon PTH using the initial dose of 18 µg proved to be efficient independently of the prior rhPTH1-84 dose. Adverse events were frequent, albeit mild to moderate and no patient withdrew from treatment.

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P205

JOINT1460

Bone health in cleidocranial dysplasia: a large single-centre UK case series and literature review

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Introduction
Cleidocranial dysplasia (CCD) primarily affects intramembranous ossification, causing hypoplastic/aplastic clavicles, delayed cranial suture closure and dental abnormalities. Endochondral ossification can also be altered with impairment of bone mineral density (BMD), but data are limited.
Methods
Three databases (Embase, Medline, Cochrane) were systematically screened for publications assessing BMD in CCD. We reviewed clinical records of our CCD cohort. Collected data included DEXA assessments (lumbar spine [LS]-BMD, total body less head [TBLH]-BMD), evidence of vertebral (VF) or long-bone fractures and bisphosphonate treatments. LS-BMD of patients with height $<$-2/$>$2 SDS was adjusted using BMAD.
Results
Literature review identified 29 patients (51.7% females, 62.1% children). DEXA scan was performed in 86.2% cases, Qualitative-Ultrasound and X-Rays in the remaining. The average LS-BMD Z-score was -1.91 ($\pm$1.16), with paediatric population displaying lower scores (-2.26$\pm$1.05), particularly in females (-2.53$\pm$1.14). Adults LS-BMD Z-score was -1.38 ($\pm$1.17). Fractures were reported in 27.6% patients. Our cohort consists of 30 paediatric patients. Twenty-four (75% males; 66.7% prepubertal; average-age 9.4 years, 5.2-17.2) had $\geq$1 DEXA scan performed. Median LS-BMD Z-score resulted -1.65 (IQR 1.84), being $\leq$-2 SDS in 41.7%. Similarly, TBLH-BMD Z-score was -1.75 (1.60) and $\leq$-2 SDS in 37.5%. Osteoporosis was diagnosed in 16.7%, always VF-related and treated with bisphosphonates. Two patients reported trauma-related long-bone fractures.
Discussion
Both literature and our cohort showed low LS-BMD Z-scores. Although the lack of height-adjustment of published cases may underestimate LS-BMD, our cohort supports these findings, as 41.7% had Z-score $\leq$-2 SDS. Additionally, LS-BMD was significantly lower in prepubertal patients, highlighting pubertal influence on BMD. Even TBLH-BMD resulted low: interestingly, paediatric females showed significant lower Z-scores than males. However, the lack of height-adjustment might have overestimated the Results. Although identification of pathological fractures in published cases is hindered by the lack of details, 16.7% of our cohort met osteoporosis criteria. Finally, there was no association between LS-/TBLH-BMD Z-scores and VF: these parameters might not independently predict VF.
Conclusion
Our work emphasizes the need of screening programs for low BMD in CCD patients. DEXA assessment and bisphosphonate treatment should be considered

Comparison of LS-BMD and TBLH-BMD Z-scores (Mann-Whitney test).

	Male vs female		Prepubertal vs pubertal	
	U-statistic	*P*-value	U-statistic	*P*-value
LS-BMD	69.5	0.32	31.5	0.049*
TBLH-BMD	86	0.035*	40.5	0.16

Association between LS-BMD or TBLH-BMD Z-scores and VF (logistic regression).

	B-coefficient	*P*-value
LS-BMD	-0.134	0.743
TBLH-BMD	-0.206	0.688

in paediatric age, with a yearly follow-up monitoring, aiming prevention and treatment of osteoporosis.

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P206

JOINT1769

Serum phosphate as a marker of disease severity in primary hyperparathyroidism

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Serum phosphate (P) is typically reduced or low-normal in patients affected by primary hyperparathyroidism (PHPT) because of the lower expression of sodium phosphate cotransporter type2a protein in the proximal renal tubule driven by elevated PTH levels. However, current guidelines on PHPT management do not specify a P level threshold or offer recommendation regarding this parameter. To our knowledge, few studies have explored the relationship between P levels and the clinical and biochemical features of PHPT. We retrospectively evaluated 425 consecutive patients, 350 females and 75 males, affected by sporadic PHPT referred to our outpatient clinic from 2018 to 2023. Eighty-six (20%) patients were classified as symptomatic and 339 (80%) as asymptomatic according to the Guidelines from the Fifth International Workshop. Hypophosphatemia (HypoP), defined as phosphate (P) levels <2,5 mg/dL, was found in 245/425 (57%) patients and it was mild (2-2,5 mg/dL), moderate (1-1,9 mg/dL) and severe (< 1 mg/dL) in 183 (75%), 62 (25%) and 0 cases, respectively. P levels were significantly lower in males than in females (2.14±0.43 *vs.* 2.50±0.43), in patients with symptomatic vs. asymptomatic PHPT (2.34±0.49 *vs.* 2.46±0.44) and in those with nephrolithiasis (2.31±0.44 *vs.* 2.50±0.44), but not in patients with osteoporosis at any site (lumbar, femoral sites and 1/3 distal radius) or fragility fractures. Patients were further divided into two groups based on the presence or absence of hypoP. According to the above data, hypoP patients were significantly more frequently males, symptomatic and stone formers, but not osteoporotic. Moreover, patients with hypoP had a more severe biochemical phenotype namely significantly higher PTH (82 *vs.* 65 ng/l), ionized calcium (1,51 *vs.* 1,43 mmol/l), total serum calcium (11,1 *vs.* 10,7 mg/dL) and 24-h urine calcium excretion (360 *vs.* 244 mg) and significantly lower 25(OH) vitamin D levels (28 *vs.* 32 mg/l). No significant correlation was found between P levels and bone turnover markers (alkaline phosphatase, osteocalcin and S-CTX), T-score at any site or trabecular bone score TBS values. All patients, except one, with moderate hypoP met at least one surgical criterion. In conclusion, hypoP is associated with a higher risk of nephrolithiasis but not osteoporosis in PHPT patients. The question of whether moderate hypoP could serve as a reliable, cost-effective, and easily accessible criterion for parathyroidectomy, particularly in cases where evaluating all systemic complications is challenging, remains an open question.

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P207

JOINT2234

Classification of bone turnover and calcium metabolism markers based on the molecular subtypes of osteogenesis imperfecta

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Introduction and Aim
Osteogenesis imperfecta (OI) is a genetic disorder characterized by bone fragility, with molecular subtypes influencing its severity and clinical presentation. This study aims to investigate how bone turnover and calcium metabolism markers vary across these subtypes.
Method
The medical records of 125 OI patients were retrospectively reviewed. Patients without genetic results, and those without pre-treatment bone turnover markers (BTMs) were excluded. A total of 83 patients (43 females) were included. Patients were classified into five molecular subgroups: Group-1 (collagen synthesis, $n = 53$), Group-2 (collagen modification, $n = 9$), Group-3 (collagen folding, $n = 10$), Group-4 (bone mineralization, $n = 6$), and Group-5 (osteoblast development, $n = 5$). Pre-treatment measurements of calcium metabolism markers (serum calcium, phosphorus, alkaline phosphatase [ALP], parathyroid hormone [PTH], and urinary calcium/creatinine [uCa/Cr]) and BTMs (osteocalcin, C-terminal telopeptide [CTX] and deoxypyridinoline [DPD]) were analyzed, and each parameter's age- and sex-adjusted standard deviation score (SDS) was calculated for intergroup comparisons. DPD and CTX could not be evaluated in all patients.

Table 1: OI molecular subtypes and comparision of BTMs and calcium metabolism markers

GROUP	1 *COL1A1 COL1A2 BMP1 SPARC*	2 *CRTAP P3H1*	3 *FKBP10 PLOD2*	4 *IFITM5 SERPINF1*	5 *WNT1 MBTPS1 SP7 LRP5*	p
OC-SDS	1,82±2,86†	-1,14±0,58†	0,12±1,48	-0,78±2,59	0,57±2,61	**0,005†**
Ca-SDS	0,04±0,05	0,04±0,04	0,02±0,054	-0,01 (-0,05-0,02)	0,01±0,03	0,27§
PO4-SDS	-0,09±1,49†	-1,68±1,87†	-0,51±1,08	-1,93±0,78†	-0,30±1,07	**0,0048†**
ALP-SDS	0,58 (-0,18-1,36)	3,11±2,78	1,33 (-0,09-4,27)	2,10±2,03	2,33±2,32	0,081§
PTH-SDS	-1,24 (-1,84- -0,34)	-1,64 (-2,11- -0,09)	-1,59±0,85	-1,32±0,46	-1,93±0,88	0,243§
uCa/Cr-SDS	0,23 (-1,15-1,53)	0,79±1,23	0,15 (-1,77-11,2)	-0,63±1,19	2,45±5,01	0,60§
DPD-SDS	0,01 (-0,04-0,16)	0,44±0,42§	-0,03±0,14§	*	*	**0,0432§**
CTX-SDS	-0,11±0,06	*	-0,002±0,15	*	*	**0,0084¥**

Results
One-way ANOVA revealed significant differences in osteocalcin levels among five groups, with post-hoc analysis identifying the difference between group 1 and 2 as the primary contributor. Phosphorus levels also showed a significant difference, driven by differences between group 1 and 2 ($P = 0.02$) and group 1 and 3 ($P = 0.03$). No significant differences were observed between groups for serum calcium, ALP, PTH, and uCa/Cr. DPD levels differed between groups 2 and 3. CTX levels differed between Groups 1 and 3 (Table).
Conclusion
High osteocalcin and phosphorus indicate active bone formation and mineralization, with low CTX suggesting lesser collagen degradation in group 1. Low osteocalcin and high DPD in Group 2 suggest impaired formation and excessive collagen degradation. Group 3 had low DPD but high CTX, reflecting ongoing osteoclast activity and unstable collagen resorption due to impaired cross-links. These findings offer insights into OI pathophysiology and support subtype-specific therapeutic approaches.

Keywords: osteogenesis, bone turnover markers, calcium metabolism
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P208

JOINT1369

Autosomal dominant hypocalcemia type 1 or type 2: baseline characteristics of pediatric participants in the CLARIFY disease monitoring study

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Autosomal dominant hypocalcemia type 1 (ADH1) and type 2 (ADH2) are rare disorders caused by activating variants of the *CASR* and *GNA11* genes, respectively. The calcium-sensing receptor (CaSR) plays a critical role in calcium homeostasis by signaling parathyroid hormone (PTH) secretion and urinary calcium (uCa) reabsorption in response to variations in blood calcium. The CaSR signals by coupling to G-proteins, including *GNA11*-encoded Gα11. The CLARIFY disease monitoring study [NCT05227287] is an ongoing global, multicenter, longitudinal, observational study to characterize disease burden, management, and progression in children and adults with ADH1/2 over a 5-year period. Of 25 pediatric participants (birth to <18y) enrolled (Mar 2022 to Jun

2024), 22 were diagnosed with ADH1 and 3 with ADH2; 64% are females. Median age at enrollment was 9 years (IQR 5-13). Median age at hypocalcemia presentation and ADH1/2 diagnosis were 0. 8 years (IQR 0. 0-3. 0) and 1. 0 year (IQR 0. 5-3. 0), respectively. Family history of ADH1/2 was reported in 64% of participants. 16 unique *CASR* and 2 unique *GNA11* variants were present, with *CASR* E767K (3) and F788C (3) the most frequent. Treatment regimen varied at baseline (Day 1 study visit): 32% (8) were on Ca and active vitamin D, 24% (6) on Ca alone, 8% (2) on active vitamin D alone, 20% (5) on PTH replacement, 20% (5) on magnesium, 12% (3) on thiazide diuretics, 12% (3) on potassium, 12% (3) on phosphate binder, 32% (8) on cholecalciferol, and 20% (5) without treatment. At baseline, 92% (23) had hypocalcemia (0-<1y <2. 1 mmol/l; 1-17y <2. 15 mmol/l), 83% (20) had low iPTH (<15 ng/l), 84% (21) had hyperphosphatemia (0-<1y >2. 5 mmol/l; 1-12y >1. 9 mmol/l; 13-17y >1. 5 mmol/l), 8% (2) had hypomagnesemia (<0. 62 mmol/l), and 84% (21) had normal total 25-OH Vitamin D (50-125 nmol/l). 32% (6) of 19 participants with 24hr uCa collected were hypercalciuric (>0. 1 mmol/kg/day); and 0% of 5 participants with spot urine collections had Ca/Cr above the aged-defined reference range (7-18mo <1. 70 mmol/mmol; 19mo – 6y <1. 16 mmol/mmol; adults <0. 59 mmol/mmol). Baseline eGFR by Schwartz equation was 117±25 mL/min/1. 73m^2 (range: 69-175). Common (proxy) self-reported ADH1-related comorbidities were seizures (36%), nephrocalcinosis (32%), dental abnormalities (20%), and long QT syndrome (16%). This study represents the largest pediatric cohort of ADH1/2 described to date. Persistent hypocalcemia and hypercalciuria, along with the high prevalence of comorbidities, highlights the ongoing medical need in this population. Long-term prospective data are needed to better understand disease progression and burden of ADH1/2.

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P209

JOINT1308

Caloric restriction exerts duration-dependent effects on marrow adiposity, bone structure, & metabolic health

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Introduction
Bone marrow adipose tissue (BMAT) is a distinct and metabolically active fat depot within the bone marrow. BMAT negatively correlates with bone mineral density (BMD) and increases in diseases such as osteoporosis and type 2 diabetes. Surprisingly, BMAT also increases in caloric restriction (CR), a well-established intervention for enhancing metabolic health. Despite inducing widespread metabolic and endocrine adaptations, CR also promotes bone loss; however, the extent to which these changes are associated with BMAT remains unclear. This study aims to investigate the effects of CR duration on BMAT expansion, bone microarchitecture, and metabolic adaptations in male and female mice, providing further insights into the interplay of bone metabolism and systemic metabolic regulation during CR.
Method
Male and female mice were fed either ad libitum (AL) or a CR diet (70% of daily AL intake) for 1, 2, 4, or 6 weeks. Oral glucose tolerance tests (OGTT) and body composition analysis were conducted to evaluate metabolic responses. Serum levels of adiponectin, leptin, corticosterone, and insulin-like growth factor 1 (IGF-1) were measured at each time point. Bone microarchitecture and BMAT volume were analyzed using micro-computed tomography and osmium staining.
Results
The effects of CR on BMAT accumulation were region-specific: the primary effect was on the tibia, followed by the femur, while effects on the humerus were negligible. These effects on BMAT were also duration-dependent, with CR's impact plateauing after 4 weeks of CR. Regarding bone microstructure, CR significantly decreased cortical bone area and thickness in both sexes but had a lesser influence on trabecular bone, decreasing only trabecular thickness in females. Notably, at the metaphysis, females exhibited greater CR-induced BMAT accumulation than males and this is accompanied by a reduction in trabecular thickness. CR improved glucose tolerance after only one week, and this effect persisted thereafter. During CR, adiponectin and corticosterone levels increased while leptin and IGF-1 levels declined. Notably, adiponectin levels plateaued around weeks 3–4 of CR, a pattern that coincided with BMAT expansion.
Conclusion
Our findings demonstrate that CR-induced BMAT expansion and bone architectural changes are influenced by CR duration, sex, and skeletal site. Moreover, the improvement in glucose tolerance observed with CR occurs independently of BMAT expansion, while BMAT accumulation may either contribute to or result from elevated adiponectin levels and cortical bone loss. Our findings highlight a potential interaction between BMAT and systemic metabolic adaptations.

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P210

JOINT777

A novel method for the detection of hypercalciuria in individuals with chronic hypoparathyroidism

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Background
Current guidelines recommend avoiding hypercalciuria to minimize the risk of renal complications during treatment of chronic hypoparathyroidism. Measurement of 24-hour urine calcium (24uCa) is the gold standard for diagnosing hypercalciuria; however, this method is inconvenient and susceptible to error. As an alternative, we evaluated calcium excretion per volume of filtrate (E_{Ca}/C_{cr}), which is calculated from measurements in simultaneous aliquots of serum and urine and does not require a timed urine collection.
Methods
This was a post-hoc analysis of the PaTH Forward trial (NCT04009291) of palopegteriparatide, in which 59 adults with chronic hypoparathyroidism were enrolled in a phase 2, randomized, double-blind, placebo-controlled 4-week trial followed by an ongoing open-label extension with palopegteriparatide. E_{Ca}/C_{cr} was calculated as $Ca_{u*}cr_s/cr_u$, where, Ca_u is urine calcium concentration, and cr_u and cr_s are urine and serum creatinine concentrations measured from simultaneous morning non-fasting samples. A 24-hr urine collection was performed 1-7 days (median 3 days) prior to E_{Ca}/C_{cr}. Paired 24uCa and E_{Ca}/C_{cr} evaluations were matched by visit. Hypercalciuria was defined as 24uCa > 300mg/day. Linear associations between E_{Ca}/C_{cr} and 24uCa were evaluated with the Pearson correlation (PC) method. Receiver operating characteristic (ROC) analysis was used to assess the diagnostic accuracy of E_{Ca}/C_{cr} in detection of hypercalciuria.
Results
There were 247 paired E_{Ca}/C_{cr} and 24uCa measurements collected through the 110-week follow-up, including 50 baseline measurements prior to palopegteriparatide initiation. At baseline, median (IQR) 24uCa was 381 (296-602) mg and 72% of individuals had hypercalciuria. Median 24uCa excretion declined to 149, 125, 108, and 150 mg/day during 26, 58, 84, and 110 weeks of open-label period. Baseline mean (SD) E_{Ca}/C_{cr} was 0. 25 (0. 13) mg/dL; it fell to 0. 13, 0. 10, 0. 10 and 0. 10 mg/dL during the same time points. E_{Ca}/C_{cr} strongly correlated with 24uCa (PC coefficient 0. 61, $P < 0.001$). $E_{Ca}/C_{cr} \geq 0.149$ mg/dL had 76% sensitivity, 85% specificity, and 84% accuracy for detecting 24uCa > 300mg/day (AUC 0. 837). E_{Ca}/C_{cr} of <0. 08 and >0. 21 mg/dL virtually excluded the presence and absence of hypercalciuria.
Conclusions
These results show that E_{Ca}/C_{cr} correlates with 24uCa in people with chronic hypoparathyroidism. Given the convenience and the accuracy of E_{Ca}/C_{cr} as compared with 24uCa, these findings suggest that E_{Ca}/C_{cr} may be useful for the detection of hypercalciuria in individuals treated for chronic hypoparathyroidism.

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P211

JOINT523

Cardiovascular disease in patients with post-surgical hypoparathyroidism

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Introduction
Hypoparathyroidism (HypoPT) is a rare disorder characterized by hypocalcemia with low levels of parathyroid hormone (PTH). The most common cause of HypoPT is due to neck surgery and is considered chronic if treatment is still needed a year after surgery. PTH has been recognized as a hormone with cardiovascular properties. However, effects of PTH on the cardiovascular system are not well-defined. A previous large retrospective cohort study of patients with chronic HypoPT showed that patients with HypoPT have a significantly higher risk of cardiovascular disease, compared to patients without HypoPT. We aimed to investigate the risk of cardiovascular disease in patients with chronic post-surgical HypoPT.
Methods
Pre-liminary data from a cross-sectional study on 50 patients with chronic post-surgical HypoPT compared to 50 randomly selected people from the general population matched on gender and age ($\pm$2 years). All participants underwent blood sampling, coronary computed tomography angiography (CCTA), measurements of pulse wave velocity (PWV) and office blood pressure (BP). Pulse wave velocity was measured using an applanation tonometer (AtCor SpygmoCor-XCEL).
Results
63 people have consented to participate in the study (35 patients and 28 controls). 56% of these have completed the entire protocol. Mean age of patients were 59 years (31-84 years), 86% female. Duration of HypoPT 13 years ($\pm$7 years). Risk factors of cardiac disease (hypertension, smoking, hypercholesterolemia, diabetes) did not differ significantly between groups ($p_{all} > 0.05$). Mean office BT was 124/76 mmHg in patients with HypoPT compared to 125/74 mmHg in controls, $P = 0.96$. Mean LDL cholesterol did not differ between groups, $P = 0.32$. Mean pulse wave velocity was 8. 49 m/s (95% CI 7. 84; 9. 14 m/s) in patients with HypoPT compared to 8. 88 m/s (95% CI 8. 24; 9. 52 m/s) in controls, $P = 0.42$. However, the proportion of HypoPT patients with one or more plaques present in the coronary arteries was 59% (95% CI 39; 78) compared to only 25% (95% CI 3; 65) of the controls, $P = 0.12$. The final results await.
Conclusion
Preliminary results suggest that patients with disturbances in calcium homeostasis due to post-surgical HypoPT may have an increased risk of coronary atherosclerosis.

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P212

JOINT2900

Deeplasia: a novel tool for the assessment of bone age in skeletal dysplasia

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Bone age assessment as a marker of skeletal maturation is a relevant biomarker in treatment decisions. Visual evaluation by the atlas methods according to Greulich-Pyle (GP) or Tanner-Whitehouse are standard procedures. However, these comparators are based on images from healthy children. Another disadvantage is the subjective nature of the procedure and in the evaluation of abnormal bone structure, e. g. skeletal dysplasia. BoneXpert was the first artificial intelligence (AI) radiology system to be marketed, but as outlined in the manual this tool excludes data analysis from subjects with bone dysplasia. To address this gap, we developed Deeplasia; an open-source prior-free deep-learning approach designed for bone age assessment, specifically validated on skeletal dysplasias incl. achondroplasia (Rassmann *et al*., 2023). To expand its validation scope, Deeplasia was integrated into the CrescNet auxological database (ClinicalTrials.gov ID: NCT03072537). All data were documented directly during the visit at participating endocrine centers. 953 images from different diagnoses were examined by both Deeplasia and by paediatric endocrinologists (Table) and analyzed using Bland-Altman plot. In particular, we included images from subjects with achondroplasia (305 images of 126 patients), hypochondroplasia (62/21), Noonan syndrome (83/16), SHOX deficiency (226/42), Silver-Russell syndrome (SRS, 24/5), Ullrich-Turner syndrome (UTS, 223/57), and others (38/23). Mean visual bone age was 8. 3 years (SD 4. 1) according to Greulich-Pyle and 8. 4 years (4. 2) according to Deeplasia. Analysis of the Bland-Altman plot between the two methods shows a high level of agreement across all ages, with few outliers.
In conclusion, our data support that Deeplasia might significantly aid in assessing BA in skeletal dysplasia.

	Achondroplasia	Hypochondroplasia	Noonan	SHOX	SRS	UTS
N	305	62	83	226	24	223
Mean difference Deeplasia vs. GP (years)	-0. 25	0. 26	0. 26	0. 47	0. 72	0. 03
SD (years)	1. 03	1. 66	0. 72	0. 88	0. 96	0. 85

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P213

JOINT3967

Switch from rhPTH1-84 to transcon PTH in patients with hypoparathyroidism normalizes phosphate, magnesium metabolism, and bone turnover

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Introduction
Hypoparathyroidism is a rare disease, 75% of cases are due to thyroid or parathyroid surgery. Conventional treatment of Hypoparathyroidism with active vitamin D and calcium is associated with high pill burden and long term complications associated with high phosphate values. Replacement therapy with recombinant human parathyroid hormone (rhPTH1-84) decreased phosphate levels, however did not normalize hypercalciuria. Palopegteriparaide (TransCon PTH) is a long-acting molecule with slow release of PTH1-34, which has recently received approval from the EMA and FDA. In this one center study, we describe the effect of treatment switch from rhPTH1-84 to TransCon PTH on bone metabolism after one, three and six months of treatment.
Methods
We analyzed data from 26 patients with chronic postsurgical HypoPT ($n = 23$) or nonsurgical ($n = 3$) HypoPT during the change of treatment. Patients were predominantly women (20f/6m) with a mean age of 56$\pm$14 years (range 33-84 years). Duration of hypoPT was 16. 6 $\pm$10 years (range 3. 9-44) and treatment with rhPTH 4. 2$\pm$1. 7 years (range1. 3-6. 5). Complications were 46% nephrocalcinosis, 11% renal insufficieny, 11% nephrolithiais, 11% Fahr's disease, and 11% cataract. TransCon PTH was available during a compassionate-use program or used after officially becoming available in Germany starting in January 2024. Independent of the last prior rhPTH-1-84 dose, all patients were started on 18 µg of TransCon PTH and doses adapted individually. Serum values and 24 h urine were collected before treatment change and after one month, three and six months. Until now 20 patients finished the six months treatment.

Results
Six months after change from rhPTH(1-84) more patients were in the normal range for calcium and phosphate (77% vs 90%) with normalization of FGF23 metabolism (64. 2±36. 1 vs 79. 1±24. 1; $P < 0.0001$). Hypercalciuria was also significantly reduced. Palopegteriparatide increased magnesium levels (0. 76±0. 07 mmol/l vs 0. 83±0. 08; $P = 0.0011$) by decreasing urinary excretion of magnesium already after one-month treatment (110. 2±61. 8 mmol/day vs 100. 7±71. 8 and 97. 0±59. 2 at six months). Treatment change significantly decreased the rhPTH(1-84)-induced high bone turnover for bone alkaline phosphatase, P1NP and desoxypyridinoline/urine. Conclusions Switching treatment from rhPTH1-84 to TransCon PTH was followed by significant changes towards normalization in calcium, phosphate, and magnesium metabolism and bone turnover during the first six months of treatment.

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P214

JOINT2945

Risk of non-completion of sequential osteoporosis therapy after teriparatide treatment - real-life data from Hungary

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The beneficial effect of antiresorptive treatment following anabolic treatment on bone fragility is well known, but there are no real-life data on the risk change in the absence of such treatment. In our retrospective longitudinal study, we examined the fracture data of patients receiving teriparatide therapy in Hungary between 1 January 2009 and 31 December 2023 using the databases of the National Health Insurance Fund Administration. There is a single health insurance fund in Hungary, so both prescription and fracture data are considered representative of the total population. We investigated the trend in hip fracture rates during and after teriparatide treatment as a function of adherence, depending on whether patients received sequential antiresorptive treatment. 13 774 patients with severe osteoporosis were treated with teriparatide during the study period. Of these, data were analysed for 8893 patients who had completed teriparatide treatment by the end of 2021 and had an adherence rate to teriparatide treatment of more than 20%. 91% of patients were female and 8. 7% of patients had a hip fracture during the entire observation period. Within 90 days of teriparatide treatment, 20% of patients received denosumab and 10% received a bisphosphonate. Even without sequential treatment three years after teriparatide treatment, the number of hip fractures was significantly lower in the group with more than 80% adherence than in the group with less than 20% adherence ($P < 0.01$). However, treatment with denosumab or a bisphosphonate after teriparatide discontinuation significantly reduced the risk of hip fracture compared with those who did not receive an antiresorptive agent. (RR: 0. 469, $P < 0.01$) The timing of treatment initiation also influenced the increase in fracture risk. If treatment was continued beyond 90 days, the relative risk increased significantly, with this delay almost doubling the risk of hip fracture if treatment was continued with denosumab (RR: 1. 48, $P < 0.01$). In conclusion, although the beneficial effect of teriparatide treatment can be demonstrated for years without continued treatment, antiresorptive treatment started within 90 days can achieve an additional fracture risk reduction of more than 50%. Our study provides fracture data to support a clear benefit of sequential therapy after teriparatide treatment.

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P215

JOINT2550

Wide clinical spectrum of GCM2-related primary hyperparathyroidism

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Primary hyperparathyroidism (PHPT) is a prevalent endocrine disease, with up to 10% risk for genetic predisposition. The *GCM2* gene p. Y394S pathogenic variant (PV), found mostly in Ashkenazi Jews, leads to an autosomal dominant disorder of familial isolated hyperparathyroidism. We aimed to compare the biochemical phenotype of patients with various hereditary PHPT.

Methods
In this prospective study, we included patients that underwent next generation sequencing due to a diagnosis of neuroendocrine neoplasms, suspected multiple endocrine neoplasia syndromes or PHPT. We compared demographic, clinical and biochemical parameters, and surgical outcome data between pathogenic variant carriers vs. non-carriers.
Results
A total of 380 patients underwent genetic analysis, of them sixty patients diagnosed with PHPT (63. 3% females, mean age at diagnosis 45. 1±2. 1 years). Eleven (18. 3% of those with PHPT) carried a PV in a PHPT-relevant gene: four patients had *MEN1* PV (6. 7%), five - *GCM2* (8. 33%) and two - *CDKN1B* gene PV. Age at diagnosis, serum and urinary calcium levels were comparable between carriers and non-carriers. However, number of parathyroid glands involved was significantly higher in the carriers vs. non-carriers group ($P = 0.011$), with a trend toward increased rate of recurrence in the carrier group ($P = 0.06$). Twelve (3. 75%) patients evaluated for other clinical diagnoses were found to carry a PV in PHPT-related genes: six in *GCM2*, three in *CDKN1B*, two in *MEN1* and one in *RET*. In the entire cohort, eleven patients, all of Jewish ancestry, carried the *GCM2* p. Y394S PV, of them seven (63. 6%) had PHPT. Clinical presentation was various, most patients with GCM2-related PHPT had a mild disease. However, one patient had a post-surgical recurrence and another patient presented with hypercalcemic crisis at the age of 32 with a three-generation history of PHPT, and a maternal grandfather deceased due to hypercalcemic crisis at the age of 47. In contrast, three *GCM2* PV carriers did not develop hypercalcemia until their evaluation at the ages of 51, 59 and 81 years.
Conclusion
Based on a large cohort of patients with hereditary PHPT, we report various biochemical phenotypes in patients with the p. Y394S *GCM2* PV, ranging between absence of hypercalcemia in adulthood, and hypercalcemic crisis at a young age.

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P216

JOINT3319

Risk of atypical femoral fractures among osteoporotic patients on denosumab treatment in real-life setting: a population-based study

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Background
Atypical femoral fractures (AFF) are rare but serious adverse events with distinct radiographic criteria but lack specific ICD-9 diagnostic codes. While the association between bisphosphonates (BP) treatment and AFF is well established, denosumab's (DMAB) risk profile remains unclear, particularly when used after BP.
Aim
To evaluate AFF risk in patients treated with DMAB after prior BP use.
Methods
This population-based study included Clalit HMO patients aged ≥50 years who received osteoporosis treatment between 2002 and 2024. Patients were classified as BPs only (at least one purchase of zoledronic acid or more than one oral BP purchase), or DMAB after BP (at least 2 purchases of DMAB following no more than 3 years from last BP purchase). AFF cases were identified using a validated algorithm combining specific femoral fracture diagnostic and surgical procedure codes, achieving 96. 88% sensitivity, 95. 10% specificity, and 38. 75% positive predictive value when validated against radiographically adjudicated cases meeting ASBMR 2014 criteria. Cases with concurrent pathological fractures, motor vehicle accidents, or peri-prosthetic fractures within 14 days were excluded. We used Cox regression with treatment status (e. g., BP, DMAB as second-line) being a time-varying covariate, to compare AFF risk between the groups. Hazard ratios (HR) were adjusted for age.
Results
262, 482 patients were included in the analysis: 242, 117 patients in the BP-only group (85% female, mean age 68. 8±10. 0 years), and 16, 629 patients in the DMAB-after-BP group (93% female, mean age 65. 9±8. 8 years). 2, 622 AFF cases occurred during 1, 866, 704 BP patient-years and 98 AFF cases occurred during 76, 743 DMAB patient-years. AFF risk was significantly lower during DMAB treatment after BP compared to BP treatment (HR: 0. 25, 95% CI: 0. 20-0. 31). Patients who developed AFF during DMAB treatment after BP had previously received BP therapy for a mean duration of 10. 8 ± 4. 6 years before switching to DMAB and had a mean DMAB exposure of 2. 9 ± 2. 4 years.

Conclusion
In our analysis, DMAB treatment following BP was associated with a lower risk of AFF compared to BP therapy. This finding is particularly relevant given the common clinical practice of transitioning patients from BP to DMAB therapy. A prospective study is needed to further support the safety of DMAB therapy after BP.

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P217

JOINT1337

Histopathological and clinical differences in primary hyperparathyroidism: a retrospective analysis of parathyroid adenomas with severe and mild hypercalcemia

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Background and Aim
Primary hyperparathyroidism (PHPT), predominantly caused by parathyroid adenomas, exhibits a broad spectrum of clinical and histopathological manifestations, ranging from mild to severe hypercalcemia. Severe hypercalcemia (Ca $>$13 mg/dL) is linked with complications such as osteoporosis and nephrolithiasis, while mild hypercalcemia (Ca $<$12 mg/dL) is often asymptomatic. This study aimed to explore differences in tumor characteristics, clinical outcomes, and histopathological markers between these groups, providing insights into their pathophysiology and prognostic implications.
Subjects and Methods
A retrospective analysis was conducted on 66 patients with PHPT due to parathyroid adenomas. Patients were divided into two age-matched groups: 46 with mild hypercalcemia (Ca $<$12 mg/dL; mean age 54. 3 $\pm$ 11. 3 years) and 20 with severe hypercalcemia (Ca $>$13 mg/dL; mean age 51. 9 $\pm$ 17. 8 years). Immunohistochemical analyses for parafibromin, cyclin D1, TP53, and Ki67 were performed on pathological specimens. Tumor size, mitotic activity, fibrosis, and clinical, hormonal, and biochemical parameters were also evaluated.
Results
The severe hypercalcemia group demonstrated significantly higher median serum calcium and parathormone levels (13. 8 mg/dL [IQR: 13. 3–14. 5], 351. 4 pg/mL [IQR: 216. 9–487. 7]) compared to the mild hypercalcemia group (11. 2 mg/dL [IQR: 10. 9–11. 6], 152. 3 pg/mL [IQR: 121. 3–227. 6]). Despite these differences, no significant variations were found between the groups in tumor size (P = 0. 43), mitotic activity (P = 1. 0), fibrosis (P = 0. 12), or immunohistochemical markers such as parafibromin (P = 0. 47), cyclin D1 (P = 0. 7), beta-catenin (P = 0. 82), and Ki67 (P = 0. 63). Additionally, there were no significant differences in the prevalence of osteoporosis (Ca $<$12, n = 17; Ca $>$13, n=2; P = 0. 17) or nephrolithiasis (Ca $<$12, n = 18; Ca $>$13, n = 12; P= 0. 18).
Conclusion
Severe hypercalcemia in PHPT reflects greater biochemical disease severity, yet histopathological and molecular profiles of parathyroid adenomas remain comparable across calcium levels. These findings suggest that hypercalcemia severity may stem from factors beyond tumor pathology, including functional variations in adenomas or host-specific influences. Further research is required to uncover mechanisms contributing to disease severity and their clinical implications.

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P218

JOINT571

Quantitative evaluation of hypophosphatemic rickets due to ENPP1 deficiency

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Introduction
ENPP1 is a critical enzyme involved in the generation of pyrophosphate, an inhibitor of skeletal mineralization, and adenosine, a regulator of vascular intimal proliferation. Patients with biallelic, loss of function *ENPP1* variants typically present at birth with severe arterial calcification and cardiovascular complications, a phenotype described as Generalized Arterial Calcification of Infancy Type 1 (GACI Type 1). Those who survive beyond infancy develop Autosomal Recessive Hypophosphatemic Rickets Type 2 (ARHR2), with deficient mineralization of the bone and growth plate leading to impaired growth and skeletal deformities.
Purpose
To describe Rickets Severity Score (RSS), height, bone age, Bone Health Index (a surrogate for bone strength), and treatments/interventions in pediatric patients with ENPP1 Deficiency under current standard of care.
Methods
Sub-group analysis of a multicenter longitudinal retrospective chart review, including patients with clinical and genetic diagnosis of ENPP1 Deficiency. In a post-hoc analysis, Bone Age and Bone Health Index were calculated using BoneXpert^{TM} software.
Results
Fourteen patients with ENPP1 Deficiency were enrolled. Two died in infancy, and 12 were enrolled at a median age of 19. 5 years (range: 4-33). Seven patients were diagnosed with GACI, and 10 with ARHR2 at a median age of 5 years (range 0. 3 – 21), including 3 with both phenotypes. All 7 with GACI required medication (n = 6) and/or respiratory support (n = 5) in infancy; 5/12 surviving patients (42%) received at least one antihypertensive in childhood or early adulthood. Nine surviving patients (75%) required medication for rickets (vitamin D analogs n = 9; phosphate supplements n = 8), 9 had at least one orthopedic surgery (epiphysiodesis n = 7, osteotomy n = 5), and 6 wore hearing aids. All 13 patients assessed were hypophosphatemic, and 11/13 had elevated alkaline phosphatase (ALP) levels. Median Global RSS in children $<$13 years of age (n = 8) was 1. 75 (range 0-3). Height Z scores tended to decline over time. At final follow up, 5 patients had short stature (Z score $\leq$-2) including 3 patients with stature Z scores more than 3. 0 standard deviations below the mean. Mean bone age was delayed by 0. 87$\pm$1. 28 years relative to chronological age (P $<$ 0. 01), as calculated by BoneXpert assessment of 33 hand X-rays across 9 patients. Mean Bone Health Index Z score was reduced at -1. 31$\pm$1. 33; P $<$ 0. 001.
Conclusions
Children with ENPP1 Deficiency under current standard of care exhibit considerable and heterogenous impairments in bone health, overlapping with other forms of genetic hypophosphatemias. In addition, surviving patients may require treatments/interventions for hypertension and hearing loss.

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P219

JOINT2911

Preliminary results from a prospective cohort study on real-world data of chronic hypoparathyroidism treated with trans-con PTH

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Background
Chronic hypoparathyroidism (HypoPT) is a rare endocrine disorder characterized by deficient parathyroid hormone (PTH) levels, leading to hypocalcemia and dependency on calcium and active vitamin D., Trans-conPTH 1-34 formulation (Yorvipath), has emerged as a potential therapeutic option for patients with uncontrolled hypoparathyroidism or those previously treated with rhPTH(1-84). This study presents preliminary results from an ongoing prospective cohort-study evaluating the real-world effectiveness of Yorvipath.
Methods
Eligible patients were adults diagnosed with HypoPT who required trans-conPTH due to inadequate control on conventional therapy or as a replacement for prior treatment with rhPTH(1-84). All included patients started Yorvipath at 18 mg and were followed regularly during the titration period.
Results
Thirty-seven patients (aged 21–70years) were included. The majority (29/37) had surgical hypoparathyroidism, including eight cases related to thyroid cancer. Six patients had idiopathic hypoparathyroidism, one developed infiltrative hypoparathyroidism due to sarcoidosis, and another due to iron deposition from transfusion-dependent thalassemia. The mean disease duration was 12 ± 9. 7 years (range 1-44y). Before initiating Yorvipath, 21 patients (56%) had been treated with rhPTH (1-84) at doses ranging from 75 to 100 mg/day. Baseline conventional treatment included an average of 2000 mg/day of calcium-supplements (divided into 3–4 doses), 1. 5 mg/day of active vitamin-D, 1400 IU/day of cholecalciferol, and 746 mg/day of magnesium. Additionally, 15 patients (40%) were on hydrochlorothiazide for hypercalciuria. The mean duration of Yorvipath treatment was 90 ± 59 days (range 11-210). By the last study visit, albumin-corrected calcium levels had significantly increased compared to baseline (9. 0 ± 0. 58mg/dL vs. 8. 15 ± 0. 65mg/dL, respectively, $P < 0.001$), while phosphate levels had decreased (4. 0 ± 0. 59mg/dL vs. 4. 64 ± 1. 12mg/dL, respectively, $P = 0.004$). Notably, 60% of the cohort (23/37) achieved independence from both calcium and active vitamin D within the first 21 days of treatment (range:7–60 days). Among the remaining patients, eight continued with low-dose calcium supplements (<600 mg/day), and only five required ongoing activated vitamin D. No significant differences were observed between drug-naïve patients and those previously-treated with rhPTH(1-84). The median dose of Yorvipath was 21mg(range 12-30mg). No adverse events were reported during treatment with Yorvipath. Two patients (5%) experienced transient hypercalcemia during the titration period.
Conclusion
Preliminary findings suggest that Yorvipath is effective in reducing or eliminating the need for calcium and activated vitamin-D treatment in patients with HypoPT. Most patients achieved Ca/active VitD independence within the first few weeks of treatment. Further studies with longer follow-up are warranted to confirm the long-term efficacy and safety of Yorvipath in this patient population.

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P220

JOINT772

Relation of body composition with 3D-DXA parameters and trabecular bone score in women with anorexia nervosa

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Anorexia nervosa (AN) is a psychiatric disorder characterized by self-imposed fasting leading to significant weight loss and consequently nutrient deficiencies that disrupt the bone metabolism. Also, the catabolic processes in muscle and adipose tissue are associated with bone loss. Curiously, caloric restriction leads to marrow adipose tissue (MAT) expansion, which is associated with low bone mineral density (BMD). This cross-sectional observational study aimed to evaluate MAT in the tibia and explore the relationships between 3D shaper parameters, dual-energy-X-ray absorptiometry (DXA), body composition, and trabecular bone score (TBS). Both groups underwent blood sampling, DXA scans, TBS assessments, magnetic resonance ^{1}H spectroscopy of the tibia, and 3D shaper analysis. The study included 12 women with AN, monitored by a multi-disciplinary team, and 11 healthy controls (C), matched by age (C:25. 6 ± 8. 6; AN:24. 2 ± 10. 0 years) and height (C:1. 62 ± 0. 05; AN:1. 59 ± 0. 09 m). The total MAT was significantly higher in the AN (93. 2 ± 6. 4 %) than C (87. 0 ± 8. 5 %). Total hip (TH) BMD (C:0. 96 ± 0. 07; AN:0. 81 ± 0. 16 g/cm^2), TH Z-score (C:-0. 32 ± 0. 57; AN:-1. 49 ± 1. 18), femoral neck (FN) BMD (C:0. 98 ± 0. 06; AN:0. 81 ± 0. 17 g/cm^2), and FN Z-score (AN:-0. 35 ± 0. 57; C:-1. 21 ± 0. 99) were significantly lower in AN. Additionally, fat mass index was reduced in women with AN (C:7. 70 ± 1. 44;AN:5. 56 ± 1. 96 kg/m^2, $P < 0.01$), while the appendicular lean mass index (ALMI) was similar between both groups (C:5. 88 ± 0. 71; AN:5. 68 ± 1. 25 kg/m^2). The 3D shaper parameters tended to be lower in the AN [e. g. cortical sBMD total (C:151 ± 14; AN:129 ± 26 mg/cm^2) and trabecular vBMD total (C:194 ± 25; AN:153 ± 53 mg/cm^3)]. A negative association was observed between MAT and FNBMD (R^2=0. 3, $P = 0.02$). There was association between total cortical volumetric BMD (vBMD) ($P = 0.02$, R^2=0. 26), cortical surface BMD ($P = 0.01$, R^2=0. 31), integral vBMD ($P = 0.03$, R^2=0. 24), and TBS. FN Z-score had a trend of association with ALMI ($P = 0.05$, R^2=0. 19) and was related with FMI ($P = 0.04$, R^2=0. 20). In addition, it was observed a negative relationship of total cortical thickness with ALMI ($P = 0.04$, R^2=0. 21) and FMI ($P = 0.04$, R^2=0. 21). The results suggest that women with AN exhibit reduced BMD compared to healthy controls, beside compromised 3D-DXA parameters of the proximal femur and decreased TBS. The present study is the first to show that the tool 3D shaper potentially can detect bone impairment in AN. Moreover, it suggests that fat mass has a stronger association with FN BMD than lean mass in AN and confirms a negative relationship between MAT and bone mass in AN.

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P221

JOINT3387

Treatment of hypercalciuria in patients with chronic hypoparathyroidism

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Background
Chronic hypoparathyroidism (hypoPT) is characterized by insufficient production of parathyroid hormone, resulting in hypocalcemia and hyperphosphatemia. This condition can lead to hypercalciuria, which is a common finding in patients with chronic hypoparathyroidism and can contribute to long-term renal complications such as nephrocalcinosis, kidney stones, and impaired renal function. Current guidelines suggest adjustment of calcium and active vitamin D and/or treatment with thiazide diuretics to reduce hypercalciuria. However, data regarding their efficacy is lacking.
Methods
We retrospectively analyzed urinary calcium excretion in 244 patients with chronic hypoparathyroidism from two different German centers (Wuerzburg $n = 224$, Augsburg $n = 20$) between 1999 and 2024 (median age 52 years [IQR 19-82], 75% female, 91% postsurgical hypoPT). A total of 1231 patient-years were recorded with a median of 4. 2 [IQR 1-24] visits per patient and a median follow-up of 5 [IQR 0-23] years.
Results
At baseline (first recorded visit), 39% ($n = 95$) of patients presented with hypercalciuria, whereas concomitant treatment with thiazide diuretics occurred only in 13% of patients. During time of data collection, thiazide treatment was initiated in 97 cases. The majority of patients received hydrochlorothiazide (73%) at a median daily dose of 22 mg [IQR 12. 5-50]. Initiation of thiazide treatment led to a significant reduction of urinary calcium excretion (-2. 31 mmol/d, $P < 0.001$) at the next recorded visit. This effect was even more pronounced in case of hypercalciuria at treatment initiation (-3. 49 mmol/d, $P < 0.001$, $n = 68$). Interestingly, higher thiazide doses did not lead to a greater reduction of urinary calcium and 70% of patients remained hypercalciuric despite initiation of thiazide treatment. Serum albumin-corrected calcium remained unchanged during treatment. Reduction of oral calcium supplementation by 833 mg/d (median) led to a significant decrease of urinary calcium (-1. 79 mmol/d, $P < 0.001$ for the whole cohort, -2. 86 mmol/l, $P < 0.001$ for hypercalciuric patients at baseline), whereas a reduction of calcitriol by 0. 5 µg/d decreased urinary calcium excretion by 2. 8 mmol/d at the following visit.
Conclusion
Hypercalciuria frequently occurs in patients with hypoPT. Thiazides, as well as dose reduction of calcium or active vitamin D significantly reduce urinary calcium excretion. However, even the combination of both approaches was still not sufficient to lower urinary calcium into the normal range.

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P222

JOINT1934

Effect of thiazide diuretics on bone turnover in osteoporotic postmenopausal patients with idiopathic hypercalciuria

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Introduction
Idiopathic hypercalciuria (IH) - defined by 24 hours urinary calcium levels (CaUr24h/kg) >4 mg/kg - is a cause of secondary osteoporosis, affecting 30% of postmenopausal women. IH is thought to lead to a compensatory increase of bone turnover and, thus, to a bone loss. The reduction of hypercalciuria is achieved through low-dose thiazide diuretics (hydrochlorothiazide, HCT), whose effect on skeletal turnover is unknown. This study evaluates the effect of HCT on bone turnover in postmenopausal osteoporotic women.
Materials and Methods
82 postmenopausal women with a median age of 59 years (interquartile range 55-66), affected by osteoporosis and IH were retrospectively enrolled from a multicenter case series. All patients had normal calcium intake (by diet and/or supplements), were supplemented with cholecalciferol and were not taking antiresorptive medications. Patients with secondary hypercalciuria (i. e., primary hyperparathyroidism, endogenous or exogenous hypercortisolism) were excluded. At enrollment (T0), calcium, phosphate, 25OH-vitamin D, parathyroid hormone (PTH), C-terminal telopeptide (CTX), alkaline phosphatase (ALP), CaUr24h/kg, and creatinine clearance (ClCr) were measured; 6-12 months (T1) and 18-24 months (T2, $n = 48$) after the initiation of a treatment with HCT (12. 5 mg or 25 mg/day), the same parameters were reassessed. Normalization of CaUr24h/kg and reduction of CTX were considered as primary outcomes.
Results
A normalization of calciuria was observed in 43. 9% patients (36/82) at T1 and in 60. 4% (29/48) at T2. Moreover, the paired data obtained from the patients were analyzed longitudinally, showing a significant reduction at T1 and T2 compared to T0 in both CaUr24h/kg values (-1. 26±0. 19 mg/kg/24h, $P < 0.001$; -1. 23±0. 25 mg/kg/24h, $P < 0.001$) and CTX values (-140±32 ng/ml, $P < 0.001$; -90±29 ng/ml, $P < 0.005$). No significant differences were observed in CaUr24h/kg values (0. 03±0. 24 mg/kg/24h, $P = 0.91$) between T1 and T2, while a slight increase in CTX values was noted (49±22 ng/ml, $P = 0.031$). A slight increase in calcium levels was observed between T0 and T1 (0. 17±0. 06 mg/dl, $P < 0.005$) and T0 and T2 (0. 13±0. 07 mg/dl, $P = 0.08$), although not statistically significant, but not between T1 and T2 (-0. 04±0. 07 mg/dl, $P = 0.52$). No significant differences were found in the levels of phosphate, 25OH-vitamin D, PTH, ALP, or renal function among T0, T1, and T2.
Conclusion
the use of HCT in osteoporosis secondary to idiopathic hypercalciuria in postmenopausal women appears to reduce the bone resorption process. However, the sample size, the short duration and the design of the study do not allow for conclusive information on the persistent effects on turnover, bone mineral density, and fracture risk.

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P223

JOINT2536

FGF23 in chronic hypoparathyroidism: clinical implications of phosphate regulation

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Introduction
Fibroblast Growth Factor 23 (FGF23) regulates phosphate homeostasis, but its systemic effects remain unclear in hypoparathyroidism. Elevated FGF23 levels have been linked to adverse renal, cardiovascular, and skeletal outcomes in patients without hypoparathyroidism. In chronic hypoparathyroidism, its role is not well defined, with limited evidence on its clinical implications.
Objective
To assess intact FGF23 levels in chronic hypoparathyroidism and their association with biochemical markers and clinical outcomes.
Methods
This observational study included 48 hypoparathyroid patients under regular follow-up at a university hospital. A cross-sectional analysis (2023–2024) evaluated clinical and biochemical parameters, complemented by a retrospective longitudinal analysis to identify predictors of FGF23 levels.
Results
The cohort (85. 4% women, 87. 5% postsurgical hypoparathyroidism, mean age 60. 6±16. 3years, disease duration 14. 8±12. 1years) was mostly on conventional therapy (44vs4 on teriparatide) and showed good biochemical control (mean serum calcium 8. 7±0. 8mg/dL, phosphate 4. 55±0. 82mg/dL, CaP product 39. 2±6. 8mg^2/dL^2). Despite this, 71% of patients had elevated FGF23 levels (157. 9±92. 4pg/mL; normal 23. 2–95. 4pg/mL), of whom only one patient on teriparatide. Higher FGF23 levels were associated with longer disease duration (19. 6±13. 1 vs 9. 6±8. 5years), reduced kidney function (49. 6±17. 3 vs 61. 5±16. 0mL/min/1. $73m^2$), higher CaP product (41. 3±7. 1 vs 37. 2±6. 0mg^2/dL^2), lower PTH (8. 7±8. 3 vs 14. 6±8pg/mL), and lower 1, 25OH vitamin D (30. 0±13. 0vs39. 8±13. 7pg/mL). However, treatments did not differ significantly in term of calcium doses (1801±1695mg/die vs 1359±1106mg/die) or calcitriol (0. 55±0. 46mg/die vs 0. 55±0. 33mg/die). Patients with higher CaP product had longer disease duration (19. 6±12. 8y vs 10. 0±9. 5 $P = 0.006$), elevated FGF23 (187. 0±111. 2 vs 128. 9±57. 5pg/mL, $P = 0.028$), and higher TmPO4/GFR (4. 4±0. 7vs3. 7±0. 7mg/dL, $P = 0.001$). Lower tertiles of CaP product levels correlated weakly with TmPO4/GFR, suggesting significant FGF23 kidney resistance (R^2=0. 082 and R^2=0. 022), whereas this association was stronger in the highest tertile (R^2=0. 268), suggesting a dose-dependent FGF-23 sensitivity. This mechanism, however, remains ineffective at inducing clinically-significant phosphate excretion. PTH level was associated with lower CaP product (34. 9±5. 6mg^2/dl^2 vs 40. 2±5. 9mg^2/dL^2 $P = 0.004$), higher serum magnesium (2. 0±0. 2mg/dl vs 1. 9±0. 2mg/dl $P = 0.047$) and lower calcium fractional excretion (1. 3±0. 5% vs 2. 2±1. 2% $P = 0.007$). Multivariate analysis identified female sex (β=88. 76±41. 38, $P = 0.032$) and mean CaP product (β=7. 99±2. 73, $P = 0.004$) as independent predictors of FGF23 levels, independent of PTH, 1, 25OH vitaminD, renal function, serum magnesium and disease duration.
Conclusions
This study is the largest in literature investigating FGF23 levels in hypoparathyroidism. Despite adequate biochemical control, most patients exhibited elevated FGF23, driven by female sex and CaP product. High FGF23 levels were ineffective in promoting phosphate excretion but contributed to reduced 1, 25OH vitamin D, complicating conventional therapy management. FGF23 is clinically relevant in hypoparathyroidism and warrants further investigation.

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P224

JOINT2352

Clinical and phenotypic features of osteogenesis imperfecta caused by fkbp10 mutations: a study of skeletal deformities and cervical abnormalities

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Introduction and Aim
Osteogenesis imperfecta (OI) is a hereditary disorder of connective tissue characterized by increased bone fragility, recurrent fractures, and skeletal deformities. Mutations in *FKBP10* cause a rare and severe form of OI, known as OI type-XI. This study aims to investigate the clinical and phenotypic characteristics, as well as the skeletal deformities and cervical abnormalities, of patients with *FKBP10* mutations.
Methods
A retrospective follow-up study of 17 children (10 male) with *FKBP10* mutations (ten different biallelic variants) evaluated between 2000 and 2024 was undertaken.
Results
The patients were diagnosed at a mean age of 3. 2±4. 2 years (range: 0. 03-13. 5 years). Consanguinity was reported in 14 patients with a family history of OI in 11. Four had antenatal fractures, 9 had fractures within the first 3 months postnatally, and 4 experienced fractures within the first 3 years. The median follow-up duration was 4. 5±4. 7 years (range: 0-14. 5 years). Multiple fractures (more than 10) occurred in 70% ($n = 12$) of the patients. All patients had long bone fractures, with additional rib (82%, $n = 14$), sacrum-coccyx (64%, $n = 11$), clavicle (23%, $n = 4$), and pelvic fractures (17%, $n = 3$). Long bone deformities caused by recurrent fractures were detected in all

patients. Bone deformities included pectus excavatum/carinatum (70%, $n = 12$), pes equinovarus (35%, $n = 6$), and genu varum (29%, $n = 5$). Vertebral issues included vertebral compression (64%, $n = 11$), spondylolisthesis (58%, $n = 10$), pars defect (23%, $n = 4$), fusion defect (23%, $n = 4$), ossified longitudinal ligament ($n = 1$), and platybasia ($n = 1$). Scoliosis was present in 88% ($n = 15$). Basilar invagination was observed in 47%. Hip deformities included coxa vara (41%, $n = 7$), pelvic rotation anomalies (41%, $n = 7$), and acetabular protrusion (23%, $n = 4$). Other findings included Wormian bones (58%, $n = 10$), JOINT contractures (58%, $n = 10$), blue sclera (29%, $n = 5$), dentinogenesis imperfecta (41%, $n = 7$), epidermolysis bullosa (23%, $n = 4$), cardiac problems in 3, hyperlaxity in 3, and no hearing loss. Additionally, 70% ($n = 12$) were immobile, and all patients had short stature. All patients received intravenous bisphosphonate treatment for 7. 2±4. 1 years (range: 0. 25-15 years). Corrective surgeries for long bone deformities were performed in ten patients. The median height SDS was −2. 3±3. 4 at the initial examination and −3. 6±2. 0 at the last examination.

Conclusion

FKBP10 mutations result in a variety of severe clinical manifestations, including fractures, deformities, and spinal abnormalities. The majority of patients experience multiple fractures early in life, highlighting the need for early intervention and continuous monitoring.

Keywords: *FKBP10,* osteogenesis imperfecta, deformities

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P225

JOINT2372

The role of FGF23 in phosphorus and calcium metabolism: lessons from diseases affecting serum phosphate levels

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Background and Objective

Fibroblast Growth Factor 23(FGF23) is a phosphate regulating hormone primarily produced by osteoblast and osteocytes. Under physiological condition, FGF23 secreting cells sense the serum phosphate and regulate it in strict range by modulating FGF23 secretion in coordination with parathyroid hormone (PTH). Additionally, FGF23 inhibits both the synthesis and secretion of PTH, while PTH stimulates FGF23 secretion, underscoring the complex interplay between these hormones. In this study, we aimed to evaluate interrelationship between FGF23 and phosphate metabolism, along with other key regulators, by analyzing their levels in various diseases conditions. Additionally, we sought to develop an FGF23-Phosphate nomogram to facilitate a better understanding of these interactions.

Methods

A total of 79 blood samples from 77 patients were evaluated. Patients with X-linked hypophosphatemia(XLH[$n = 22$]), fibrous dysplasia ($n = 3$) and tumor induced osteomalacia/nonosseous fibroma ($n = 3$) were classified under phosphate independent FGF23 secretion (PI-FGF23[$n = 29$]). Conversely, patients with nutritional rickets ($n = 6$), *SLC34A3/A1* mutations ($n = 8$), and nephrocalcinosis of unknown etiology, whose FGF23 levels were consistent with phosphorus levels, were classified under phosphate dependent FGF23 secretion (PD-FGF23[$n = 41$]). Additionally, patients with hypoparathyroidism/pseudohypoparathyroidism (HP/PHP[$n = 6$]) and hyperparathyroidism ($n = 3$) were evaluated as separate groups. Samples were collected from patients either before treatment or after the discontinuation of treatment. Serum FGF23 concentrations were measured using the Sandwich Immunoassay method.

Results

In PD-FGF23, FGF23 showed a positive correlation with P-SDS ($r = 0.634$, P=< 0. 0001) and Tmp/GFR ($r = 0.463$, $P = 0.002$); in contrast, no correlation was detected in PI-FGF23 group. Additionally, P-SDS demonsrated a negative correlation with ALP-SDS ($r = -0.554$, $P = 0.0002$) and PTH (r:-0. 585, P=< 0. 0001) in PD-FGF23 group, whereas a positive correlation was observed between P-SDS and PTH ($r = 0.573$, $P = 0.0053$) in XLH group. Additionally, the P/FGF23 nomogram demonstrated that FGF23 levels were undetectable when serum phosphate <-3 SDS. Between -2 SDS and -3 SDS, FGF23 cutoff value of 30 could differentiate PI-FGF23 from PD-FGF23. Furthermore, patients with a homozygous SLC34A3 mutation exhibited undetectable FGF23 levels despite normal phosphorus levels. In HP/PHP group, FGF23 levels were inappropriately low relative to phosphorus levels, whereas in the hyperparathyroidism, FGF23 levels were inappropriately high relative to phosphorus levels.

Conclusion

Our findings suggest that FGF23 plays a pivotal role in phosphorus metabolism, with distinct regulation patterns depending on the underlying etiology of hyperphosphatemia or hypophosphatemia. The interplay between FGF23 and PTH is essential in maintaining phosphate homeostasis, yet neither can fully compensate for the absence of the other.

Keywords: FGF23, phosphate, Phosphate/FGF23 PTH

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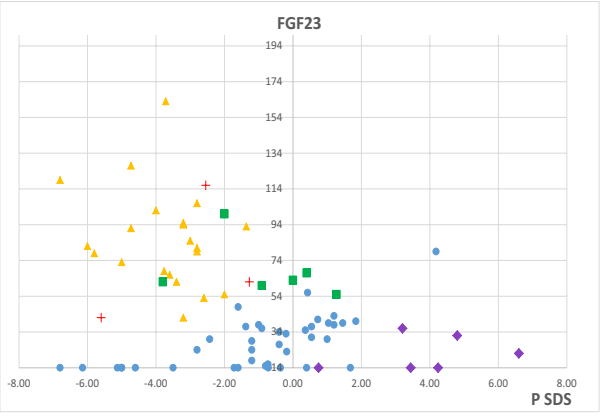

Figure:Phosphate/FGF23 nomogram

▲=XLH, ● =PI-FGF23, ■=nonosseous fibroma/fibrous dysplasia/tumor induced osteomalacia, + = hyperparathyroidism, ◆=hyopoparathyroidism/pseudohypoparathyroidism

P227

JOINT1543

Gain-of-function CASR variants identified as a major genetic contributor of non-surgical hypoparathyroidism: findings from over 300 participants in a sponsored genetic testing program

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Hypoparathyroidism is a rare condition characterized by insufficient production of parathyroid hormone, resulting in low serum calcium and an imbalance in mineral homeostasis. Hypoparathyroidism is most commonly caused by damage to or removal of parathyroid glands during surgery, however, genetic causes have become increasingly recognized with advances in genetic testing and growing awareness of non-surgical etiologies. Genetic forms of hypoparathyroidism can occur in isolation or as part of a syndrome, and include disorders related to the formation of parathyroid glands, secretion of parathyroid hormone, and autoimmune damage to the parathyroid glands. Individuals with a clinical diagnosis of non-surgical hypoparathyroidism, positive family history or suspicion of genetic hypoparathyroidism, are eligible to participate in a no-charge sponsored genetic testing program in the United States and Canada. The next-generation sequencing panel leveraging a whole exome backbone includes 26 genes associated with hypoparathyroidism: *ACADM*, *AIRE*, *ATP1A1*, *CASR*, *CHD7*, *CLDN16*, *CLDN19*, *CNNM2*, *DHCR7*, *EGF*, *FAM111A*, *FXYD2*, *GATA3*, *GCM2*, *GNA11*, *HADHA*, *HADHB*, *KCNA1*, *NEBL*, *PTH*, *SEMA3E*, *SLC12A3*, *SOX3*, *TBCE*, *TBX1* and *TRPM6*. A total of 327 samples were tested over four years (2020 – 2024) from participants with a mean age of 26. 7 years (range 0-81). 191 variants were identified in 149 individuals (46%) which were classified as pathogenic, likely pathogenic, or variants of uncertain significance. Among these 149 individuals with detected variants, *CASR* was the most frequently affected (35%), followed by *AIRE* (17%), *GATA3* (10%), *TBX1* (7%), *HADHA* (3%), *GNA11* (3%), *GCM2* (3%), *SEMA3E* (2%), *SLC12A3* (2%), *NEBL* (2%), *DHCR7* (2%), *HADHB* (2%), *FAM111A* (2%), *CHD7* (2%), *ACADM* (1%), *TRPM6* (1%), *EGF* (1%), *PTH* (1%), *KCNA1* (1%), *CNNM2* (1%), *CLDN19* (1%), and *TBCE* (1%). Notably, 36 individuals had variants identified in multiple genes. Genetic etiologies should be considered in all patients with hypoparathyroidism without a history of neck surgery as the identification of a genetic etiology can impact patient management and guide further medical evaluation. In our data, the most common genetic form of hypoparathyroidism was found to be autosomal dominant hypocalcemia type 1 (ADH1), caused by gain-of-function variants in the *CASR* gene (18. 4%; 60/327). An ongoing global Phase 3 study [NCT05680818] is investigating encaleret, an oral calcilytic, which has the

potential to be the first targeted treatment for ADH1. The sponsored genetic testing program offers an efficient pathway for diagnosing genetic causes in patients with non-surgical hypoparathyroidism and, in accordance with consensus guidelines, enables improved care for those with an identified genetic etiology.

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P228

JOINT1411

Skeletal characterization of patients with PLS3-associated early onset osteoporosis in comparison to patients with osteogenesis imperfecta type i

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Introduction
PLS3-associated X-linked early-onset osteoporosis (EOOP) is a rare condition that was first described in 2013. Consistent with the X-linked inheritance, males are more severely affected, although varying degrees of severity have also been documented for females. The function of PLS3 and the effects of pathogenic *PLS3* variants are poorly understood. The aim of this retrospective analysis was to describe the clinical features of patients with EOOP due to variants in *PLS3* in comparison to patients diagnosed with Osteogenesis imperfecta type I.
Materials and methods
We retrospectively collected clinical data from patients diagnosed with EOOP who carry (likely) pathogenic genetic variants in the *PLS3* gene. The data were collected at the specialized outpatient clinic of the National Bone Board at the University Medical Center Hamburg-Eppendorf and include fracture history, treatment history, laboratory parameters, HR-pQCT and DXA data, as well as muscle function tests (Chair Rising Test, grip strength).
Results
Patients with variants in the *PLS3* gene had an increased number of fractures, low Z-scores and severely reduced microstructural parameters, with men being more affected than women. Compared with OI type I patients, there were no statistically significant differences in fracture frequency, but women with pathogenic variants in the *PLS3* gene had significantly higher Z-scores on DXA scans. In men with causative *PLS3* variants, HR-pQCT measurements showed a significant reduction in structural parameters compared to OI type I, especially in the cortical compartment. There were no significant differences regarding relevant laboratory parameters.
Discussion
The results of this study highlight the specific influence of pathogenic *PLS3* variants on the clinical presentation and bone structure of affected patients. In particular, the significantly reduced cortical thickness on HR-pQCT measurements in affected men suggests specific effects of the *PLS3* variants. These microstructural deficits may play a central role in the clinical presentation of patients with *PLS3*-associated X-linked early-onset osteoporosis. However, larger studies are needed to further elucidate the pathogenesis of this rare condition.

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P229

JOINT2164

X-linked hypophosphatemic rickets and FGF23 levels: the importance of a correct reference range

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Introduction
X-linked hypophosphatemic rickets (XLH) is caused by variants in the PHEX gene, leading to hypophosphatemia and significantly elevated FGF23 levels. However, there is limited data in the literature regarding reference values for FGF23 in healthy paediatric subjects and cut-off in patients with XLH.
Case report
We present the case of a 3-year-old female patient referred to our clinic for an abnormal gait, characterized by clumsy running and frequent falls. Blood tests showed normal calcium and magnesium levels, severe hypophosphatemia, elevated alkaline phosphatase and bone isoenzyme levels, normal parathormone levels, normocalciuria, and increased level of urinary phosphate. FGF23 levels were within the reference range at 24. 2 pg/mL (reference range: 23. 2–95. 4 pg/mL). X-rays revealed lateral bowing of the femurs and tibias, predominantly tibial varus deformity, widened metaphyses of the tibia and femur, irregular physeal contours, medial sclerosis, and bilateral femoral neck varus. Initial diagnosis of inherited non-FGF23-mediated hypophosphatemic rickets was made. Calcitriol and inorganic phosphate salts treatment was started. During follow-up, FGF23 levels progressively increased (44. 6 pg/ml at 3 months and 80. 6 pg/ml at 6 months). Alkaline phosphatase remained elevated while phosphate levels were low (2. 8 mg/dl at 6 months). Other blood tests showed no significant changes. Based on these clinical and laboratory findings, a genetic evaluation was performed. Genetic analysis identified the c. 1601C>T, p. Pro534Leu heterozygous variant in the PHEX gene, classified as pathogenic and associated with XLH.
Conclusions
Generally, FGF23 levels appear significantly elevated in patients with XLH, but they can sometimes appear falsely normal. Moreover, reference values for the paediatric age group have not yet been standardized: FGF23 levels exhibit diurnal fluctuations and vary based on age, pubertal stage, and clinical context, as demonstrated in a 2024 Italian monocentric study (Baroncelli *et al*.). Multicentric studies are needed to establish FGF23 reference values for paediatric patients and those with XLH genetically confirmed. In clinically and radiologically suspicious cases for XLH, without definitive laboratory tests, paediatric endocrinologists should frequently reassess the complete calcium-phosphorus profile, including FGF23 and urinary tests, while also considering genetic evaluation even when FGF23 levels continue to appear normal. A change in the diagnostic suspicion, awaiting the results of genetic investigation, and the early start of specific PHEX's treatment could improve the patient's clinical outcome.

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P230

JOINT1449

Getting bone health right from the start: new tools for bone mineral density evaluation and determinants of BMD from pregnancy to 12 months of life

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Introduction
Bone health begins with maternal well-being and nutrition, which influences skeletal mass and bone mineral density (BMD) in utero. BMD preservation during skeletal growth is a main goal of primary prevention of osteopenia and osteoporosis in adulthood. Bone health can be determined by fetal programming where oxidative stress, endocrine disrupting chemicals (EDCs), and microRNAs (miRNAs) play an important role. The radiofrequency echographic multi spectrometry (REMS) technique has been extensively used for the measurement of BMD in adults.
This project aims to evaluate skeletal status from the perinatal period up to 12 months of life, assessing the feasibility of REMS in newborns, and to explore new associations regarding oxidative stress, EDCs, and miRNAs between mother-infant dyads and BMD.
Methods
200 mother-infant dyads were enrolled in this ongoing prospective multicenter longitudinal study. We are assessing BMD of the proximal femur with REMS technology in mothers, fetuses, newborns, and infants at 1, 3, 6, and 12 months of life. Blood and urine samples have been collected for the assessment of oxidative stress, miRNAs, and EDCs, respectively. The creation of a reference database, including 100 fetuses/newborns, was required to apply REMS technology for the first time in this population.
Results
Preliminary data from the REMS reference database showed that the specific settings for acquiring structures located between 10- and 15-mm depth appeared suitable for children from 0 to 1 month but not for babies aged 3 months. Therefore, the final adopted configuration of REMS for the evaluation of children from 0 to 3 months

included the following: BeamFormer: Echo Blaster 128 Rev. C; Linear Probe 40 mm: HL9. 0/40/128Z-4; Focus: Dynamic Focus: No; Focus Number: 1; Focus Set 4; Focus Depth: 18 mm (Coverage: 0–25 mm); Depth: Fixed at 60 mm; Frequency: 5 MHz; Power: 54%; Gain: 58%.
Conclusion
REMS technology seems to be applicable for the assessment of BMD in infants. Further investigations will be performed to develop settings for children up to 1 year, by defining age-appropriate reference data, and to examine associations of oxidative stress, EDC exposure, and expression levels of miRNAs in cord serum with BMD obtained by REMS.

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P231

JOINT2638

Genotype-phenotype insights and longitudinal outcomes in WNT1-related osteogenesis imperfecta type XV: a 14-year study of 44 chinese patients

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Background
Osteogenesis imperfecta (OI) type XV, caused by biallelic WNT1 variants, is a rare autosomal recessive skeletal dysplasia linked to impaired osteoblast differentiation. Despite growing recognition of WNT1-related OI, longitudinal clinical data on disease progression and treatment efficacy remain sparse.
Methods
This 14-year cohort study analyzed 44 Chinese patients from 42 unrelated families with OI type XV. The pathogenic mutations were detected by Whole-Exome Sequencing (WES) and verified by Sanger sequencing. Longitudinal assessments included fracture history, spinal radiography, dual-energy X-ray absorptiometry (DXA), and biochemical markers (serum β-CTX, P1NP, calcium, phosphate, ALP).
Results
Two hotspot variants, c. 677C>T(p. S226L) (19. 2%) and c. 301C>T(p. Arg101Cys) (11. 5%), predominated. Key phenotypic features included severe skeletal fragility (mean fracture rate: 19. 3±18. 9; range: 4–100), early-onset fractures (66. 7% within 1 year), universal thin cortical bone (100%) and metaphyseal enlargement (100%), spinal compression fractures (84. 2%), humeral curvature (64. 1%), and extraskeletal manifestations: ptosis (70. 0%), scoliosis (61. 0%), blue sclera (32. 4%), and intellectual abnormalities (28%). Bisphosphonate therapy, initiated at a mean age of 3. 7 years (duration: 7. 7±4. 0 years), improved vertebral height in 80. 9% of patients within 1 year. However, β-CTX and P1NP levels not decreased in 97. 7% of patients, with no long-term reduction in fracture risk or skeletal deformity progression. Two patients died during follow-up.
Conclusions
This study delineates the natural history of OI type XV, marked by profound skeletal fragility and distinct extraskeletal features. While bisphosphonates transiently improved vertebral architecture, their limited long-term efficacy highlights the necessity for WNT pathway-targeted therapies. Our findings expand the genotypic and phenotypic spectrum of OI and provide critical insights for mechanistic studies and genotype-phenotype correlations.

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P232

JOINT3340

Increased MMP13-bip interaction and activated ER stress contribute to SEMD in patient-ipsc-derived chondrogenic with MMP13 variant

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Background
Spondyloepimetaphyseal dysplasia (SEMD) is a rare developmental disorder of bone and cartilage with short stature and skeletal deformities affecting the extracellular matrix of cartilage. MMP13 (collagenase-3) has been considered to have an important role in skeletal biology in view of its exclusive presence in the skeleton during embryonic development in cartilaginous growth plates and primary centers of ossification. MMP13 takes part in catalyzing ECM components in the growth plate and at the same time cleaving and releasing biologically active molecules stored in the ECM, such as VEGFA, essential for chondrogenic differentiation, apoptosis, and matrix remodeling. Although previous studies had identified the association of $SEMD_{MO}$ with a missense *MMP13* mutation, the mechanism by which $SEMD_{MO}$ is associated with MMP13 is poorly understood.
Patient and Methods
The proband was a 5. 5years old male exhibiting short stature(-3. 27SD). His X-ray examination revealed ulnar and radial bones with widened metaphysis, "brush and cup-like"changes, irregular edges. The WES analysis showed the probably pathogenic variant c. 124T>G in heterozygosity in exon2 of the MMP13 gene, described in the literature in patients with SEMD. The proteins which possibly could interact with MMP13 were preliminarial identified through CoIP-MS method and a bioinformatic analysis has been made as well. CoIP-WB experiment was used to verify the *in vivo* interaction. We generated induced pluripotent stem cells (iPSCs) from peripheral blood mononuclear cells (PBMCs) via nucleofection with episomal plasmids. These iPSCs were further differentiated into chondrogenic via mesenchymal stem cells (MSCs). RT-PCR and Western blot methods were used to substantiate whether both transcription level and protein level of PERK, ATF6, IRE1a are upregulated by BiP.
Results
Cell lines harboring the variant displayed decreased amount of MMP13 proteins in culture medium and degraded misfolded protein fragments of approximately 30kDa of the mutant protein intracellular through the ubiquitin-proteasome system. The results of CoIP-MS experiments and related bioinformatics analysis showed that the *MMP13* Y42D variant increased the interaction between MMP13 and Bip and these proteins were mainly involved in several biological processes, including protein folding, protein processing in ER, response to ER stress. In patient-iPSC-derived chondrogenic, both transcription level and protein level of PERK, ATF6, IRE1a are upregulated by BiP.
Conclusion
Our study indicate that the variant in *MMP13* lead to increasing MMP13-Bip protein interaction, activating endoplasmic reticulum stress. Under ER stress, Bip could upregulate transcription and expression level of PERK, ATF6, IRE1a and promote cell death.

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P233

JOINT73

Non-interventional post-authorisation safety study of burosumab in the treatment of children and adolescents with X-linked hypophosphataemia: second interim analysis

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Burosumab, a fully human anti-FGF23 antibody is approved for treating X-linked hypophosphataemia (XLH), a rare, genetic, progressive, deforming bone disease. As part of the burosumab risk management plan, a post-authorisation safety study (PASS) was initiated, utilizing International XLH Registry (NCT03193476) data. The PASS is a 10-year multi-centre, non-interventional, observational study. Primary objectives assessed safety outcomes in children and adolescents with XLH, including participants with chronic kidney disease (CKD). The secondary objective compared burosumab and conventional therapy safety outcomes. Of participants enrolled by the 29-Sep-2023 datacut, 340 received burosumab

Table 1: Safety outcomes

	SAF participants				
n, (%)	Total (n = 340)	Normal: GFR ≥90 mL/min/1.73 m^2[n = 43]	CKD* (n = 51) Mild-to-moderate/severe: GFR ≥30–<90 mL/min/1.73 m^2[n = 6]	Severe CKD-to-kidney failure: GFR <30 mL/min/1.73 m^2 [n = 2]	CSAF participants (n =91)
Any AE	**127 (37. 4)**	**14 (32. 6)**	**3 (50. 0)**	**0**	**20 (22)**
Possibly/probably related to treatment	54 (15. 9)	9 (20. 9)	1 (16. 7)		5 (5. 5)
Possibly/probably related to burosumab	49 (14. 4)	8 (15. 7)	0		
Leading to death	0				0
Leading to treatment withdrawal	2 (0. 6)				1 (1. 1)
Possibly/probably related to treatment leading to treatment withdrawal	0	0			1 (1. 1)
Any serious AE	**12 (3. 5)**	**1 (2. 3)**			**0**
Possibly/probably related to burosumab	3 (0. 9)	0			
Hospitalisations	**244 (71. 8)**				**65 (71. 4)**
Hyperphosphataemia	**1 (0. 3)**				**0**
Elevated parathyroid hormone	**7 (2. 1)**				**1 (1. 1)**
Ectopic mineralisation	**5 (1. 5)†**				**1 (1. 1)**

*Defined as abnormalities of kidney structure or function, present for >3 months. †Nephrocalcinosis. AE, adverse event; CKD chronic kidney disease; CSAF, cohort SAF; GFR, glomerular filtration rate; SAF, safety analysis set.

(Safety Analysis Set [SAF]), 91 received conventional therapy (Cohort SAF [CSAF]). Of SAF participants, 51/340 (15. 0%) had CKD. SAF and CSAF adverse event (AE) reporting were solicited and unsolicited, respectively (Table). Hospitalisation data were separate and independent from AE reporting and not necessarily linked to AEs. Most common AEs in the SAF cohort were 'Pain in extremity, ' 'Headache' and 'Arthralgia. ' Of CSAF participants, most common AEs were 'Pain in extremity, ' 'Headache' and 'Abdominal pain. ' No deaths were reported in either cohort. Hospitalisations (inpatient and outpatient) were common in both cohorts; hyperphosphataemia, ectopic mineralisation and elevated parathyroid hormone were rare. The safety profile of burosumab was consistent with previous reports, with no new safety concerns. The most common AEs were typical of paediatric populations or frequent manifestations of XLH. AE frequency in CKD participants was similar compared with SAF participants. Long-term safety outcomes were similar between the SAF and CSAF cohorts.

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P234

JOINT712

CALIBRATE-PEDS: a phase 2/3, multicenter, single-arm study evaluating the pharmacokinetics, efficacy, and safety of encaleret in pediatric participants with autosomal dominant hypocalcemia type 1

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Objectives
Autosomal dominant hypocalcemia type 1 (ADH1), caused by gain-of-function variants in the calcium-sensing receptor gene, is characterized by low/-inappropriately normal parathyroid hormone (PTH), hypocalcemia, and hypercalciuria. Standard-of-care (SoC) treatment (calcium and active vitamin D) worsens hypercalciuria, increasing renal morbidity. Encaleret, a negative allosteric modulator of the calcium-sensing receptor, is under investigation as a potential ADH1 treatment. In a Phase 2b study [NCT04581629] in 13 adults with ADH1, encaleret led to sustained normalization in PTH, albumin-corrected calcium (cCa), phosphorus, magnesium and 24-hr urine calcium (UCa) excretion over 24 weeks, without serious adverse events reported. A Phase 3 study [NCT05680818, CALIBRATE] in adults with ADH1 is ongoing. CALIBRATE-PEDS is a Phase 2/3 study evaluating pharmacokinetics (PK), efficacy, and safety of encaleret in children with ADH1.
Methods
Approximately 28 children (birth-18y) will be enrolled in 4 age cohorts sequentially, starting with the oldest cohort (12-18y). After 3-6 months of stable SoC/PTH treatment, eligible participants will enter Period 1, an inpatient stay lasting up to 6 days, for PK sampling and individualized dose titration. Period 2 follows, during which encaleret doses will be optimized to maintain target cCa while minimizing UCa over 20 outpatient weeks. Period 3 is a 4-week dose maintenance period, when the dose is intended to be fixed. Participants may then continue into a long-term extension period for safety monitoring and continued access to encaleret. PK data from Period 1 will be used to refine population-based PK modeling and inform dosage in younger cohorts.
Results
The primary endpoint is the composite endpoint of a) cCa within 2. 1 to 2. 6 mmol/l in participants aged ≥1year, and within 2. 0to 2. 8 mmol/l in participants aged <1year and b) UCa <0. 1 mmol/kg/d in toilet-trained participants or spot ratio of UCa/UCr within the age-specific reference range in non-toilet-trained participants. Participants meeting both criteria at the end of Period 3 will be considered responders. Key secondary endpoints include safety and tolerability, mineral homeostasis, renal ultrasound, bone density, and self-reported outcomes. The statistical analyses will be descriptive; no statistical testing is planned.
Conclusions
CALIBRATE-PEDS is the first pediatric study of encaleret. It is under development and is expected to be initiated globally in 2025.

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P235

JOINT2575

Triptorelin effects on linear growth and bone mineral density in transgender adolescents: a longitudinal study

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Background
Gonadotrophin-releasing hormone (GnRH) analogues are widely used to suppress puberty in adolescents with gender dysphoria. While effective in halting endogenous pubertal progression, concerns persist regarding their impact on linear growth and bone mineral density (BMD) during a crucial period of skeletal growth. Understanding this impact is essential to optimise care and mitigate potential long-term risks.
Objective
To assess the effects of triptorelin on linear growth and BMD in transfeminine and transmasculine adolescents followed in a paediatric endocrinology clinic.
Methods
This was a longitudinal study conducted in a paediatric endocrinology clinic between January 2020 and December 2024. The study included adolescents with gender dysphoria who were treated with triptorelin for at least two years. Growth parameters and BMD (measured by dual-energy X-ray absorptiometry, DXA) were evaluated at baseline and follow-up. BMD Z-scores were analysed using reference values based on sex assigned at birth. Biochemical markers of bone metabolism, including blood calcium, phosphate, vitamin D, parathormone (PTH), and alkaline phosphatase, were also assessed.
Results
22 adolescents were analysed: 15 transmasculine and 7 transfeminine; aged 14–19 years; referred to the clinic between 12 and 15 years old. Triptorelin use was associated with transient growth deceleration, with partial catch-up after discontinuation. Transmasculine individuals showed greater preservation of height SDS compared to transfeminine individuals. BMD Z-scores declined during GnRH analogue treatment in both groups, with more pronounced reductions in transfeminine individuals. Of the 15 individuals who commenced gender-affirming hormone therapy (GAHT), a partial recovery in BMD was observed; however, some remained below expected reference values for their age. Mean blood calcium levels were 2. 30 ± 0. 10 mmol/l, phosphate 1. 20 ± 0. 15 mmol/l, 25-hydroxyvitamin D 45 ± 10 nmol/l, PTH 4. 5 ± 1. 2 pmol/l, and alkaline phosphatase 150 ± 40 U/l, indicating transient bone turnover alterations.
Conclusion
Our findings highlight the effects of triptorelin on growth and bone health in adolescents undergoing puberty suppression. The observed decline in BMD

underscores the importance of regular monitoring and early interventions to support bone health. While GAHT appears to facilitate partial BMD recovery, further research is needed to establish optimal management strategies. These results contribute to a growing body of evidence guiding best practices in gender-affirming care for adolescents.

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P236

JOINT370

Vitamin D supplementation during pregnancy does not improve maternal bone mineral density at 4 years post-partum

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Objectives
During pregnancy and lactation, mobilisation of the maternal skeleton ensures sufficient calcium is available for fetal skeletal mineralisation. Maternal bone mineral density (BMD) typically reduces during these stages of the life course, with subsequent recovery after lactation ends. Recent trials have shown that pregnancy vitamin D supplementation can increase offspring BMD in childhood, but the effect on the maternal skeleton is poorly described. We previously demonstrated reduced maternal bone turnover (measured by urinary c-telopeptide) in pregnant women supplemented with cholecalciferol compared to placebo, but an effect on maternal BMD immediately after delivery was not detected in a subset of the women. Here, we assessed the effect of pregnancy vitamin D supplementation on the maternal skeleton in the medium term.
Materials and Methods
MAVIDOS was a randomised placebo-controlled trial of 1000 IU/day cholecalciferol from 14-17 weeks gestation until delivery. Participants were invited to have a Dual-Energy Xray absorptiometry (DXA) scan of the whole-body (analysed less head: WBLH), lumbar spine (LS) and left hip at 4 years after delivery. A subset of the women also had a DXA scan within 2 weeks of delivery. BMD at 4 years postpartum was compared between groups using linear regression in unadjusted and adjusted models (age, further pregnancy, duration of lactation, height, weight). β (95%CI) represents the effect of cholecalciferol compared to placebo. In women with DXA at both time points, the effect of cholecalciferol was assessed using mixed effects modelling to account for repeated measures.
Results
DXA imaging was performed on 443 participants (225 placebo, 218 cholecalciferol) at a median of 4. 1 years (IQR 4. 0, 4. 2) after delivery. Late pregnancy serum 25-hydroxyvitamin D was higher in the supplemented women (placebo 42. 0 nmol/l (SD 21. 5), cholecalciferol 70. 4 nmol/l (SD 19. 0), $P < 0.001$). BMD measured 4 years after delivery did not differ between the two randomization groups in unadjusted or adjusted analyses (adjusted WBLH $\beta = 0.000$ g/cm^2 (0. 012, 0. 012), LS $\beta = 0.009$ g/cm^2 (-0. 010, 0. 027), total hip $\beta = 0.004$ g/cm^2 (-0. 014, 0. 022)). 223 women had DXA at birth and 4 years. BMD increased between the two scans in both groups (placebo WBLH 6. 3%, LS 1. 2%, hip 2. 2%; cholecalciferol WBLH 6. 2%, LS 1. 0%, hip 2. 4%, $P < 0.05$ for all). However, the randomisation group had no effect on BMD ($p > 0.05$ for all).
Conclusions
Despite previously demonstrated increases in offspring BMD in childhood in the same trial, in this study, pregnancy supplementation with 1000 IU/day cholecalciferol did not benefit maternal BMD measured by DXA.

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P237

JOINT933

Characterization of bone density, strength, and mineral metabolism in 20 adults with monoallelic ENPP1 pathogenic variants

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Background
Biallelic loss-of-function (LOF) *ENPP1* variants cause generalized arterial calcification of infancy type 1 (GACI1) and autosomal recessive hypophosphatemic rickets type 2 (ARHR2). *ENPP1* encodes an enzyme that generates inorganic pyrophosphate (PPi), a mineralization inhibitor. Loss of ENPP1 function leads directly to PPi deficiency and indirectly to fibroblast growth factor 23 (FGF-23) excess. Animal data support a role for ENPP1 as a regulator of bone mass; case reports suggest that humans with monoallelic *ENPP1* variants may develop osteoporosis. The objective of this study was to characterize bone density, strength, and mineral metabolism in adults with monoallelic *ENPP1* variants.
Methods
Symptomatic (atraumatic vertebral or long bone fractures, pain interference, early onset cardiovascular disease) and asymptomatic individuals with monoallelic *ENPP1* variants were eligible. Outcome measures included whole body, hip, lumbar spine, and forearm areal bone mineral density (aBMD) by dual energy X-ray absorptiometry (DXA, Hologic), cortical and trabecular volumetric BMD (vBMD) and strength (stiffness, failure load) of the radius and tibia by high resolution peripheral quantitative computed tomography (HR-pQCT, Scanco) expressed as Z-scores for age and sex. Mineral metabolism markers were determined by standard clinical assays, PPi by an ATP sulfurylase/luminescence-based enzymatic method (Inozyme).
Results
Twenty individuals (11 female, 10 symptomatic), median age 38 years (range 20-54) completed the study. Thirteen participants (65%) reported a total of 27 lifetime fractures. Within the symptomatic cohort, pain interfering with daily activities was the most prevalent symptom (80%); demographics did not differ by symptomatic status. Mean ($\pm$SD) aBMD-Z ranged from -0. 4$\pm$0. 8 (forearm) to 0. 3$\pm$0. 6 (whole body); no subjects had low aBMD at any site. HR-pQCT analysis revelaed relative deficits in trabecular vBMD vs cortical vBMD at distal radius (-0. 9$\pm$1. 1 vs 0. 3$\pm$0. 7, $P < 0.01$) with a similar trend at distal tibia (-0. 9$\pm$1. 1 vs -0. 3$\pm$1. 2, $P = 0.18$). Failure load and stiffness Z-scores were both -0. 4$\pm$0. 6 at the radius and -0. 8$\pm$0. 9 at the tibia. Blood phosphate and alkaline phosphatase were normal in all participants; FGF-23 was elevated in one male. PPi did not differ by symptomatic status and was not correlated with bone outcomes.
Conclusion
Fractures and musculoskeletal pain were common in this cohort of adults with monoallelic *ENPP1* variants. In contrast to prior reports, aBMD was normal in all participants. Mild deficits in trabecular vBMD and bone strength were found by HR-pQCT; however, these were not related to symptomatic status, serum PPi, or markers of mineral metabolism. Further genotype/phenotype studies may clarify the contribution of ENPP1 to bone health.

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P238

JOINT637

Estimating the risk of chronic kidney disease progression in chronic hypoparathyroidism: a retrospective matched cohort study, using real world data from England

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Hypoparathyroidism is an endocrine disease caused by insufficient levels of parathyroid hormone (PTH). Postsurgical hypoparathyroidism accounts for most cases; other etiologies include genetic, autoimmune, and idiopathic (non-surgical). Conventional therapy, active vitamin D and calcium, aims to alleviate hypocalcemia but does not address insufficient PTH levels and is associated with hypercalcemia which may increase chronic kidney disease (CKD) risk. We assessed CKD risk in patients with hypoparathyroidism compared to non-hypoparathyroid individuals using routinely collected healthcare data from England. English linked primary (Clinical Practice Research Datalink [CPRD] Aurum) and secondary care (Hospital Episode Statistics) data were used to identify patients aged $\geq$18 years with incident chronic postsurgical ($n = 215$) or prevalent chronic non-surgical ($n = 730$) hypoparathyroidism between 01/Apr/2008–22/Mar/2019. Patients were matched 1:10 to non-hypoparathyroid controls on 5-year age bands, gender, and $\geq$1 year overlap in CPRD registration periods. CKD progression was compared between patients with

Table 1: CKD progression in patients with hypoparathyroidism

Outcome	Post-surgical hypoparathyroidism N progressed (N considered)	HR (95%CI)	Adjusted HR (95%CI)	Non-surgical hypoparathyroidism N progressed (N considered)	HR (95%CI)	Adjusted HR (95%CI)
CKD1/2 to CKD3	13 (144)	2. 74 (1. 52-4. 94)	3. 02 (1. 67-5. 47)	56 (536)	3. 06 (2. 30-4. 07)	4. 05 (3. 03-5. 42)
CKD3 to CKD4	<5 (25)	1. 53 (0. 44-5. 33)	2. 21 (0. 59-8. 29)	17 (158)	2. 44 (1. 39-4. 29)	2. 94 (1. 54-5. 63)
CKD4 to CKD5	<5 (9)	2. 00 (0. 17-23. 18)	*	14 (57)	2. 30 (0. 99-5. 32)	1. 80 (0. 71-4. 56)
CKD4 to dialysis	<5 (9)	3. 67 (0. 21-63. 87)	*	6 (57)	2. 92 (0. 73-11. 71)	2. 13 (0. 45-10. 03)

*Insufficient sample CI = confidence intervals; HR = hazard ratios

hypoparathyroidism and controls using Cox proportional hazards regression adjusted for age (at surgery for postsurgical and follow-up start for non-surgical), gender, and cardiovascular disease presence. Progressions of CKD1/2 to CKD3, CKD3 to CKD4, CKD4 to CKD5, and CKD4 to dialysis were determined from recorded diagnoses. Patients without CKD at hypoparathyroidism diagnosis were conservatively assumed as CKD1/2. Each progression comparison was limited to patients with the starting CKD stage at hypoparathyroidism diagnosis or during follow-up, and censored at earliest of CKD progression, death, end of CPRD registration, or 22/Mar/2020. Patients with postsurgical hypoparathyroidism had a 3-fold increase in CKD1/2 to CKD3 progression compared to matched controls (Table 1). Patients with non-surgical hypoparathyroidism had a 4-fold and 3-fold increase in CKD1/2 to CKD3 progression and CKD3 to CKD4 progression, respectively. Our results show increased risks of early-stage CKD progression amongst patients with hypoparathyroidism compared to non-hypoparathyroid individuals. The small sample size in this rare disease precludes definitive analysis of late-stage risk difference.

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P239

JOINT3147

Evaluation of ALP and PLP as a screening tool for ALPL mutations in hypophosphatasia: a study in chinese pediatric patients

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Background
Hypophosphatasia (HPP), an inherited metabolic disorder caused by ALPL gene mutations, manifests through deficient tissue-nonspecific alkaline phosphatase (TNSALP) activity, leading to skeletal complications and systemic morbidity. Persistent low serum alkaline phosphatase (ALP) activity is a hallmark biochemical feature, yet its non-specificity and overlap with other conditions often delay diagnosis. With the advent of enzyme replacement therapy, establishing a pediatric-specific diagnostic framework is imperative to prevent life-threatening sequelae and avoid mismanagement.
Methods
Based on the lower limit of the ALP reference interval for age-and gender-specific ranges in children, as outlined in the 'Health Industry Standards of the People's Republic of China', we included children and adolescents with persistently low ALP activity in this study. These participants underwent whole-exome sequencing (WES) and plasma pyridoxal-5′-phosphate (PLP) measurement. By analyzing the genetic mutation positivity rate in the low ALP population, we calculated the cutoff value for PLP using ROC curve analysis. Clinical phenotype data were collected to clarify the characteristics of hypophosphatasia (HPP) in the Chinese population and to explore the genotype-phenotype correlation.
Results
Among 94, 467 analyzed samples, 246 subjects had persistently low ALP activity. ALPL variants were detected in 76 of 246 individuals (30. 9%) by WES. ROC curve analysis identified a PLP cutoff value of 21. 3 ng/mL (sensitivity 74. 6%, specificity 84. 4%). When PLP $\geq$ 21. 3 ng/mL, the positive predictive values for ALP mutation was 62. 4% (58/93). Further analysis revealed that PLP (AUC = 0. 819, P < 0. 05) was a better predictor of ALPL gene positivity than ALP (AUC = 0. 784, P < 0. 05). The carrier frequency of ALPL heterozygous mutations was approximately 1/500 to 1/133, missense mutations accounted for 80. 7% of ALPL mutations, with the most common being p. Arg136His (10. 8%). Not all carriers exhibited clinical symptoms, genotype-phenotype correlation study showed that 100%, 88% and 77% of carriers with severe dominant negative effect (DNE) mutation, severe haploinsufficiency (HI) mutation and moderate HI mutation of ALPL gene had clinical symptoms. The proportion of severe DNE mutation carriers with 1 or 2 symptoms was the highest, 60% and 40%, respectively. p. Arg136His were recognized in patients with fractures and epilepsy.
Conclusion
Our study identified PLP as a cost-effective screening biomarker for HPP in children and as a reliable biomarker for predicting ALPL mutations. We found that the carrier frequency of p. Arg136His is relatively high in the Chinese population. These findings also provide valuable insights into the genetic and phenotypic characteristics of HPP in the Chinese population.

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P240

JOINT2379

Renal safety of zoledronic acid infusion in osteoporosis patients: a retrospective analysis

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Introduction
Zoledronic acid (ZA) is a bisphosphonate used for osteoporosis and malignancy-associated hypercalcemia. It is given intravenous infusion annually. While generally safe, isolated cases of acute kidney injury (AKI) have been reported, particularly in cancer patients receiving high cumulative doses, those with pre-existing renal insufficiency, and those with nephrotoxic therapy history. Kidney function monitoring, especially in older adults, is essential as AKI can also occur in low-risk patients. ZA is not recommended for patients with creatinine clearance below 35 mL/min. Osteoporosis guidelines suggest using the Cockcroft-Gault formula to estimate renal function before infusion, though many labs now report eGFR using the 2021 CKD-EPI formula. This study evaluates changes in serum creatinine (SCr), AKI incidence, and renal safety using eGFR (2021 CKD-EPI).
Methods
We retrospectively analyzed data from patients receiving at least two ZA infusions. Changes in SCr before and after infusion and AKI incidence within one year were recorded.
Results
A total of 452 infusions from 226 patients met the criteria. The mean age was 74. 2 $\pm$ 9. 8 years, and 93. 4% were female. The baseline T-score was -2. 95 $\pm$ 0. 86. 11. 5% had a baseline GFR <60 mL/min/1. 73 m^2 (stage 3 CKD). The mean baseline SCr was 0. 80 $\pm$ 0. 18 mg/dL, with an average GFR of 78. 5 $\pm$ 14. 8 mL/min/1. 73 m^2. The mean SCr increase was 0. 04 mg/dL ($P < 0.0001$). Table 1 outlines renal outcomes. There was 5 (%2. 2) AKI, two of them progressed to chronic renal failure due to additional comorbidities. 124 of the patients were >75 years old. In older patients The average baseline SCr was 0. 83 ($\pm$ 0. 19) mg/dl, corresponding to an average GFR of 71. 8 ($\pm$ 13. 4) mL/min/1. 73 m2. The mean difference in SCr was 0. 06 (95% confidence interval, 0. 109–0. 02, $P = 0.002$) lower in the after-period which was statistically significant.
Discussion
Our study results show no clinically meaningful changes in serum creatinine (SCr) levels following zoledronic acid (ZA) infusions, and ZA-induced acute kidney injury (AKI) or renal failure was rare, occurring only in older patients receiving treatment for osteoporosis. While the 0. 04 mg/dL increase in SCr was statistically significant, we do not consider it clinically significant. Additionally, since the study had a maximum follow-up of one year, we cannot evaluate the long-term effects of treatment.

	Preinfusion (n = 226)	Postinfusion (1. year) (n = 226)	p
Serum Creatinine (mg/dl)	0.80 $\pm$ 0.18	0.84 $\pm$ 0.24	<0.001
GFR (mL/min/1. 73 m2)	78.5 $\pm$ 14.8	74.0 $\pm$ 16.8	<0.001
Distribution (n, %)			
$\geq$60	197(87. 2)	177(78. 3)	
45-59	21(9. 3)	34(15)	
30-44	4(2. 2)	12(5. 3)	
<35	0(0)	3(1. 3)	

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P241

JOINT3571

Real-world bone health outcomes in surgical, medical, and monitored patients with primary hyperparathyroidism

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Background
Primary hyperparathyroidism (PHPT) leads to hypercalcemia and increased fracture risk due to parathyroid hormone overproduction. While surgery is the standard curative treatment, optimal bone health management strategies remain unclear. This study evaluates real-world bone mineral density (BMD) changes, fracture risk and treatment in PHPT patients undergoing surgical, medical, or monitoring-based management.
Methods
A retrospective analysis was conducted on patients diagnosed with PHPT between 2012-2019. Data collected included demographics, PHPT management, baseline and longitudinal BMD, fracture risk (assessed with Fracture Risk Assessment Tool, FRAX), and osteoporosis management. Statistical analysis was performed using Prism software.
Results
A total of 758 patients (81% female, mean age 65 $\pm$ 16 years) were included. Of these, 52% underwent parathyroidectomy, 14% received long-term cinacalcet (medical group), and 34% were monitored without active treatment. Baseline BMD at the spine, hip, and wrist was comparable across groups (wrist BMD: 0. 68 $\pm$ 0. 2 g/cm^2 vs. 0. 67 $\pm$ 0. 1 g/cm^2 vs. 0. 68 $\pm$ 0. 2 g/cm^2; $P > 0.9$). Mean follow-up duration for repeat DXA was 2. 8 years. The monitored cohort had the highest baseline major osteoporotic fracture (MOF) risk (35 $\pm$ 21%) compared to the medical (16. 3 $\pm$ 0. 1%, $P < 0.001$) and surgical groups (16 $\pm$ 0. 2%, $P < 0.001$). Hip fracture risk was highest in the monitored group (12. 7 $\pm$ 7%) compared to the medical (6. 7 $\pm$ 0. 1%, $P < 0.001$) and surgical groups (4. 8 $\pm$ 0. 2%, $P < 0.001$). On repeat DXA, the surgical group demonstrated the greatest BMD gains at all sites: **Spine BMD change:** +3. 1% (surgical) vs. -2. 78% (medical) vs. -0. 91% (monitored), $P < 0.001$. **Hip BMD change:** +1. 18% (surgical) vs. -5. 69% (medical) vs. -3. 87% (monitored), $P < 0.001$. **Wrist BMD change:** +4. 71% (surgical) vs. -4. 71% (medical) vs. -6. 17% (monitored), $P < 0.001$. There were no significant differences in BMD changes between the medical and monitored groups. As per National Osteoporosis Guideline Group thresholds, high/very high fracture risk was identified in 43% (medical & monitored) vs. 31% (surgical) of patients, $p < 0.02$. Despite this, only 42% (surgical), 57% (medical), and 56% (monitored) received osteoporosis treatment, indicating suboptimal management.
Conclusion
In this large cohort, surgical treatment resulted in significant BMD improvements at all sites, with the greatest gains at the wrist. No differences were observed between the medical and monitored groups, suggesting cinacalcet *alone* is insufficient to improve bone health in PHPT. A more proactive osteoporosis management strategy is needed, particularly for non-surgical cohorts.

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P242

JOINT747

Exploring parathyroid carcinoma: clinical and pathological observations from a two-decade review

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Background
Parathyroid carcinoma is an extremely rare endocrine malignancy, comprising less than 1% of primary hyperparathyroidism cases and only 0. 005% of all cancers. Its clinical presentation and symptoms primarily result from hypercalcemia rather than from local invasion or distant metastasis.
Material and methods
A retrospective study was performed, analysing all histopathologically confirmed cases of parathyroid carcinoma identified among primary hyperparathyroidism cases between 2004 and 2024. The demographics and clinical characteristics of these parathyroid carcinoma cases were compared to a randomly selected group of parathyroid adenoma cases in a 2:1 ratio. Clinical and laboratory parameters of all parathyroid carcinoma cases were thoroughly evaluated.
Result
In our study, the prevalence of parathyroid carcinoma was 3% ($n = 16$) among all diagnosed cases of primary hyperparathyroidism. The mean age at presentation was 50. 3$\pm$11 years in the carcinoma group and 47$\pm$18 years in the adenoma group. Males were predominant in the parathyroid carcinoma group, while females were more prevalent in the adenoma group. Compared to parathyroid adenoma, carcinoma cases showed more palpable masses (82% vs. 6. 3%; $P < 0.001$), higher rates of gastrointestinal symptoms, nephrolithiasis, pancreatitis. One patient had reversible Mobitz Type 1 heart block in carcinoma group. Investigations showed that carcinoma group had lower albumin (3. 6$\pm$0. 8 g/dL vs. 4. 2$\pm$0. 7 g/dL; $P < 0.01$), and higher serum creatinine (1. 4$\pm$0. 6 mg/dL vs. 1. 1$\pm$0. 5 mg/dL; $P < 0.05$). In patients with parathyroid carcinoma mean levels of calcium, phosphorus, alkaline phosphatase, iPTH and vitamin D were 13. 7$\pm$2. 1 mg/dL, 2. 3$\pm$0. 6 mg/dL, 301$\pm$169 IU/l, 123. 3$\pm$137 pmol/l, 43. 5$\pm$32. 2 nmol/l respectively (no significant difference from parathyroid adenoma). Mean size of involved parathyroid gland in USG was 2. 7$\pm$1. 1 cm. Most involved gland was inferior parathyroid. Histopathology of the carcinoma group revealed capsular invasion (88%), vascular invasion (68%), necrosis (88%), mitotic figures (50%), and perineural invasion (63%). Predictor of risk factors for parathyroid carcinoma were palpable mass and gland size >3 cm. All patients underwent surgical resection, with additional treatments including cinacalcet 3 (19%), radiotherapy 3 (16%), and TACE 1 (6%). Recurrence was observed in 5 (31%) patients.
Conclusion
Palpable neck mass, gland size >3 cm were key predictors of parathyroid carcinoma, while recurrence was predicted by calcium >14 mg/dL, gland size > 3 cm, and extrathyroidal extension with recurrence rate of 31%.

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P243

JOINT983

Obesity and blunted FGF23 response associate with kidney impairment in patients with hypoparathyroidism

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Hypoparathyroidism is an endocrine disease characterized by low or insufficient parathyroid hormone secretion leading to alterations in calcium-phosphate and skeletal metabolism. Chronic kidney disease (CKD) is a common complication of patients affected by chronic hypoparathyroidism managed with conventional therapies. However, no data are currently available regarding the endocrine and metabolic determinants of renal function in these patients. This was a multicenter observational study performed in three health-care centres. Patients with hypoparathyroidism were consecutively enrolled during follow-up visits in 2022-2023. These exclusion criteria were adopted: patients managed with dialysis, proteinuria (>200 mg/24h), use of antihypertensive drugs including thiazides, ACE-inhibitors, angiotensin-II-receptor antagonists, alpha-beta blocking-agents, aldosterone-antagonists, and insulin-treated diabetes. A total of 46 patients were enrolled. Median age was 53 years, 34 (74%) were female and the median disease duration was 11 years. All patients were managed with conventional treatment with active vitamin D and calcium supplements, and the calcium-phosphate product was within the normal range in all patients. The 23. 7% of patients was obese (BMI $\geq$30 kg/m2) and CKD (defined with an eGFR<60 mL/min1. 73m2) was found in the 21. 7% of patients. Patients with CKD were older, affected by a longer-disease, and were more frequently obese (62% vs 13%, $P = 0.01$) and characterized by a non-significant trend toward higher BMI (30. 4 vs 24. 1 kg/m2, $P = 0.07$) as compared to those without. In multivariate analyses, obesity resulted as the only significant independent risk factor associated with CKD ($P = 0.035$, OR 3. 05, CI 1. 38–6. 77). In addition, a significant negative correlation was found between BMI and eGFR ($P = 0.034$; $r = 0.54$), and ROC analyses showed a significant global-performances of BMI to predict CKD with the best youden index of 27. 5 kg/m2 (75% sensitivity, 74% specificity and AUROC 77%, $P = 0.008$, CI 0. 42–0. 94). Patients with CKD were characterized also by higher FGF23 levels. A significant negative correlation was found between FGF23 and eGFR ($P < 0.001$; $r = 0.78$). However, evaluating separately patients with eGFR above and below 60 mL/min/1. 73m2, the correlation between FGF23 and eGFR remained statistically significant only in the first group ($P = 0.028$; $r = 0.61$) and not in those with CKD ($P = 0.7$; $r = 0.22$).

In conclusion, for the first-time, obesity was demonstrated to be independently associated with CKD in patients with hypoparathyroidism, and a blunted eGFR-related response of FGF23 was shown in patients with CKD potentially worsening the renal function in the context of hypoparathyroidism.

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P244

JOINT2173

Effects of different dietary patterns on bone health: mouse models

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Background
Bone is a dynamic tissue that undergoes continuous remodeling to maintain its shape and structural integrity. Bone remodeling, essential for maintaining bone health, involves the resorption of mineralized bone by osteoclasts, followed by the formation of new bone matrix by osteoblasts, which is subsequently mineralized. Various factors, including diet, influence this process.
Aim
Our aim was to evaluate the effects of different dietary patterns on bone health in mouse models. We fed mice for 16 and 20 weeks with normal diet (ND16w, ND20w) or Western diet (WD16w, WD20w), and for 20 weeks with combinations of normal diet + Western diet (ND20w + WD20w), normal diet + ketogenic diet (KD) (ND20w + KD20w) or Western diet + KD (WD20w+ KD20w).
Results
Micro-computed tomographical analysis of trabecular region of femoral bones showed that mice fed WD20w + KD20w had a decrease in bone volume to tissue volume ratio (BV/TV%) and trabecular thickness (Tb. Th) compared to mice fed only with western diet (WD20w) (P-values: 0. 04 and 0. 039, respectively). In cortical bone, a significant decrease in cortical thickness (Ct. Th%) comparing mice fed WD16w or WD20w with those fed ND16w or ND20w was observed (P= 0. 049 and P = 0. 0039, respectively). Interestingly, mice fed WD20w showed a significant decrease in Ct. Th% compared to mice fed the combined WD20w + ND20w (P = 0. 0011). Furthermore, mice fed the combined WD20w + KD20w diet showed a significant decrease in Ct. Th% with respect to mice fed the combined WD20w + ND20w diet (P = 0. 0018). An increase in the number of osteoclasts was observed in the trabecular bone in mice fed ND20w + KD20w vs ND20 (P = 0. 020), or WD20w + KD20w vs WD20w (P = 0. 028). In addition, the number of osteoblasts decreased significantly comparing ND + KD20w vs ND20w (P = 0. 041), as well as ND20w + KD20w vs WD20w + ND20w (P = 0. 020). An increase of osteoblast's number in mice fed WD20w + ND20w combined diet vs WD20w was observed (P = 0. 019).
Conclusions
The ketogenic diet causes an alteration of bone remodeling by shifting it towards an increase in the number of osteoclasts and a reduction in osteoblasts. The combination of the normal diet and the Western diet reduces the detrimental effects on bone of the Western di*et al*one.

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P245

JOINT2283

Efficacy of anastrozole in adolescent boys with limited growth potential: a retrospective analysis

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Introduction
Managing short stature can be challenging, often due to delayed diagnosis, as many patients have already entered puberty by their first endocrinological assessment. During puberty, sex hormones accelerate epiphyseal fusion, restricting growth potential. In adolescent boys, aromatase inhibitors may slow estrogen-driven growth plate closure, potentially enhancing adult height.
Objectives
To retrospectively assess the effectiveness of Anastrozole in increasing height Standard Deviation Score (SDS) in adolescent boys with restricted growth potential.
Methods
Medical records of 53 adolescent boys who received Anastrozole for at least three months were reviewed, collecting data on diagnosis, previous treatments, pubertal stage, anthropometrics, and bone age (BA) at treatment initiation (TI) and conclusion (TC).
Results
Among 53 patients, 9 (17%) were born small for gestational age (SGA), 3 (5. 7%) had growth hormone (GH) deficiency, and 4 (7. 5%) had central precocious puberty. In this cohort, 11 (20. 7%) had prior treatment with recombinant human GH (rhGH), while 4 (7. 5%) received GnRH analogues. At TI, the mean (± standard deviation) age was 14. 7 (±1. 8) years, with a mean BA of 14. 7 (±1. 6) years, a mean height SDS of -1. 37 (±0. 83), and BMI SDS of -0. 33 (±1. 02). The average treatment duration was 1. 1 years. At TC, there was no significant change in height SDS (-1. 38 ± 0. 90) or BMI SDS (-0. 23 ± 0. 92). However, in the subgroup of 13 (24. 5%) patients with a BA below 14 years at TI (mean BA 12. 9 ± 1. 2, mean age 12. 9 ± 1. 9 years, mean duration 1. 4 years), height SDS significantly increased from -1. 19 (±0. 72) to -0. 90 (±0. 93) (P < 0. 005). Notably, one patient did not respond to Anastrozole (height SDS at TI -2. 18 and at TC -2. 53) and was later diagnosed with an *ACAN* mutation. Furthermore, treatment was less effective in SGA patients, as their mean height SDS decreased from -0. 99 (±0. 85) at TI to -1. 29 (±0. 83) at TC, likely due to accelerated puberty. During follow-up, one patient developed transient bilateral knee synovitis and discontinued Anastrozole, but no other adverse events were reported.
Conclusion
Anastrozole may be a promising intervention for improving height outcomes in adolescent boys with limited growth potential, particularly when initiated in those with a BA below 14 years. Further research is necessary to determine the efficacy of aromatase inhibitors in specific subgroups, such as individuals with ACAN mutations or those born SGA. Regular monitoring is essential to identify potential adverse effects.

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P246

JOINT3290

Atypical parathyroid tumor in patients with primary hyperparathyroidism: predictive preoperative characteristics

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Introduction
Atypical parathyroid tumor (APT) is a rare lesion of uncertain malignant potential with characteristics similar to parathyroid carcinoma, making early diagnosis crucial to adequately plan surgery and follow-up. To date, no predictive criteria exist to differentiate APT from typical adenoma (TA) before surgery.
Aims
To identify predictive preoperative characteristics of TA and APT and compare their biochemical response to parathyroidectomy.
Methods
We retrospectively analyzed patients who underwent parathyroidectomy for primary hyperparathyroidism in our center between March 2022 and August 2024. In patients with TA and TPA, we compared: i) pre-intervention: demographic characteristics, calcium-phosphorus metabolism tests, renal and bone complications, tumor site; ii) post-intervention: type and duration of surgery after excluding patients who also underwent other interventions contextual to parathyroidectomy, histological characteristics, calcium-phosphorus metabolism at discharge.
Results
150 patients were included (age 59. 5±10. 5 years; 113 females), of whom 14 (9. 3%) had TPA. These patients were predominantly male compared to TA (78. 6% vs. 19. 1%, respectively, P < 0. 001). TPA and TA patients were similar in age and had a higher prevalence of history of other malignancies (50% vs 22. 6%, respectively, P = 0. 02). APT patients had higher calcium levels than TA (11. 7

vs. 11. 2 mg/dL, respectively, $P = 0.03$), with no significant differences in other parameters or complications. SestaMIBI scintigraphy localized APT better than TA (100% vs 79. 2%, respectively, $P = 0.04$). APT had more frequently a right-sided parathyroid location than TA (92. 9% vs. 50. 7%, $P = 0.003$), with no differences in adenoma size. Logistic regression analysis showed that male sex (OR 11. 5, 95%CI 2. 7–47, $P < 0.001$) and right-side location (OR 12. 5, 95%CI 1. 4–111, $P = 0.02$) or their combination ($P < 0.001$) were independently associated with APT. APT patients underwent longer (70 ± 26. 5 vs 52 ± 18. 4 min, $P = 0.007$) and more extensive surgery, such as "en bloc" resections and neck exploration ($P < 0.001$). APT were heavier as compared with TA (2.8 ± 2.9 vs. 1.2 ± 1.4 g, respectively, $P = 0.04$) and had more fibrosis ($P < 0.001$), but no difference in Ki-67 values was found. Finally, APT patients had higher disease persistence and/or recurrence than TA patients (21. 4% vs. 1. 5%, respectively, $P < 0.001$).

Conclusion

These preliminary data suggest that TPA and TA have similar preoperative clinical and biochemical presentations. Male gender and/or right parathyroid location appear to be associated with TPA. These patients should be cautioned as they are at higher risk for longer and more complex surgery and postoperative persistence.

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P247

JOINT2051

Does an aggressive onset affect prognosis? insights into atypical parathyroid tumors

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Introduction

Parathyroid tumors are the most frequent cause of primary hyperparathyroidism (PHPT), affecting approximately 0. 1% to 0. 3% of the general population. Most cases are attributed to benign parathyroid adenomas (PA), with hyperplasia being less common, while parathyroid carcinomas (PC) are rare, accounting for less than 1% of cases. Atypical parathyroid tumors (APT) are parathyroid tumors with uncertain malignant potential, distinguished by certain histological features commonly seen in PCs, such as a solid growth pattern, fibrous bands, and cellular atypia. However, they do not exhibit definitive signs of malignancy, such as capsular, vascular, or perineural invasion, or evidence of local invasion or metastasis. Due to the uncertain malignant potential of APT, long-term follow-up is recommended. We followed patients with PA or APT and compared the outcomes in this study.

Methods

This retrospective study includes patients who were followed up in 2 tertiary centres with PA or APT diagnoses between June 2007 and January 2025. Demographic data, including age and gender, along with biochemical parameters serum Ca, corrected calcium (cCa), phosphorus, albumin, alkaline phosphatase (ALP) parathormone (PTH), 24-hour urinary Ca, estimated glomerular filtration rate (eGFR), fractional calcium excretion (FECa), and 25-hydroxyvitamin D (25OHD) were collected. Renal imaging and dual-energy X-ray absorptiometry were used to assess nephrolithiasis and osteoporosis. The patients' data were compared at the time of diagnosis, preoperatively and at the last follow-up.

Results

47 patients with APT were compared with 596 patients with PA. Median age was similar (53 years for PA vs. 51 years for APT, $P=0.11$). PTH levels were significantly higher in APT (209 ng/l vs. 172 ng/l, $P=0.006$), while serum 25-hydroxyvitamin D levels were lower (9. 4 µg/l vs. 14. 9 µg/l, $P=0.03$). Other biochemical markers, including FECa, 24-hour urinary calcium, ALP, and corrected calcium, showed no significant differences ($P>0.05$). Osteoporosis was more prevalent in APT (64% vs 41. 9%, $P = 0.029$), while nephrolithiasis was similar ($P = 0.84$). Ultrasonographic tumor volume was significantly larger in APT (1. 65 cm^3 vs. 0. 53 cm^3, $P<0.001$). Follow-up data were available for 309 PA and 35 APT patients. The median follow-up period was 55 months for PA and 75 months for APT ($P=0.88$). Serum calcium levels remained similar (9. 12 mg/dL vs. 9. 13 mg/dL, $P=0.368$). The incidence of osteoporosis and nephrolithiasis during follow-up was comparable between groups ($P=0.31$ and $P=0.76$, respectively).

Conclusion

Despite elevated baseline PTH levels, larger tumor size, and suspicious pathological findings, APT demonstrated no significant differences in long-term outcomes compared to PA during follow-up.

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P248

JOINT940

Tumour induced osteomalacia in a teenager: successful tumour localisation (68-Ga DOTATE PET-CT), tumour genetics (FGFR1 fusion gene) and tumour removal

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Tumour induced osteomalacia (TIO) is rare and difficult to diagnose and treat in children. We report an adolescent with TIO, his diagnostic pathway, and recovery after surgery. A 14-year-old male presented with a one-year history of generalised bone pain with a prior distal radius/ulna fracture. He had normal growth, development and unremarkable family history. Examination was normal with no leg bowing. Investigations revealed severe hypophosphataemia (0. 48 mmol/l), renal phosphate loss (TMP/GFR 0. 26 mmol/l), mild hypocalcaemia (2. 15 mmol/l), high ALP (791U/l), high-normal PTH (6. 5pmol/l), undetectable urine calcium, elevated FGF23 [177RU/mL(<100)] and low 1, 25 vitamin D3 [38nmol/l(108-246)]. He had normal knee X-rays, renal ultrasound and urine aminoacids, and low bone mineral density (L1-4 BMD -2. 5 SD). TIO was diagnosed. He was started on oral phosphate, alfacalcidol and vitamin D. Genetic testing [hypophosphatemia panel (PHEX/renal phosphate wasting) and whole-genome sequencing] was normal, as expected. Imaging to identify the tumour was initiated. X-ray skeletal survey was normal. Whole body MRI suggested a 33mm ovoid lesion in the distal left femur. Ga-68 DOTATATE PET-CT was chosen for further imaging and confirmed the juxtacortical soft tissue lesion. A dedicated MRI showed the lesion was 35x14x9mm. Peripheral venous sampling from legs and arm showed very high FGF23 (898–1019mU/mL) but was unable to localise the FGF23 production. The lesion was surgically excised. Histopathology showed osteoclast-like cells and calcification, in line with a phosphaturic mesenchymal tumour. Tumour RNA analysis (TruSight RNA Pan Cancer panel) showed a *FN1-FGFR1* fusion gene. Postoperatively, phosphate supplementation was discontinued, and alfacalcidol tapered. FGF23 decreased rapidly (24RU/mL after 14 days), phosphate concentration improved, but with concomitant increase in PTH (14. 9pmol/l), 1, 25 vitamin D (919pmol/l), ALP (415 mmol/l), undetectable calciuria, and worsening bone pain suggestive of hungry bone syndrome. His symptoms improved after 2-3 months, and all medications were stopped. Three months after surgery, 1, 25 vitamin D was still high but other biochemical indices had normalised.

Conclusion

Localisation of the tumour in TIO is often unsuccessful. Whole body MRI, peripheral venous FGF23 sampling, octreotide scan and octreotide SPECT-CT are commonly used. Recently, Ga-68 DOTATATE PET-CT has shown better sensitivity in adults, although it has high radiation dose. Ga-68-DOTATATE PET-CT performed best in identifying our patient's tumour, whereas peripheral sampling for FGF23 was unsuccessful. Tumour RNA sequencing can reveal the underlying mechanism of TIO. Post-operatively, FGF23 drops rapidly, 1, 25 vitamin D rises, and hungry bone syndrome and bone pain can occur.

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P249

JOINT1802

Pathways to facilitate early recognition and diagnosis of hypochondroplasia

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Background
Hypochondroplasia (HCH) is a disproportionate short statured skeletal dysplasia caused by gain-of-function pathogenic variants in the fibroblast growth factor receptor 3 gene (*FGFR3*) that lead to reduced endochondral bone growth. HCH typically becomes clinically apparent after the first year of life, when growth velocity begins to decline and height discrepancy widens relative to average height peers. Reaching an initial suspicion of HCH can be challenging due to wide phenotypic variability and subtle clinical and radiographic features, which in turn can lead to delayed or missed diagnosis. Early diagnosis may facilitate implementation of appropriate clinical management and psychosocial support. However, there are currently no standardized diagnostic criteria for HCH nor are diagnostic pathways well described in the literature.
Methods
In October 2024, 14 experts across multiple specialties (pediatric endocrinology, medical genetics, maternal fetal medicine, pediatrics, family medicine, radiology, genetic counseling) completed an online survey on current clinical practices for diagnosing HCH. A subset of participants convened to discuss strategies to optimize clinical diagnostic pathways. Insights and recommendations were refined by the collective group during the drafting of this communication.
Results
Sonographic features of HCH may be detectable prenatally from approximately 20 weeks' gestation, becoming more pronounced in the third trimester, and typically include a short femur and a relatively larger head circumference. Prenatal diagnostic testing options include targeted *FGFR3* analysis via non-invasive prenatal testing or multi-gene sequencing in DNA from invasive procedures such as amniocentesis, which also allows wider exploration of other skeletal dysplasias when diagnostic uncertainty exists. Postnatally, features suggesting HCH include a sustained fall in height centiles over the first two years, macrocephaly, seizures, and specific radiographic and neuroimaging findings. Between ages 2-3 years, a characteristic growth pattern including body disproportion with shortened limbs may become evident. Occasionally a history of learning differences may become apparent. HCH should be considered in the differential diagnosis of idiopathic or isolated short stature in children. Genetic testing for growth disorders using panels that include *FGFR3* and evaluation of short statured parents are also useful to establish the diagnosis of HCH.
Conclusions
Early diagnosis of HCH is achievable by the detection of key clinical and radiological features and supported by molecular analysis using different diagnostic platforms. Timely diagnosis may enable interventions to reduce complications and potentially enhance vertical growth in the future. This work represents an important initial step towards consensus-based diagnostic criteria and guidelines for HCH.

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P250

JOINT1850

The IMPACT survey: healthcare experiences reported by individuals with osteogenesis imperfecta and their caregivers

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Introduction/Objectives
The healthcare journey of people with osteogenesis imperfecta (OI)—a rare genetic connective tissue disorder—is not completely understood. This study provides insights on self-reported healthcare experiences and barriers to care.
Materials and Methods
The IMPACT Survey, developed by the OI Federation Europe, the OI Foundation and an international steering committee of experts, explored the clinical, humanistic and economic impact of OI. The survey was fielded online from July–September 2021 and open to adults (aged ≥18 years) and adolescents (aged 12–17 years) with OI, caregivers (CGs; with or without OI) and other close relatives. This analysis presents self-reported findings from individuals with OI and CGs, who responded on behalf of their care recipients with OI: children (aged 0–11 years), adolescents (aged 12–17 years) and adults (aged ≥18 years). Data were analysed using Microsoft Excel.
Results
Among respondents with OI, 1, 440 were adults and 92 adolescents; CGs ($n = 700$) provided proxy data on 474 children, 171 adolescents and 118 adults with OI. Over 12 months, respondents reported visits to a wide range of healthcare professionals (HCPs; mean [standard deviation] visits 60. 0 [79. 4] children; 53. 9 [56. 5] adolescents; 40. 5 [78. 1] adults) including generalists, specialists and therapists. When asked about healthcare experiences, 41. 0% of adults and 15. 2% of adolescents felt unsupported in their transition from paediatric to adult care. CGs of children (85. 2%) and adolescents (86. 4%) reported worrying about their child's future care transition. Most adults (69. 9%) felt they needed to coordinate their own care, and many (32. 7%) felt care was not continuous. CGs of adults (27. 0%), adolescents (21. 2%) and children (19. 4%) felt care was uncoordinated; CGs of adults (27. 0%), adolescents (11. 8%), and children (10. 1%) felt care was not continuous. Many adults (34. 7%) and adolescents (26. 1%) avoided healthcare. The most common reasons given were past trauma/negative experiences (62. 0%, adults; 58. 4% adolescents), HCPs being unfamiliar with OI (66. 6%, adults; 66. 7% adolescents) or fear (46. 0%, adults; 41. 6% adolescents). CGs who avoided seeking care for their care recipient (18. 8% children; 24. 6% adolescents; 24. 7% adults) indicated this was driven by past trauma/negative experiences (67. 2% children; 48. 3% adolescents; 66. 6% adults), ability to provide better care themselves (52. 5%, children; 41. 3% adolescents; 52. 3% adults) or HCPs being unfamiliar with OI (62. 3%, children; 75. 9% adolescents; 61. 9% adults).
Conclusion
The IMPACT Survey highlights the need for integration of multidisciplinary paediatric and adult care, and increased awareness of OI and healthcare barriers across all life stages.

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P251

JOINT899

A case of heterozygous PTHLH deletion causing brachydactyly type E2

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Background
Brachydactyly type E (BDE), a rare skeletal dysplasia (OMIM: 113300), is characterized by metacarpal/metatarsal shortening and variable skeletal anomalies. BDE2 (OMIM: 613382), a distinct subtype, arises from pathogenic variants in the PTHLH gene (12p12. 1-p11. 22), which regulates endochondral ossification via parathyroid hormone-related protein signaling. Heterozygous loss-of-function variants in PTHLH are associated with a characteristic skeletal pleiotropy, classically manifesting as severe generalized bilateral brachydactyly, proportionate short stature, pectus carinatum deformity, and radiologically confirmed premature epiphyseal fusion.
Clinical Case
A 5-year-7-month-old girl presented with symmetrical brachydactyly. Her height(115 cm, 50th percentile), weight(19 kg, 50th percentile) and neurodevelopment were age-appropriate. Her hand radiographs showed dysplastic epiphyses in all digits, and her bone age was 6 years old with mild thoracolumbar scoliosis (Cobb angle 10°). Familial evaluation revealed no brachydactyly or skeletal anomalies. Trio-based whole-exome sequencing (WES) identified a de novo 1. 90 Mb heterozygous deletion at 12p12. 1-p11. 22 (GRCh37: chr12:26, 217, 430-28, 122, 427), encompassing PTHLH exons 3-4. Quantitative PCR confirmed the proband-specific deletion, absent in parental genomes. Decipher/ClinVar databases classified this CNV as pathogenic for BDE2. During 3-year follow-up, scoliosis remained stable (Cobb angle 10°), with height growth velocity of 6 cm/year. She did not yet exhibited signs of pubertal development at eight and half years old.
Conclusion
This study expands the mutational spectrum of BDE2 by identifying the PTHLH intragenic deletion. The absence of familial transmission supports de novo dominance. Notably, preserved stature and non-progressive scoliosis contrast with typical BDE phenotypes, highlighting the broad phenotypic spectrum of PTHLH-related skeletal dysplasias, and necessitating integrated genomic diagnostics to delineate genotype-phenotype correlations. Despite preserved anthropometric parameters (height Z-score: 0. 0) and age-appropriate neurodevelopment, structured surveillance protocols remain critical to monitor potential skeletal sequelae, including scoliosis progression and metaphyseal dysplasia.

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P252

JOINT3344

Insufficient bone mineralization to sustain mechanical load of weight in obese girls: a cross-sectional study

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Context
Despite an apparent increase in bone mineral content (BMC) and bone mineral density (BMD) in obese compared to lean children, the fracture risk is higher. On the one hand, mineralization measurements by dual-energy X-ray absorptiometry (DXA) may be falsely raised by the increase in height and width in obese children. On the other hand, the rise in BMC and BMD measured by DXA may not sustain the mechanical load associated with weight.
Objective
We described bone mineralization in overweight/obese girls and lean girls in relation to body composition.
Methods
This was a cross-sectional study in the Pediatric Endocrinology Unit of Angers University Hospital. Three hundred and twenty-eight overweight/obese girls aged 7-18 underwent DXA measurements. Using the same DXA model, their bone mineralization was compared with data from 441 lean girls of similar age and height from the NHANES 2011-2015 studies.
Results
The mean age- and height-adjusted difference in total-body-less-head BMC (TBLH BMC) between obese and lean girls was 186 ± 11 g (P <. 001). Each 1 kg/m2 increase in body mass index (BMI) was associated with a gain of +21 ± 2 g of TBLH BMC in lean girls vs +19 ± 1 g in obese girls (P <. 05 for the difference). Each 1 kg/m2 increase in lean BMI (LBMI) was associated with a gain of +63 ± 4 g of TBLH BMC with no difference between lean and obese girls, whereas fat mass index (FMI) did not have a significant effect on TBLH BMC.
Conclusion
The increase in bone mineralization in obese girls does not adapt to the rise in body mass.

Keywords: obese, girls, bone mineral content, mechanical load, lean mass, fat mass

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P253

JOINT3456

Clinical significance of chloride-to-phosphorus and chloride-to-magnesium ratios in primary hyperparathyroidism

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Background
Primary hyperparathyroidism (PHPT) is a common endocrine disorder classified into hypercalcemic and normocalcemic subtypes. Traditional biochemical markers such as serum calcium, phosphorus, and parathyroid hormone (PTH) aid in diagnosis; however, additional markers may improve diagnostic accuracy. The chloride-to-phosphorus (Cl/P) and chloride-to-magnesium (Cl/Mg) ratios have been proposed as novel biomarkers for distinguishing PHPT subtypes and predicting skeletal and renal complications.
Methods
A retrospective observational study was conducted on 116 PHPT patients who underwent parathyroidectomy at Ankara Bilkent City Hospital from 2019 to 2022. Preoperative clinical and biochemical parameters, including serum Cl, P, and Mg levels, were analyzed. Cl/P and Cl/Mg ratios were calculated and correlated with PHPT subtypes and complications such as bone mineral density (BMD) loss and nephrolithiasis.
Results
The Cl/P ratio was significantly higher in patients with hypercalcemic PHPT compared to those with normocalcemic PHPT (median 42. 4 vs. 38. 3, $P = 0.0125$). ROC curve analysis determined that a Cl/P ratio greater than 43. 6 had a specificity of 80. 0% and a sensitivity of 43. 4% (AUC: 64. 1%) in distinguishing PHPT subtypes. Additionally, the Cl/P ratio was lower in patients with osteopenia and osteoporosis ($p < 0.0001$), suggesting its role in predicting skeletal complications. The Cl/Mg ratio, on the other hand, was significantly associated with nephrolithiasis risk. A cut-off value of ≤55 demonstrated 82. 4% sensitivity and 66. 7% specificity (AUC: 70. 5%, $P = 0.0002$) in identifying patients at risk for nephrolithiasis. However, the Cl/Mg ratio did not show a significant difference between PHPT subtypes.
Discussion
The Cl/P ratio demonstrated potential as a diagnostic adjunct for PHPT subtype differentiation and as a predictor of skeletal health. Its ability to identify normocalcemic PHPT cases, which often go undiagnosed due to normal serum calcium, highlights its clinical utility. The Cl/Mg ratio, while not useful for subtype differentiation, emerged as a valuable marker for nephrolithiasis risk assessment, reinforcing the role of chloride metabolism in PHPT complications.
Conclusion
Cl/P and Cl/Mg ratios are promising, cost-effective biomarkers for PHPT diagnosis and risk stratification. Their integration into clinical practice may enhance diagnostic precision and aid in early intervention strategies. Further multicenter studies are needed to validate these findings and establish standardized cut-off values.

Table 1: ROC Analysis of Cl/P and Cl/Mg Ratios

Parameter	Cut-off Value	Sensitivity (%)	Specificity (%)	AUC	p-value
Cl/P Ratio	>43.6	43.4	80.0	64.1%	0.0096
Cl/Mg Ratio	≤55	82.4	66.7	70.5%	0.0002

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P254

JOINT2644

Phenotypic heterogeneity and long-term bisphosphonate outcomes in osteogenesis imperfecta type V: an 8-year retrospective study of 143 chinese patients

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Background
Osteogenesis imperfecta type V (OI-V), driven by the recurrent *IFITM5* c. -14C>T mutation, is characterized by fractures, hyperplastic callus formation, and progressive interosseous membrane calcification. Despite bisphosphonate use in OI management, their long-term efficacy in OI-V remains poorly defined. This study evaluates phenotypic variability and longitudinal bisphosphonate outcomes in the largest OI-V cohort to date.
Methods
This 8-year retrospective analysis included 143 molecularly confirmed OI-V patients from 105 unrelated families (median age: 12. 4 years; follow-up: 8. 4 years). Patients received intravenous bisphosphonates (zoledronic acid: 0. 05 mg/kg/6 months; pamidronate: 1 mg/kg/day ×3 days/4 months). Clinical, radiographic (spinal radiographs, DXA), and biochemical markers (β-CTX, P1NP, calcium, phosphate, 25-OH-vitamin D) were analyzed.
Results
All patients carried the *IFITM5* c. -14C>T variant. Phenotypic features included radial head dislocation (57. 8%; median onset: 10. 2 years), interosseous membrane calcification (85%; earliest onset: 4 years), and hyperplastic callus (52. 3%; onset: 4–8 weeks post-fracture). Bisphosphonate therapy (median initiation age: 5. 2 years) reduced annual fracture rates from 2. 1 to 0. 4, improved lumbar spine BMD Z-scores (−2. 6 to −1. 3), restored vertebral height in 68% (>15% increase), and elevated height Z-scores (−2. 5 to −1. 8). Bone turnover markers declined (β-CTX: ↓42%, P1NP: ↓38%). However, JOINT deformities and ectopic calcification progressed despite treatment: radial head dislocation prevalence increased from 24% (<10 years) to 82% (>15 years), correlating with reduced elbow mobility ($r = -0.71$, $P<0.001$).
Conclusions
Bisphosphonates significantly improve bone density and reduce fractures in OI-V but fail to halt ectopic calcification or JOINT degeneration. These findings underscore the need for early rehabilitation and novel therapies targeting pathological ossification. This study refines the clinical spectrum of OI-V and provides critical evidence for optimizing multidisciplinary management strategies.

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P255

JOINT3831

Solving pancreatic insufficiency as a clue to normal vitamin D serum concentrations in cystic fibrosis

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Introduction
Vitamin D deficiency has been repeatedly found in individuals with cystic fibrosis (CF). Therefore, substitution is recommended by all relevant professional societies. However, the effect of novel treatment strategies such as CFTR modulators on vitamin D metabolism in CF has not been extensively studied yet.
Methods
We have reviewed the medical records of all children and adolescents followed up at our tertiary care Cystic Fibrosis Center. The age, sex, pancreatic function status and CFTR modulators use were collected. The last three assessments of serum concentration of 25-hydroxyvitamin D (25-OHD) and forced expiratory volume within the first second (FEV1) were noted and the mean was calculated. Also the respective doses of vitamin D substitution in international units were recorded.
Results
There were 169 patients (89 females) actively followed at our center. Mean age was 9. 3 $\pm$ 5. 3 years. Eighty six percent (149/169) presented with pancreatic insufficiency and sixty two percent (105/169) were on CFTR modulators. The mean 25-OHD serum concentration was 74. 9 $\pm$ 18. 6 nmol/l and mean FEV1 (percent of the reference) was 100. 7 $\pm$ 14. 3. There was no difference in these two measures between pancreatic sufficient and insufficient patients and between treated and untreated with CFTR modulators. In the linear regression model, 25-OHD concentrations were only slightly negatively influenced by age (beta -1. 14 $\pm$ 0. 33, $P < 0.001$) but not CFTR modulator use or pancreatic sufficiency. However, vitamin D substitution dose was positively influenced by age (beta 97. 2 $\pm$ 17. 6, $P < 0.001$) and negatively by pancreatic sufficiency (beta -580. 6 $\pm$ 247. 7, $P = 0.020$) but not CFTR modulators.
Conclusion
It seems that patients with CF with pancreatic insufficiency need higher doses of vitamin D to keep their 25-OHD serum concentrations within reference range, as compared to patients with pancreatic sufficiency. Despite the expected positive effect of CFTR modulators on vitamin D metabolism in CF, we could not prove that in our study. Longitudinal studies collecting data before and after commencement of the CFTR modulators may elucidate whether vitamin D doses could be decreased or maybe completely discontinued in patients with CF treated with the modern drugs.

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P256

JOINT2747

Predictors of long-term morbidity and mortality in patients with chronic post-surgical hypoparathyroidism

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We aimed to examine factors associated with long-term morbidity and mortality for patients with post-surgical hypoparathyroidism (HypoPT), as a means of assisting healthcare providers in identifying patients at high risk of long-term adverse outcomes. We included 160 patients with post-surgical HypoPT and at least five years of follow-up from the Central Denmark Region. The majority were females (87. 5%) and the main indications for surgery were atoxic goiter and thyroid cancer. Median age was 46 years (interquartile range [IQR], 37-57 years). During the first year after surgery, the median ionized calcium level was 1. 18 mmol/l (IQR, 1. 14-1. 22). Thirty-nine percent of patients experienced episodes of hypocalcemia, whereas 31. 2% had episodes of hypercalcemia. Over a five-year period starting a year after surgery, 16. 4% of patients developed incident chronic kidney disease (CKD), 43. 8% had more than two hospitalizations, and 16. 3% had either a cardiovascular event, incident CKD or died. Patients with prevalent disease were excluded. Multivariable models were used to access factors associated with morbidity and mortality in patients with HypoPT. Higher age and more episodes of hypercalcemia were factors associated with of an increased risk of incident CKD. Elevated levels of phosphate and the presence of comorbidity were associated with a higher risk of two or more hospitalizations. In conclusion, episodes of hypercalcemia and higher age may be associated with the development of CKD. Furthermore, elevated levels of phosphate and comorbidity were linked to two or more hospitalizations. While this study provides new insight into the prognosis of postsurgical HypoPT, study findings should be validated externally in a larger cohort.

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P257

JOINT1042

Effective management of rebound hypercalcemia during denosumab therapy in pediatric osteogenesis imperfecta through individualized calcium supplementation

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Context
Osteogenesis Imperfecta (OI) is a rare genetic condition, primarily caused by mutations in the *COL1A1* and *COL1A2* genes. Denosumab, a monoclonal antibody inhibiting the receptor activator of nuclear factor kappa-B ligand (RANKL), reduces osteoclast activity and bone resorption. Although it has demonstrated efficacy as an anti-resorptive treatment, its clinical utility is constrained by concerns regarding rebound hypercalcemia. This study was conducted as part of the multicenter trial NCT02352753, which was prematurely terminated due to calcium-related adverse events. At our center, we implemented a sub-study to monitor the dynamics of bone resorption markers and calcium levels during denosumab treatment in pediatric OI patients to prevent rebound-associated complications in this population.
Methods
A total of 40 children and adolescents aged 2 to 17 years with moderate to severe OI were treated with subcutaneous denosumab at a dose of 1 mg/kg body weight every six months. Urinary bone resorption markers (NTX and DPD) and calcium levels were measured at weeks 2, 8, 12, 16, 18, 20, and 22 post-injection. Calcium supplementation was individually adjusted based on age-specific thresholds.
Results
Bone resorption was effectively suppressed during the first two months following denosumab administration. However, levels of uNTX and DPD began to rise already after eight weeks, returning to baseline after three months, with a mild rebound observed at four months. No serious calcium-related adverse effects occurred in these patients.
Conclusion
Individualized monitoring of urinary calcium levels, along with timely adjustments to calcium supplementation, successfully prevented rebound hypercalcemia in children treated with denosumab for OI, without causing hypocalcemia shortly after administration.

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P258

JOINT3963

The significance of gender regarding the effects of primary hyperparathyroidism on the cardiometabolic profile of the patients: a single-center experience

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Background and Aim
Emerging scientific data supports the theory that non-syndromic pHPT may be associated to increased risk for various cardiometabolic disorders. The aim of the present study was to decipher the potent role of gender with respect to the impact of pHPT on the lipid and glucose profile of the patients.
Material and methods
A cohort of 227 pHPT (61 male and 166 female) patients from our endocrinology outpatient clinics were included in the retrospective study. Demographic, clinical and laboratory data of these patients were evaluated retrospectively.
Results
The female-to-male ratio was 2. 7:1 with comparable mean age and body mass index among female and male patients (60. 5 vs 58. 4 years, $P = 0.3$ and 29. 3 vs 27. 1 kg/m^2, $P = 0.14$, respectively). No significant differences were recorded regarding the parameters of calcium metabolism between the 2 groups. Bone mineral density was lower in both the lumbar spine ($P = 0.033$) and the femur

neck ($P = 0.029$) for female patients. With reference to the lipid metabolism, male patients presented with significantly higher levels of LDL (127vs111 mg/dl, $P = 0.031$) and triglycerides (116vs100 mg/dl, $P = 0.04$) whilst LpA values were as well more elevated among the male compared to the female patients (38vs31 mg/dl, $P = 0.022$). Additionally, the prevalence of arterial hypertension was 55% among men compared to 52% among women ($P = 0.17$). Furthermore, diabetes mellitus was more often diagnosed among the male patients (20/61 [32%] vs 40/166 [24.1%], $P = 0.012$). The same observation applied for obesity ($P = 0.024$) and impaired fasting glucose ($P = 0.031$), which more frequently affected the male group of pHPT patients. Finally, mean uric acid levels were significantly higher among male pHPT patients compared to the female ones (7.7 vs 6.7 mg/dl, $P = 0.011$), contrary to the CRP levels, which were equal for both groups ($P = 0.24$). It should also be highlighted that parathormone levels were strongly and positively associated with both LDL, TGs and Lpa values in both groups of patients, implying no gender difference towards a plausible direct association of the abnormal parathyroid gland function to the lipid metabolism.

Conclusion

Non-syndromic pHPT may be associated with greater risk for concomitant glucose and lipid profile disorders, especially among the male population. Thus, clinicians should be alert and routinely evaluate pHPT patients for the previously mentioned pathological entities in order to promptly diagnose and treat the latter and preserve cardiometabolic health of these patients.

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P259

JOINT854

Histological and laboratory factors associated with negative 99mtc-sestamibi scintigraphy in primary hyperparathyroidism: insights from a retrospective analysis

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Introduction

The 99mTc-sestamibi scintigraphy is commonly used for preoperative localization of the affected gland in primary hyperparathyroidism (PHPT) due to its affinity for well-perfused, mitochondria-rich tissues. However, false-negative results occur in 12-25% of cases. Several factors can affect the sensitivity of 99mTc-Sestamibi scintigraphy, including the size and location of the affected gland, the lesion's mitochondrial and fat composition, P-glycoprotein expression, the presence of multiglandular disease, and coexisting thyroid pathology.

Aim

To analyse the association between the histopathological and laboratory findings of patients who underwent parathyroidectomy and had false-negative results in 99mTc-Sestamibi scintigraphy.

Methods

A retrospective study was conducted on patients diagnosed with PHPT who underwent parathyroidectomy and had a 99mTc-Sestamibi scintigraphy performed.

Results

A total of 143 patients were identified and included in the study. The sample was predominantly composed of women (84.6%) with a mean age of 58.4 ± 13.7 years. The preoperative laboratory study revealed median values of ionized calcium of 1.41 mmol/l (IQR:1.37–1.50), phosphate of 2.6 mg/dL (IQR:2.2–3.0), PTH of 178.1pg/mL (IQR:138–291.2), and 25-OH vitamin D of 19.4 IU (IQR:14.0–27.4). The histopathological study revealed 104 (72.7%) typical adenomas, 5 (3.5%) atypical adenomas, 6 (4.2%) carcinomas, 20 (14.0%) hyperplasia, and 8 (5,6%) other histology. The 99mTc-Sestamibi scintigraphy allowed the localization of the affected glands in 123 (86.0%) cases. Comparatively, in the remaining 20 (14.0%) cases where the scintigraphy was negative, the frequency of typical adenoma was significantly lower (50.0% *vs*. 76.4%; $P=0.014$). However, no significant differences were found regarding hyperplasia (20.0% *vs*. 13.0%), atypical adenoma (0.8% *vs*. 3.3%), and parathyroid carcinoma (0% *vs*. 4.9%). In the scintigraphy-negative group, the lesions tend to be smaller (median weight 0.46g [AIQ: 0.61] *vs*. 0.74g [AIQ: 1.02]; $P=0.035$). The analysis of laboratory parameters related to phosphocalcic metabolism revealed that vitamin D levels were significantly higher in patients with a negative scintigraphy result (23.6 UI [AIQ: 19.3-23.6] *vs*. 17.6 [AIQ:13.9-25.7]]; $P=0.033$).

Discussion

PHPT is caused by benign single-gland adenoma in 85% of cases, and precise identification of the affected gland can be challenging. The lesions in the negative scintigraphy group were generally smaller. Both groups present a high prevalence of Vitamin D deficiency, which is linked to a higher volume of parathyroid adenoma. The group with negative scintigraphy showed a higher vitamin D level, which is consistent with the literature.

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P260

JOINT3828

The complex link between obesity and bone mineral density: exploring the role of body composition

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Introduction.

Traditionally, obesity was thought to be a protective factor against osteoporosis. This assumption has influenced clinical practice, as Body Mass Index (BMI) is incorporated into the Fracture Risk Assessment Tool (FRAX), where a higher BMI is associated with a lower fracture risk. However, recent studies have challenged this perspective, indicating that excess adiposity may be linked to osteopenia and osteoporosis. Other finding suggest that this relationship is more complex and site dependent. This study aims to assess the correlation between bone mineral density (BMD) and body composition parameters.

Methods

Inclusion of obese individuals followed in an Obesity Endocrinology appointment who underwent dual-energy X-ray absorptiometry (DEXA) scans to evaluate BMD at the spine, femur (neck and proximal regions), and forearm. Additionally, body composition was also assessed using DEXA. The relationship between BMD and body composition variables was examined.

Results

A total of 101 patients were included, of whom 81.2% were female and 18.8% were male. The mean age was 44.4 ± 12.1 years (between 18 and 67), with 62.4% being under 50 years. Mean BMI was $41.09 \pm 5.68 kg/m^2$. Mean total BMD was $1.097 \pm 0.11 g/cm^2$. BMD was significantly higher in males ($P < 0.001$) and in individuals younger than 50 years ($P = 0.019$). After adjusting for age and sex, no significant correlation was found between BMI and total BMD ($P = 0.859$), spine BMD ($P = 0.199$) and forearm BMD ($P = 0.131$). A weak positive correlation was observed for femoral neck ($r = 0.220$; $P = 0.031$) and proximal femur ($r = 0.282$; $P = 0.005$). A weak negative correlation was identified between fat mass percentage and total BMD ($r = -0.274$; $P = 0.013$), though no significant correlation was found at other sites. This correlation was stronger in males ($r = -0.581$; $P = 0.032$) compared to females ($r = -0.274$; $P = 0.013$) A weak positive correlation was observed between lean mass and total BMD ($r = 0.215$; $P = 0.032$), as well as at all analyzed skeletal sites. No correlation was found between BMD and visceral tissue adiposity index.

Conclusion

In this study, BMI did not demonstrate a protective effective on overall BMD, with only a weak positive correlation found for femoral neck and proximal femur. Additionally, fat mass percentage showed a weak negative correlation with total BMD, particularly in males. In contrast, lean mass exhibited a weak positive correlation with BMD across all analyzed segments, reinforcing its protective role in bone health. No significant relationship was identified between BMD and visceral tissue adiposity index. These findings highlight the complex interplay between body composition and bone health in obese individuals.

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P261

JOINT3970

The diagnostic incidence of normocalcaemic hyperparathyroidism decreases and diagnostic concordance of parathyroid hormone (PTH) assays improves with assay- and age-specific PTH reference intervals

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Background

Parathyroid hormone (PTH) assays lack standardization, leading to the interpretation of PTH results using manufacturer-specific reference intervals.

These intervals do not account for inter-assay differences, resulting in discordant diagnoses of normocalcaemic hyperparathyroidism (NCPHPT). PTH levels increase with age independently of vitamin D, renal function, phosphate, and ionized calcium. Variations in age-nonspecific PTH reference intervals may stem from differing age distributions in reference interval studies.
Aim
This study aimed to evaluate the effect of newly derived age-specific reference intervals for Abbott and Roche PTH assays on the diagnosis of NCPHPT, focusing on diagnostic concordance when applying age- and assay-specific intervals to previously identified cases of NCPHPT.
Methods
Age- and assay-specific intact parathyroid hormone (iPTH) reference intervals from recent studies were applied to serum samples from patients previously diagnosed with NCPHPT in a prior diagnostic test assessment. The study included adult outpatients ($\geq$18 years) with NCPHPT, whose serum samples were collected between February and June 2021. Serum samples were analysed using Abbott and Roche second-generation immunoassays. Patients with vitamin D deficiency ($<$50 nmol/l), impaired renal function (eGFR $<$60 mL/min/1. 73 m^2), malignancy, pregnancy, or medications influencing calcium/PTH levels were excluded. Reference intervals from previously published studies for both Roche and Abbott iPTH derived from large population datasets using the refineR algorithm were used to assess diagnostic concordance.
Results
Among the 46 individuals initially diagnosed with NCPHPT based on elevated Abbott PTH levels, only 16 (35%) remained concordant for NCPHPT by Roche method when the results were interpreted using the manufacturer provided method-specific reference intervals. The remaining 30 (65%) had normal PTH levels. However, when method- and age-specific reference intervals were applied, diagnostic concordance improved: 31 individuals (67%) were classified with normal PTH levels by both methods, 8 (17%) remained concordant for NCPHPT, and 7 (15%) were discordant (NCPHPT diagnosed by Abbott but normal PTH by Roche). This indicates that age- and assay-specific reference intervals significantly reduced NCPHPT diagnoses and improved agreement between the assays.
Conclusion
The use of age- and assay-specific reference intervals for PTH assays enhances diagnostic accuracy, reduces unnecessary NCPHPT diagnoses, and improves concordance between different commercially available assays. This approach minimises the risk of misdiagnosis, unnecessary testing, and inappropriate management, particularly for older patients.

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P262

JOINT2126

Profile of patients initiating abaloparatide treatment

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Introduction and Objectives
Abaloparatide is part of the arsenal of osteoforming drugs, marketed in Europe since May 2024 for postmenopausal women at very high risk of fractures. Abaloparatide has been shown to reduce the risk of vertebral and non-vertebral fractures. However, there is scarce evidence in real life about the patient profile receiving this treatment. Therefore, this work aims to evaluate the clinical and analytical profile of the patient who is receiving abaloparatide in our center.
Material and Methods
Descriptive observational study of the profile of patients who started treatment with Abalopratide in the Endocrinology Service of the HUCSC of Granada in 2024. The results were analyzed in the SSPS 25. 0 program. Analytical variables, bone mineral density (BMD) and TBS were measured.
Results
Twenty women with mean age at diagnosis of osteoporosis of 62. 5 years were included. 20 % family history of hip fracture. 65% had a fragility fracture before treatment, 60% of which were vertebral and 10% hip fractures, with a mean number of fractures of 1. 9 +-1. 7 SD. 100% of the sample presented a very high risk of fracture. 55% received previous osteoporotic treatment. The mean T-SCORE value for femoral neck and total spine was -2. 3 and - 2. 6 respectively. The mean TBS level in the spine was 1. 17 and the mean Tscore was -3. The mean BMD value in the total spine was 0. 94 with a mean Tscore of -2. 6. The mean value of Creatinine, Calcium, Vitamin D and Parathormone was 0. 66 mg/dl, 9. 3 mg/dl, 30. 5 ng/mL and 68. 2 pg/mL respectively. The mean value of the remodeling markers C-terminal Telopeptide collagen type I and Procollagen I, N-terminal propeptide was 0. 51 ng/mL and 80. 3 ng/mL.
Conclusion
The patients who started Abaloparatide complied with the indications for treatment since they presented a high risk of fracture with greater involvement of trabecular bone in addition to presenting calcium and parathyroid hormone levels in the normal range.

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P263

JOINT3786

Birth outcomes and educational level among patients with post-surgical and non-surgical hypoparathyroidism

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Background
Hypoparathyroidism (HypoPT) is most often caused by complications following neck surgery, post-surgical HypoPT, but genetic or autoimmune causes are seen, called non-surgical HypoPT (Ns-HypoPT). Calcium is vital for the mineralization of the fetal skeleton. Studies have shown that inadequate managed maternal HypoPT may cause preterm labor, miscarriage and stillbirth. Patients with HypoPT often complain of impaired cognitive skills, i. e. confusion, brain fog and forgetfulness. Studies have found that HypoPT patients, regardless of etiology, have reduced executive functions, processing speed, visual – and auditory memory. However, the impact on education level are still unknown. We aimed to investigate birth complications and education level in patients with post-surgical HypoPT and Ns-HypoPT compared to controls from the background population.
Material and Methods
We conducted a case-finding study, identifying patients with postsurgical hypoparathyroidism between 1988-2012 and patients with Ns-HypoPT between 1977-2012. Patients with HypoPT were identified through the National Patient Registry on ICD-codes combined with the regional prescription database. Controls were randomly selected from the background population using the Danish Civil Registration System. These were matched by gender and year of birth ($\pm$ 2 years), using the incidence-density sampling technique. From Statistics Denmark registers we received all relevant information including fertility, childbirth and educational status.
Results
688 patients with post-surgical (88% female, median age 49 years, mean follow-up 8. 4 years)) and 180 patients with Ns-HypoPT were identified (53% females, 49. 7 years at time of follow-up, 21% genetically verified), and matched to 2604 controls. No differences in birth outcomes including length, weight, head-, abdominal circumference or placenta weight were seen. We found a trend towards a shorter gestational age among post-surgical patients, $P = 0.07$. Fewer patients with post-surgical HypoPT (80%) and Ns-HypoPT (32%) have completed an education, defined as vocational/short or higher, compared to controls (88% and 43%, respectively), $P < 0.01$. No differences in age when receiving a higher education were seen. Investigations on the level of education show that 50% of patients with NS-HypoPT have primary school as their highest completed education. This is opposite controls, where only 30% have primary school as their highest completed education. Grades in primary school are significantly lower among Ns-HypoPT patients compared to controls, this concerns both written and verbal grades, $P < 0.01$. In conclusion, no differences in birth outcomes were found. However, it seems that patients with HypoPT have a lower educational level compared to controls and grades among patients with Ns-HypoPT are significantly lower than controls.

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P264

JOINT762

Bone phenotype in infantile hypercalcemia-1 caused by CYP24a1 pathogenic variant

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Infantile hypercalcemia-1 (HCINF1) is a rare disorder of mineral metabolism caused by homozygous loss-of-function variants of the *CYP24A1* gene which induce an increase of serum 1, 25$(OH)_2$D3 concentration, and consequently hypercalcemia, hypercalciuria, and low-to-undetectable plasma PTH levels. The aim of this study was

to evaluate the bone phenotype in a cohort of patients affected by HCINF1 disease followed at our outpatient clinic. We included 5 patients (1 female and 4 males) carrying homozygous (Group A) and 7 patients (3 females and 4 males) carrying heterozygous *CYP24A1* variants (Group B). In group A, the median age was 26 (IQR: 25-52), while in group B, it was 30 years (IQR 30-60). No patient experienced clinical fragility fractures or morphometric fractures as assessed by DXA. One male patient aged 69 years of the group A and another male patient aged 63 years of the group B exhibited osteoporosis at 1/3 distal radius, with T-score: -3 and -3. 3, respectively. Both patients did not have risk factors for osteoporosis. Two of the 5 patients of group A had osteopenia at femur (both total and neck regions) and 1 patient showed osteopenia at 1/3 distal radius. Conversely, 1 of the 7 patients in group B exhibited osteopenia at lumbar spine. The remaining patients had normal BMD at all sites and normal trabecular bone score values. Regarding bone turnover biomarkers, all values were in the normal range. Specifically, in the group A the value of bone-specific alkaline phosphatase (BAP) was 13 mg/l in the female and the median of BAP was 15 mg/l (IQR: 13-16, 5) in males, while in group B the median was 12 mg/l (IQR: 11, 65-12) in females and 13 mg/l (IQR 11, 25-16, 25) in males. Osteocalcin levels were 20, 45 mg/l (IQR: 19, 13-23, 63) in group A and 11 mg/l (IQR 9, 5-29, 45) in group B. In group A, the value of serum CTX was 0, 36 mg/l in the female and the median value was 0, 464 mg/l (IQR: 0, 344-0, 667) in males while in group B CTX was 0, 186 mg/l (IQR 0, 125-0, 199) in females and the median was 0, 14 mg/l (IQR: 0, 133-0, 234) in males. Our findings seem to suggest that the BMD in homozygous patients with HCINF1 tend to be lower compared to heterozygous patients. Moreover, the levels of BAP, osteocalcin and sCTX are in the half/lower half of the reference range, this could reflect a low bone turnover secondary to low PTH levels, as occurs in hypoparathyroidism.

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P265

JOINT2578

Pseudohypoparathyroidism type 1b diagnosed in adulthood: a novel family deletion in the GNAS locus

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Introduction
Pseudohypoparathyroidism type 1b (PHP-1b) is characterized by resistance to parathyroid hormone (PTH), primarily in renal tissues, leading to hypocalcemia, hyperphosphatemia, and elevated PTH levels. In some cases, it may also present with resistance to thyroid- stimulating hormone. Features of Albright hereditary osteodystrophy are usually absent. This condition is caused by genetic and epigenetic imprinting defects of the GNAS locus on chromosome 20q13. 32. It is typically sporadic, although familial cases with autosomal dominant inheritance have been reported. We describe a novel deletion in the GNAS-AS1 and GNASXL transcripts, which has not been previously documented in the literature in a family with PHP-1b.
Clinical Case
A 36-year-old male presented with massive calcifications of the basal nuclei and thalami, along with dispersed calcifications in both cerebellar hemispheres, identified on a head CT scan conducted due to his complaints of vertigo and headache. Subsequent testing revealed severe hypocalcemia (5. 6 mg/dL) and elevated PTH levels (260. 8 pg/mL). His medical history included cataract surgery at a young age and complaints of paresthesias since adolescence. He was referred to the Endocrinology department, where pseudohypoparathyroidism was suspected. The patient started calcium and vitamin D supplementation, with correction of the hypocalcemia (Ca2+ 8. 9 mg/dL) and persistent elevated PTH (273 pg/mL). Given the clinical presentation and imaging findings, genetic testing for mutations in the STX16 and GNAS genes was performed, but results were negative. Subsequently, a methylation-specific MLPA test was requested, revealing a heterozygous deletion of the GNAS-AS1 and GNASXL transcripts, as well as a hypomethylation pattern in the DMR A/B region of the GNAS gene, attributed to the deletion of the maternal allele. To this date, this deletion has not been previously documented in the literature or in polymorphism databases. The patient was referred for genetic counselling where his family was evaluated: his sister exhibited the same deletion and clinical manifestations and his mother also have the same deletion, although she has no clinical symptoms and no analytical or imaging abnormalities. The genetic study of his aunt and cousin are pending.
Conclusion
PHP-1b is a rare endocrine disorder with genetic aetiology. While some mutations have been described, the identification of new mutations, such as the one presented in this case, may enhance our understanding of the underlying genetic mechanisms and facilitate future diagnoses.

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P266

JOINT889

The united kingdom adult northstar network consensus recommendation of management of osteoporosis in adults with duchenne muscular dystrophy and transition to adult care

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Objectives
Osteoporosis is a common complication in Duchenne muscular dystrophy (DMD) . Current clinical guidelines focus primarily on paediatric care, with limited guidance for managing osteoporosis during the transition to adulthood and long-term management of osteoporosis therapy initiated in paediatric care.
Methods
In 2023, a UK expert working group was formed with the task of developing national expert consensus on the management of osteoporosis in adults with DMD in the adult NorthStar Network. The working group included 13 adult and 5 paediatric bone specialists, 3 adult neuromuscular clinicians (2 with paediatric experience), a clinician-scientist/densitometrist, and 3 patient representatives. Systematic and scoping reviews of osteoporosis therapies for DMD, glucocorticoid-induced osteoporosis guidelines for adults, and DXA-based fracture predictions in DMD were conducted. A survey was distributed via patient organisations to paediatric clinicians managing DMD-related osteoporosis, with focus on care during transition. Feedback on bone health management was also gathered through a focus group of adults with DMD. Four online meetings of the expert working group were held. Using a modified Delphi approach, consensus clinical recommendations were developed.
Results
Consensus recommendations were established through three Delphi voting rounds, with 80% agreement required. Thirteen clinical guidance statements were developed. Key recommendations include:

- Adults with DMD should undergo osteoporosis and fracture risk assessments, including vertebral fracture (VF) assessment and DXA bone density, if expected to influence clinical decision making.
- VF reassessments are recommended every two years for those on glucocorticoids and should be individualised for those who are not on glucocorticoid treatment and/or, those with metal instrumentation for scoliosis.
- For young people on long-term bisphosphonate therapy (> 10 years) initiated in childhood and who have completed puberty, discontinuation of therapy should be considered at transition, depending on clinical risk factors. The clinical risk factors include glucocorticoid therapy, presence of VF at most recent evaluation, new VF and/or worsening VF during treatment with osteoporosis therapy or recent low trauma long bone fracture.
- Upon discontinuation of osteoporosis therapy, re-evaluation of the need to re-initiate osteoporosis treatment is recommended if low trauma fractures are sustained off treatment or if there is significant bone density decline, or at two years post-discontinuation.

Conclusion
Using a Delphi-based systematic process, this UK expert working group developed national consensus guidance for managing osteoporosis in adults with DMD. These recommendations address critical gaps in care during the

transition from paediatric to adult services, ensuring a comprehensive and individualised approach to bone health management.

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P267

JOINT2366

Vitamin d-dependent rickets type 2a in a 1-year-old girl: a rare case of alopecia and hypocalcemic jerking episodes

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Background
Vitamin D-dependent rickets type 2A (VDDR2A) is a rare autosomal recessive disorder caused by mutations in the vitamin D receptor (VDR) gene, leading to resistance to 1, 25-dihydroxyvitamin D. It results in hypocalcemia, secondary hyperparathyroidism, and severe rickets. Alopecia is a hallmark feature, particularly in cases with mutations in the DNA-binding domain of the VDR gene. We report a case of VDDR2A in a 1-year-old girl presenting with jerking movements and alopecia.
Case Report
A previously healthy 1-year-old girl presented with brief jerking movements involving the trunk and upper extremities, initially occurring once daily and increasing in frequency. There was no history of seizures, consanguinity, or family history of epilepsy. She was born full-term with normal birth weight and had no perinatal complications. Growth parameters were within normal limits, but gross motor development was delayed. Physical examination revealed diffuse alopecia, frontal bossing, and absent teeth. Chvostek's sign was positive, suggesting hypocalcemia. Laboratory investigations showed hypocalcemia, low-normal phosphorus, elevated alkaline phosphatase (1, 677 U/l), and markedly elevated parathyroid hormone (565 ng/l). Her 1, 25-dihydroxyvitamin D level was strikingly high ($>$1, 500 pmol/l). Radiographs revealed classic rickets features. Whole-exome sequencing identified a homozygous c. 238C$>$T (p. Arg80*) mutation in the VDR gene, confirming VDDR2A. She was initially treated with intravenous calcium gluconate for symptomatic hypocalcemia, followed by high-dose oral calcium (up to 285 mg/kg/day) and calcitriol (0. 6 mg/kg/day). Over seven months, her biochemical markers and radiological features significantly improved. By 1 year and 11 months, healing was evident, and treatment was gradually reduced. However, alopecia persisted. Her motor development improved, and her height velocity increased from 2 cm over six months to 6. 2 cm in the following six months.
Discussion
This case highlights the importance of considering VDDR2A in infants with early-onset rickets, hypocalcemia, and alopecia. The key diagnostic clue is high 1, 25-dihydroxyvitamin D despite hypocalcemia and secondary hyperparathyroidism. Mutations in the DNA-binding domain of the VDR gene cause complete receptor dysfunction, resulting in severe disease and alopecia.
Conclusion
Early recognition and genetic confirmation of VDDR2A are crucial for timely intervention. High-dose calcium and calcitriol therapy improve biochemical markers and bone health, but alopecia remains irreversible. Long-term follow-up is necessary to adjust treatment as calcium homeostasis changes with age.

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P268

JOINT1120

Design of the ACCEL study: a prospective clinical assessment study in children with hypochondroplasia

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Background
Hypochondroplasia (HCH) is a disproportionate short statured skeletal dysplasia caused by gain-of-function pathogenic variants in the fibroblast growth factor receptor 3 gene (FGFR3) that lead to reduced endochondral bone growth. The natural history of HCH is not well characterized and longitudinal growth data for this condition are limited. Management of HCH is currently focused on treating specific complications.
Methods
ACCEL (NCT06410976) is a non-interventional clinical assessment study designed to characterize the natural history of children with HCH aged 2. 5 to $<$ 17 years. The primary objective is to collect baseline height velocity measurements of children who may participate in an interventional study with infigratinib, an oral FGFR1–3 selective tyrosine kinase inhibitor in development for HCH. Secondary objectives are to collect other baseline growth measurements including height z-score and body proportion ratios, assess cognitive functions, evaluate HCH-related medical events and surgical procedures, and assess health-related quality of life. Evaluation of biomarker indicators of growth is an exploratory objective. Key inclusion criteria include diagnosis of HCH documented clinically by the presence of disproportionate short stature and confirmed with a molecular test. Participants will be assessed for a minimum of 6 months and a maximum of 2 years.
Results
The first participant enrolled in June 2024 and recruitment is ongoing in multiple countries.
Conclusion
Prospective data from this study will contribute to the characterization of the natural history of HCH and serve as a baseline for evaluation of infigratinib as a potential treatment option for children with HCH in future interventional studies.

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P269

JOINT1249

The impact of parathyroid adenoma removal on the quality of life of patients with primary hyperparathyroidism

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Objective
To investigate the effect of surgical treatment (parathyroid adenoma removal) on the quality of life of patients with primary hyperparathyroidism.
Materials and Methods
Forty patients aged 38 to 65 who underwent parathyroid adenoma removal were examined. The patients were divided into three groups: asymptomatic (8 individuals), manifest (24 individuals), and hypercalcemic (8 individuals). The average parathyroid hormone level before surgery was 454. 7 pg/ml. The quality of life was assessed using the Primary hypoparathyroidism quality of life questionnaire (PHPQoL), which provided quantitative data on 16 indicators related to health status and functional limitations.
Results
Six months after surgery, quality of life assessments revealed that, despite the successful reduction in parathyroid hormone levels, most patients reported symptoms, including pain during prolonged walking 29 (72, 5%), and limitation of recreational activities detected in 24 patients, 67, 5 % patients complained to bone and JOINT pain during prolonged walking, Insomnia during the first three months post-surgery noted in 6 patients and difficulty concentrating at work 10 patients out of 40. These findings suggest that despite successful surgical intervention, a significant number of patients experience symptoms that impair their quality of life.
Conclusion
The study demonstrated that while parathyroid adenoma removal significantly reduces parathyroid hormone levels and improves the overall condition of patients with primary hyperparathyroidism, certain symptoms, such as bone and JOINT pain during prolonged walking, persist in the postoperative period. This indicates the need for further optimization of diagnostic and therapeutic approaches to PHPT to improve patients' long-term quality of life. Enhancing postoperative care and early rehabilitation may significantly improve the quality of life for these patients.

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P270

JOINT1255

Denosumab treatment of two children with inoperable spinal aneurysmal bone cysts

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Background
Aneurysmal Bone Cysts (ABC) are rare, benign, osteolytic tumours of bone, characterized by locally aggressive and rapid growth, and treatment experience thus scarce. Despite its benign nature, ABC tends to regrow until end-of-growth and medical treatment is therefore suggested to be continued until final height. We present two childhood cases of inoperable ABC and their medical treatment. **Case 1:**A 6-year-old girl presented with a limp and muscle pain for some months. MRI revealed a large cystic process at the os sacrum, involving S2 and S3, embedding the ischiadic nerve. Biopsy revealed multinucleated giant cells of osteoclast appearance with no signs of malignancy, and by RNA NGS, a CTNNB1-USP6 fusion, confirming ABC. Fluorodeoxyglucose (FDG) PET/CT revealed increased uptake in ABC. Due to considerable risk for nerve damage/instability of the lower spine, surgical removal of ABC was impossible with medical treatment as the only option. Denosumab treatment was initiated, 70 mg/m^2 weekly, the first four weeks, thereafter 4-weekly. Pain disappeared rapidly. MRI after three months revealed ABC regression and some consolidation. **Case 2:**An 11-year-old boy presented with a previous history of lower limb weakness and back pain due to a T5 ABC, which had already required 3 surgeries in one year for recurrent symptoms. As further surgeries were with risk of permanent spinal cord damage, denosumab was initiated, 1mg/kg monthly, alongside zoledronate 0. 05 mg/kg 6-monthly to offset risk of rebound hypercalcaemia. ABC has shrinked with no further significant neurological episodes, and no calcium disturbance.
Discussion
Case 1: Continued treatment plan: denosumab 4-weekly for 6 months. If MRI shows continued ABC regression, and normal metabolic activity on FDG PET/CT, tapering of denosumab initially alternating with zoledronate 0. 025 mg/kg followed by extended dosing intervals is planned. As ABC growth is expected to continue until end-of-growth, medical treatment is suspected to continue at intervals permitting ABC control until end-of-growth. Case 2: As treatment has been ongoing for >2 years (planned to continue until end-of-growth), cautious stretching of dose frequency to 6-weekly has commenced, with ongoing biochemical and MRI monitoring. The dose of zoledronate has been reduced due to increased bone density.
Conclusion
As updated treatment advice describing the use of denosumab in ABC in children are warranted, we would like to invite colleagues treating children with ABC to share their experiences aiming to collaborate on the development of a statement publication on the treatment of ABC in children of different ages.

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P271

JOINT3009

Bone mineralization in children aged 7-10 years born after assisted reproductive technology with frozen and fresh embryo transfer

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Background
Birth weight (BW) is positively associated with Bone Mineral Content (BMC) and Bone Mineral Density (BMD) later in life. Children conceived after assisted reproductive technology (ART) by frozen embryo transfer (FET) have an increased BW compared to naturally conceived (NC) children, while the opposite association is known for children born after ART by fresh-embryo transfer (fresh-ET). Bone health in children born after ART is scarcely explored and with inconsistent Results
Methods
This study was a retrospective cohort study as part of the 'Health in Childhood following Assisted Reproductive Technology' (HiCART) cohort, consisting of 606 children (292 boys) aged 7-10 years, conceived after FET ($n = 200$), fresh-ET ($n = 203$), and NC ($n = 203$) born from November 2009 to December 2013. The children were identified through Danish Medical Birth Registry and Danish IVF registry. The clinical examination involved anthropometric measurements, pubertal staging, fasting blood samples, and whole-body dual-energy x-ray absorptiometry scan (DXA). The three groups were compared pairwise using univariate linear regression model and possible confounders and mediators were adjusted for using multiple linear regression analysis.
Results
Crude values of BMC corrected for height did not differ between children born after FET, fresh-ET, or NC. When adjusted for relevant confounders children born after FET had a statistically significant higher BMC corrected for height compared with both fresh-ET and NC. After further adjustment for BW standard deviation score (SDS), the differences in BMC corrected for height disappeared, and no statistically significant differences in BMC corrected for height between any of the three groups was found. Factors potentially affecting bone mineralization, such as calcium, parathyroid hormone (PTH), insulin-like growth factor-I (IGF-I), lean mass, and physical activity in childhood did not differ between the three groups.
Conclusion
Increased BW in children conceived after FET was associated with increased BMC corrected for height at age 7-10 years when compared to children conceived after fresh-ET and NC. This difference was primarily mediated by the higher BW found in children conceived after FET compared with fresh-ET and NC. Longitudinal studies of pregnancies and newborns after FET are needed to explore the causes of the increase in BW and the possible effects on long-term bone health.

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P272

JOINT1736

Machine learning model on opportunistic computed tomography for predicting vertebral fracture risk in women undergoing hormone deprivation therapy for breast cancer

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Introduction
Women under hormone-deprivation therapies (HDTs) for breast cancer are at high fracture risk, but currently available fracture prediction tools are imprecise. Emerging evidence suggests that radiomics may contribute to fracture risk assessment in general population, but its application in this context is unknown.
Objective
To identify radiomic features (RFs) on opportunistic computed tomography (CT) associated with vertebral fractures (VFs) in women under HDTs, and to develop a radiomics-based model predictive of VFs.
Methods
Radiomics analyses were performed on CT scans of 109 women (median age 61. 1 years, range 27-85) exposed to HDTs (median 27. 1 months). Lumbar vertebrae were automatically segmented (convolutional neural network) for RFs extraction. Each feature was tested for its ability to predict VFs. Patients were randomly divided into training and test cohorts for the development and validation of the predictive model.
Results
Morphometric VFs were diagnosed in 23 women (21. 1%), in association with older age ($P = 0. 013$), lower total hip T-score ($P = 0. 041$) and higher FRAX score for major fractures ($P = 0. 045$). The machine-learning model based on 20 RFs showed a high ability to predict VFs (ROC 0. 832), outperforming that of T-score and FRAX score, even when lower thresholds than conventional ones were used (ROC 0. 77 and 0. 45, respectively). The RF "information measure of correlation" was the most relevant feature in the model, suggesting that a reduction in texture cross-correlation is positively associated with the development of VFs ($P < 0. 001$).
Conclusion
The radiomics-based machine learning model showed high potential in identifying women at high fracture risk during HDTs.

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P273

JOINT2228

Nonsurgical hypoparathyroidism: insights from a single-center experience

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Hypoparathyroidism (HypoPT) is a rare endocrine disorder characterized by hypocalcemia and absent, low, or inappropriately normal PTH levels. The most common cause is neck surgery (75%), while nonsurgical forms, including idiopathic and genetically determined HypoPT, account for the remaining 25%. These forms are rarer and less well understood. This retrospective study investigates the clinical and biochemical characteristics, as well as complications, in 26 patients with idiopathic or genetically determined HypoPT followed at our Endocrinology Unit. We included 26 patients (15 women, 11 men) with a mean age at diagnosis of 22 ± 14 years (5–59) and a mean disease duration of 10. 8 ± 11 years (1–48). Genetic screening identified pathogenic variants in seven patients: five deletions of 22q11. 2 (DiGeorge syndrome), one GATA variant associated with hypoparathyroidism, sensorineural deafness, and renal dysplasia (HDR) syndrome, and one *AIRE* variant (APS type 1). Two variants of uncertain significance in *GCM2* and *AIRE* genes and one benign *GNAS* variant was identified. The remaining patients had no detectable mutations. The mean daily calcium and calcitriol supplementation was 1200 mg (0–3000) and 0. 9 μg/day (0. 5–1. 5), respectively. Despite treatment, 10 patients (38. 5%) experienced hypocalcemic symptoms. Baseline biochemical tests showed mean albumin-corrected serum calcium of 9. 04 ± 0. 6 mg/dL (7. 5–11. 3), phosphorus 3. 5 ± 0. 58 mg/dL (2. 2–6. 2), ionized calcium 1. 19 ± 0. 08 mmol/l (0. 93–1. 53), and magnesium 1. 9 ± 0. 14 mg/dL (1. 4–2. 5). Mean urinary calcium excretion was 255 mg/day (156–387). Corrected calcium, phosphorus, and magnesium levels were within target in 62%, 65%, and 53% of patients, respectively. Complications included basal ganglia calcifications (46. 2%), audiometric abnormalities (34. 6%), cardiac alterations (7. 7%), and recurrent infections (15. 4%). Renal involvement was observed in 46% of patients, with eight cases of nephrolithiasis and four of renal insufficiency. Reduced bone mass was documented in only one patient, and one vertebral fracture was reported. Bone evaluation showed a mean lumbar spine BMD of 1. 176 g/cm^2 (T-score 1. 2, Z-score 1. 2); a mean femoral neck's BMD of 1. 003 g/cm^2 (T-score 0. 5, Z-score 0. 7); a mean total hip's BMD of 1. 059 g/cm^2 (T-score 0. 5, Z-score 0. 7) and a mean one-third radius' BMD of 0. 705 g/cm^2 (T-score -0. 7, Z-score -0. 3). These findings highlight the heterogeneity of disease and its complications in patients with non-surgical HypoPT. Furthermore, many patients fail to achieve optimal biochemical targets despite treatment. This underlines the need for further studies to better understand this condition and develop improved therapeutic strategies to optimize patient outcomes.

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P274

JOINT3020

Association of size at birth and bone mineral density in adolescents

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Introduction
Persons born small for gestational age (SGA) are more prone to various adverse growth and metabolic outcomes later in life. Previous studies showed worse body composition in adults born SGA compared to those born appropriate for gestational age (AGA). The data on bone mineral density (BMD) in subjects born SGA are inconsistent. We aimed to analyze BMD in adolescents born SGA in relation to body composition and size at birth.
Methods
We investigated 107 children from prospective cohort followed from birth (43 SGA and 64 AGA). Birth weight and/or length in SGA individuals were below 2 standard deviations (SD) of the mean according to sex and gestational age and in AGA - between -2 and + 2 SD score (SDS). Children were born at 32-42 weeks of gestation. The anthropometric data were obtained at birth, 5, 12, 24 months and 11-13 years of age. DXA scan and laboratory parameters were assessed in adolescence.
Results
Adolescents born SGA were shorter and leaner than AGA (height SDS: -0. 52 ± 1. 31 vs. 0. 36 ± 1. 01, $P < 0.001$; weight SDS: -0. 49 ± 1. 69 vs. 0. 59 ± 1. 57; $P = 0.010$; BMI SDS: -0. 20 ± 1. 30 vs. 0. 31 ± 1. 25, $P = 0.048$). There were no differences in waist to height ratio, lean and fat mass percent in adolescents born SGA vs. AGA. There were no difference in ionized calcium, phosphate, PTH and vitamin D levels in SGA and AGA adolescents. Additionally, there were no differences in IGF-1 and IGF-BP-3 levels ($P = 0.119$ and $P = 0.128$, respectively). IGF-1/IGF-BP-3 ratio was lower in adolescent born SGA (0. 11 ± 0. 07 vs. 0. 15 ± 0. 12, $P = 0.027$). There was no difference in BMD (g/cm2) and apparent BMD (BMAD, g/cm3) between the groups. BMD Z-score was lower in adolescents born SGA compared to AGA (-0. 22 ± 1. 10 vs. 0. 21 ± 0. 83, $P = 0.035$). BMD Z-score in adolescence was directly related to gestational age and birth weight, weight SDS and length ($P = 0.024$, $P = 0.011$, $P = 0.022$ and $P = 0.011$, respectively). Analyzing SGA and AGA data separately, significant relations remained only in the SGA group. BMD Z-score in adolescence correlated with height and weight gain during first 2 years of life, but in separated analysis, relations remained only in AGA group.
Conclusion
Adolescents born SGA were leaner and had lower BMD Z-score. In SGA subjects, birth size is more important for further bone mineral accrual than early postnatal growth. Ethics: The study was approved by Lithuanian University of Health Sciences Kaunas regional biomedical research ethics committee (Nr. BE-2-42, 2011. 06. 14). Informed written consent was obtained from all parents prior to the study.

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P275

JOINT3667

Hypertension in primary hyperparathyroidism: predictive factors and post-parathyroidectomy outcomes

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Introduction
Hypertension is common among primary hyperparathyroidism (PHPT) patients and may contribute to increased cardiovascular morbidity. The impact of parathyroidectomy on blood pressure and cardiovascular outcomes remains unclear and is not typically considered when evaluating a patient for surgery.
Objectives
This study aims to identify predictors of hypertension in PHPT and to assess the impact of parathyroidectomy on blood pressure regulation.
Methods
This observational, retrospective study included 178 PHPT patients at a tertiary center. Logistic regression, adjusted for age, was used to analyze the association between clinical and biochemical variables and hypertension risk.
Results
Our population (84. 8% women, mean age 63 years) showed a hypertension prevalence of 60. 1% ($n = 107$), with hypertensive patients being significantly older (mean age 67 vs. 57 years, $P < 0.001$). After adjusting for age, no significant associations were found between hypertension and calcium, phosphate, PTH, vitamin D, or magnesium levels. Neither chronic renal disease nor disease duration increased hypertension risk. Among hypertensive patients, 60. 7% ($n = 65$) underwent parathyroidectomy, achieving a PHPT remission rate of 81. 5% ($n = 53$). At 6 months post-surgery, 7, 5% of patients ($n = 4$) experienced hypertension remission, and antihypertensive medication usage decreased from 1. 79 to 1. 62 drugs on average ($P = 0.031$).
Conclusion
Hypertension is prevalent in PHPT patients, regardless of laboratory values, renal disease, or disease duration. Parathyroidectomy appears to modestly reduce hypertension prevalence and antihypertensive medication use, suggesting long-term cardiovascular benefits.

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P276

JOINT2926

30 Years later: cracking the mystery of x-linked hypophosphatemic rickets

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Introduction
X-linked hypophosphatemic rickets (XLH; OMIM 307800) results from renal phosphate wasting, impaired intestinal calcium and phosphate absorption, and abnormal vitamin D metabolism due to elevated fibroblast growth factor 23 (FGF23). Patients present with early-onset rickets, skeletal deformities, short stature, bone pain, craniosynostosis, and dental anomalies. XLH is the most common inherited rickets form, with a prevalence of 1 in 20, 000 to 60, 000 individuals. It is caused by dominant inactivating variants in the PHEX gene on XP22. 11. This report discusses two siblings initially diagnosed with achondroplasia but later confirmed to have XLH.
Patients
I. B., a 60-year-old female, had a history of achondroplasia and osteoporosis but had not sought medical care for years. She presented with widespread leg pain and walked with two crutches. Her height was 110 cm, weight 33 kg, and she exhibited genu varum deformity. She had multiple past fractures but was not on regular medication. N. B., a 52-year-old female, had achondroplasia, osteoporosis, bilateral hearing loss, and primary hyperparathyroidism (surgically treated 24 years ago). She sought evaluation due to body pain and walked with one crutch. Her height was 115 cm, weight 35 kg, and she also exhibited genu varum. She had a history of leg fractures and was not taking medication. Family history revealed their father's height was 110 cm, their mother's 140 cm, with no consanguinity. The family had six children (three females, three males); all females had short stature, while males were at least 160 cm tall. Both sisters were misdiagnosed with achondroplasia 30 years ago without genetic testing. Recent genetic analysis identified a heterozygous c. 207_212del (p. K69_V70del) variant in *PHEX* (NM_000444. 6), classified as a 'Variant of Uncertain Significance' (VUS) per American College of Medical Genetics (ACMG)guidelines. Genetic counseling and segregation analysis were recommended.
Conclusion
These cases highlight diagnostic challenges in distinguishing XLH from achondroplasia, stressing the importance of genetic evaluation for accurate diagnosis. Misdiagnosis can delay appropriate management, underscoring the need for increased awareness and thorough genetic assessments in such cases.

Table 1:

	Patient 1	Patient 2
Serum phosphate (2. 5-4. 5 mg/dl)	1. 76	1. 8
Serum calcium (8. 6-10. 2 mg/dl)	9. 4	9
Serum ALP (35-105 U/l)	73	95
Serum 25 (OH)D (20-120 μg/l)	21. 7	14
Serum PTH (15-65 pg/ml)	81	65
Serum creatinine (0. 5-0. 9 mg/dl)	0. 53	0. 5
TRP (%) %85-95		78. 2
TmP/GFR (mg/dl) (2. 6-3. 8 mg/dl)		1. 41

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P277

JOINT3810

Pediatric parathyroid adenomas: a single tertiary care center experience

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Introduction
Parathyroid adenoma is a rare cause of primary hyperparathyroidism in children, with a prevalence of 2–5 per 100, 000. Pediatric cases have been reported to often present with more severe manifestations and higher rates of end-organ involvement, though symptoms may be nonspecific and lead to delayed diagnosis. This study evaluates the clinical characteristics, management, and outcomes of pediatric parathyroid adenoma at our center.
Methods
We retrospectively analyzed pediatric patients diagnosed with parathyroid adenoma at our hospital between 2022 and 2024. Patient records were reviewed for clinical presentation, laboratory findings, imaging studies, biochemical evaluations for MEN syndromes, perioperative management, and pathological assessments.
Results
Nine patients (4 females, 5 males; mean age 13. 80 $\pm$ 1. 69 years) were included. At diagnosis, the mean serum calcium was 12. 53 $\pm$ 0. 97 mg/dL and the mean PTH level was 203. 58 $\pm$ 127. 11 ng/l. Surgery was performed 19. 44 $\pm$ 14. 84 days after diagnosis, with an average follow-up of 8. 56 $\pm$ 7. 18 months. Preoperative imaging included parathyroid ultrasound (100%), sestamibi scintigraphy (88. 89%), and urinary ultrasound (88. 89%), with the left superior gland most commonly affected (44. 44%). Only one patient required a PTH washout study. Biochemical screening for MEN syndromes was performed in 66. 67% of patients, and genetic testing for MEN1, RET, and CDKN1B, performed in three patients, was negative. Notably, no patients had a family history of parathyroid adenoma or nephrocalcinosis. Clinically, 55. 56% of patients were asymptomatic with incidentally detected hypercalcemia, while 44. 44% presented with symptoms such as abdominal pain, gastrointestinal disturbances, and facial acne. Postoperative calcium levels normalized within 2. 33 $\pm$ 1. 41 days. No significant difference in preoperative calcium levels was found between symptomatic and asymptomatic groups ($P = 0.240$). All pathology was benign. Perioperative management included intravenous hydration (88. 89%), furosemide (88. 89%), pamidronate (22. 22%), calcitriol (44. 44%), and calcium supplementation (55. 56%), with two patients remaining on calcitriol therapy at 15-month follow-up.
Conclusion
Our findings underscore the sporadic nature of pediatric parathyroid adenoma, with no familial cases or nephrocalcinosis observed. Despite benign pathology, the variability in clinical presentation demands high diagnostic vigilance. Early surgical intervention resulted in rapid normalization of calcium levels, though prolonged calcitriol therapy in some patients suggests ongoing endocrine monitoring is essential. Further studies with larger cohorts and extended follow-up are warranted to refine management strategies for this uncommon pediatric condition.

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P278

JOINT1481

Patient-reported outcomes and quality of life in children and adults with hpp treated with asfotase alfa

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Introduction
Hypophosphatasia (HPP) is a rare disease caused by deficient tissue-nonspecific alkaline phosphatase activity. The objective of this analysis was to assess the effectiveness of asfotase alfa enzyme replacement therapy on patient-reported outcomes and quality of life (QoL) in patients with HPP.
Methods
Patients in the Global HPP Registry (data cutoff: July 2024) who received asfotase alfa treatment for $\geq$6 months after age 2 years were included. Pediatric Quality of Life Inventory (PedsQL) was administered to children (2-18 years). Brief Pain Inventory-Short Form (BPI-SF) and Short Form-36 version 2 Health Survey (SF-36v2) were administered to adults ($\geq$18 years). Data from patients with baseline and $\geq$1 follow-up assessments within 2 years were analyzed. Significance of changes was assessed by 95% confidence intervals (calculated assuming normal distribution, $\alpha = 0.05$).
Results
The study included 136 children and 202 adults. The most common baseline manifestations were dental manifestations among children (61%) and pain among

adults (76%). Muscular manifestations were common (children: 49%; adults: 38%). Pain and/or QoL (PedsQoL/SF-36v2) data were available for 26 children and 63 adults, among whom mean scores improved significantly following treatment (**Table**). No mean scores worsened over time. Injection site reactions were the most common event of interest.

Conclusions

Pain in adults and QoL in children with HPP significantly improved following asfotase alfa treatment.

Table 1: Comparison of LS-BMD and TBLH-BMD Z-scores (Mann-Whitney test).

Outcome	Baseline	6 Months	12 Months	24 Months
BPI-SF pain severity, n	61	49	41	28
Mean (SD)	**5. 2 (1. 9)**	**4. 5* (2. 2)**	**4. 0* (2. 1)**	**3. 9* (1. 7)**
Change from baseline, mean (95% CI)		-0. 8 (-1. 2, -0. 3)	-1. 1 (-1. 6, -0. 6)	-0. 9 (-1. 5, -0. 3)
BPI-SF pain interference, n	61	50	40	28
Mean (SD)	**5. 5 (2. 6)**	**4. 6* (2. 8)**	**4. 3* (2. 9)**	**3. 7* (2. 4)**
Change from baseline, mean (95% CI)		-0. 9 (-1. 5, -0. 3)	-1. 3 (-2. 0, -0. 6)	-1. 1 (-1. 9, -0. 2)
SF-36v2 Physical Component Summary, n	56	47	36	21
Mean (SD)	**34. 7 (10. 2)**	**36. 8 (9. 7)**	**36. 9* (8. 6)**	**40. 6 (10. 6)**
Change from baseline, mean (95% CI)		2. 2 (-1. 2, 5. 5)	4. 6 (1. 8, 7. 4)	3. 4 (-4. 1, 10. 9)
SF-36v2 Mental Component Summary, n	56	47	36	21
Mean (SD)	**39. 4 (12. 5)**	**41. 9 (12. 9)**	**45. 7* (10. 4)**	**47. 5 (9. 3)**
Change from baseline, mean (95% CI)		2. 1 (-1. 6, 5. 8)	6. 1 (2. 2, 9. 9)	4. 3 (-1. 9, 10. 5)
PedsQL Total, n	26	22	18	13
Mean (SD)	**63. 1 (15. 8)**	**73. 1* (16. 9)**	**75. 4* (15. 8)**	**77. 4* (13. 3)**
Change from baseline, mean (95% CI)		8. 8 (3. 3, 14. 4)	11. 0 (2. 4, 19. 7)	10. 1 (1. 8, 18. 4)

*Significantly different from baseline based on 95% CIs.

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P279

JOINT1326

Hospitalizations in people with rare bone diseases across age groups: a population-based cohort study in switzerland

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Introduction

Rare bone diseases pose challenges for both affected people and healthcare systems, necessitating optimized multidisciplinary and individualized care. However, comprehensive data on age-specific hospitalization rates, associated clinical conditions, causes of hospitalization, and in-hospital outcomes across different age groups remain limited.

Design and Methods

This is a population-based nationwide cohort study using administrative claims data from Switzerland between January 1, 2012, and December 31, 2021. We identified individuals across all ages with a diagnosis of a rare bone disease: Achondroplasia, fibrous dysplasia (FD), fibrodysplasia ossificans progressiva (FOP), osteogenesis imperfecta (OI), pseudohypoparathyroidism, and X-linked familial hypophosphatemia (XLH). Incidence rates, main causes of hospitalization, and in-hospital outcomes were assessed and compared with those of the general population.

Results

Among 11, 103, 800 hospitalizations, 2, 878 involved individuals with at least one rare bone disease: 218 hospitalizations of people with achondroplasia, 436 with FD, 62 with FOD, 926 with OI, 87 with pseudohypoparathyroidism, 1, 148 with XLH, and one individual with both FD and pseudohypoparathoyroidism. Hospitalizations were disproportionately high in pediatric patients (ages 0-17 years) with achondroplasia (52. 1% vs. 7. 3% in the general population) and OI (41. 1% vs. 7. 3%). In contrast, most hospitalizations of people with XLH occured in adulthood (18-90 years), similar to the general population (95. 2% vs. 92. 7%). Locally estimated scatterplot smoothing (LOESS) plots highlight distinct hospitalization patterns across rare bone diseases, with fractures being a significantly more common cause, particularly in pediatric OI cases.

Conclusions

This study shows distinct age-specific hospitalization patterns across rare bone diseases, emphasizing the need for tailored management strategies. The findings highlight the importance of an age-inclusive approach to optimize care in this population.

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P280

JOINT1235

Clinical features of pediatric hypophosphatasia and eight-year outcomes of enzyme replacement therapy in korea

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Introduction

Hypophosphatasia (HPP) is a rare genetic disorder caused by loss-of-function mutations in ALPL, which encodes tissue-nonspecific alkaline phosphatase (ALP). HPP is classified into six forms according to the onset and severity of manifestations: perinatal lethal, perinatal benign, infantile, childhood, adult, and odontohypophosphatasia. Perinatal and infantile forms have high mortality, making early diagnosis and intervention critical. Enzyme replacement therapy (ERT) with human recombinant tissue-nonspecific ALP (asfotase alfa) became available in Korea since 2016. This study describes the clinical characteristics of Korean HPP patients and presents an 8-year ERT experience in two patients with perinatal lethal and infantile HPP, highlighting their clinical course and long-term outcomes.

Patients and Methods

HPP was suspected in patients with markedly low ALP levels, and the diagnosis was confirmed by mutations in ALPL. We collected information on patients' demographics, laboratory findings, radiographic features, genetic variants, and clinical courses. Among HPP patients (one perinatal lethal, one perinatal benign, one infantile, two childhood, one odontohypophosphatasia, and two siblings presumed to develop into adult HPP based on family history), six were followed without ERT due to the absence of severe skeletal deformities, motor dysfunction, or pain. Two patients with infantile and perinatal lethal HPP received ERT. Both patients received asfotase alfa (2 mg/kg 3 times per week subcutaneously, adjusted to 3 mg/kg 3 times per week if required) for 8 years.

Outcomes

Radiographic improvements were observed: in the infantile HPP patient, the Rickets Severity Scale (RSS) score decreased from 10 to 7, and the Radiographic Global Impression of Change (RGI-C) score was +2. 3; in the perinatal lethal HPP patient, the RSS improved from 8 to 0, with an RGI-C score of +3. 0. Growth also improved: height standard deviation score (SDS) increased from -6. 37 to -5. 08 (infantile) and from -3. 00 to -1. 84 (perinatal lethal). The perinatal lethal patient had no radiographic signs of rickets after 3 years of ERT. Mechanical ventilation and supplemental oxygen were discontinued after 4. 5 years (infantile) and 2 months (perinatal lethal). Despite a more severe initial condition, the perinatal lethal patient showed greater improvement, emphasizing the importance of early treatment.

Conclusion

HPP should be considered when serum ALP is consistently low. Early diagnosis is important to ensure appropriate monitoring of patients with HPP. In particular, patients with perinatal lethal and infantile HPP should receive prompt treatment to avoid premature mortality and improve long-term prognosis.

Keywords: alkaline phosphatase, ALPL, bone, enzyme replacement therapy, hypophosphatasia

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P281

JOINT3564

Persistent hypercalcaemia in trisomy 21: consider ABCD syndrome

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Background
The ABCD syndrome (ABnormal Calcium, Calcinosis, and Creatinine in Down syndrome) is a rare cause of persistent hypercalcemia in children with trisomy 21, which typically occurs in the first 2 years of life. To date, 12 patients have been reported. Here we present a new case and review the literature of this under-reported clinical entity. **Case**: A 21-month-old toddler with trisomy 21 presented with a 6-month history of recurrent vomiting, failure to thrive, and bilateral nephrocalcinosis grade IIb of unknown origin. Laboratory results revealed hypercalcaemia (3. 37 mmol/l), hypermagnaesemia (1. 16 mmol/l), normophosphataemia and impaired renal function (creatinine 0. 80 mg/dl, (normal range 0. 19-0. 39 mg/dl)). Further tests showed undetectable serum PTH, low 1, 25(OH) 2D, elevated urinary calcium/creatinine ratio (3. 6 mmol/mmol). Vitamin A and 25-hydroxyvitamin D (74. 3 ng/mL) were both outside toxic ranges. The patient had received only routine vitamin D supplementation, with no other medication or supplements and no special diet, without excess of milk products. Adrenal insufficiency and malignancy were excluded. Trio whole exome sequencing identified no pathogenic variants linked to hypercalcemia. Since intravenous fluids failed to normalize calcium levels, a single dose of pamidronate (1mg/kg) was administered and low-calcium diet commenced. Serum calcium levels and renal function subsequently normalized before discharge. Follow-up examinations at two and four weeks confirmed sustained normal values for calcium, phosphate, PTH and calcium excretion, under continued dietary calcium restriction.
Discussion/Conclusion
Most reported cases of ABCD syndrome had similar biochemical profiles of calcium overload of PTH-independent cause, such as hypercalcaemia, hypercalciuria, nephrocalcinosis and acute kidney injury. The rapid improvement of hypercalcaemia following calcium intake reduction suggests increased intestinal calcium absorption as a potential mechanism. The diagnostic approach requires exclusion of other causes of hypercalcemia. Our case and literature review highlight the importance of raising awareness about ABCD syndrome to ensure timely diagnosis and intervention. Early recognition can help reduce the risk of complications such as kidney injury and prolonged failure to thrive.

	Admission	*Follow-up (2 weeks)*	*Follow-up (4 weeks)*
Serum Calcium (2. 25 – 2. 75 mmol/l)	3. 37	2. 53	2. 70
Serum Phosphate (1. 00 – 1. 95 mmol/l)	1. 75	1. 22	1. 08
Urine Calcium/Creatinine Ratio (0. 07 – 1. 50 mmol/mmol)	3. 615	0. 733	1. 072
PTH (18. 5 – 88. 0 pg/ml)	undetectable	20. 3	14. 0
25OHD (< 12 ng/ml)	74. 3	56. 8	59. 5
1, 25$(OH)_2$D (40-100 pg/ml)	22	n. d.	n. d.

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P282

JOINT2645

Genotype-phenotype correlations and therapeutic outcomes in osteogenesis imperfecta type vi: an 11. 5-year cohort study of 36 chinese pediatric patients

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Background
Osteogenesis imperfecta type VI (OI-VI), caused by biallelic *SERPINF1* mutations disrupting pigment epithelium-derived factor (PEDF) production, is a rare autosomal recessive skeletal disorder. Despite its distinct clinical profile, long-term therapeutic outcomes and genotype-phenotype relationships remain poorly characterized.
Methods
This retrospective cohort study analyzed 36 pediatric OI-VI patients from 33 families (median follow-up: 11. 5 years). Genetic testing identified *SERPINF1* variants, while clinical evaluations included bone mineral density (DXA), spinal radiographs, biochemical profiling (PEDF, β-CTX, P1NP, calcium, phosphate, 25-OH-VD), and treatment responses to bisphosphonates or denosumab with calcium/vitamin D supplementation.
Results
Thirty-eight *SERPINF1* variants (25 copy-number variations, 13 single-nucleotide variants) were identified, with recurrent pathogenic mutations c. 907C>T (p. Arg303Ter), c. 271_279dup (p. Ala91_Ser93dup), and c. 79G>T (p. Glu27Ter). Key clinical features included severe growth impairment (mean height Z-score: −2. 9), early-onset fractures (mean age: 1. 37 years), dentinogenesis imperfecta (82. 3%), blue sclerae (71. 4%), and vertebral compression fractures (51. 7%). Serum PEDF levels were universally deficient (mean: 0. 0017 μg/mL). All patients required surgical interventions (mean: 3. 79 procedures) combined with pharmacotherapy: 18 received bisphosphonates, and 18 switched to denosumab (11 after bisphosphonates). Hypercalcemia occurred in 5 denosumab-treated patients (mean onset age: 3. 6 years) . Fracture frequency decreased post-treatment, though detailed analyses of spinal deformity progression and biomarker trends are ongoing.
Conclusions
This study delineates the genotypic spectrum and phenotypic severity of OI-VI, emphasizing early fracture onset and multisystem involvement. While bisphosphonates and denosumab reduce fracture burden, denosumab-associated hypercalcemia in young children warrants cautious monitoring. Longitudinal data on spinal remodeling and bone turnover dynamics will further clarify therapeutic efficacy, guiding optimized management strategies for this ultrarare OI subtype.

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P283

JOINT2715

Onset of puberty in achondroplasia

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Prediction of adult height is important in treatment decisions of children with short stature. However, an important contributing factor is the variable range of puberty start and duration. To calculate the residual growth during adolescence, age at onset of puberty is a valuable indicator. Holmgren *et al*. described a remaining growth potential after onset of puberty of 28. 8–29. 2 cm in healthy boys ($n = 1174$) and 26. 2 to 26. 6 cm in healthy girls ($n = 1165$) (Gothenborg study, 2022). In comparison, del Pino *et al*.

reported a mean residual growth of 17. 8 cm and 19. 7 cm, respectively in 17 girls and 10 boys, respectively with untreated achondroplasia (ACH) (JPEM, 2020). In achondroplasia (ACH), correction of lower limb axis deviation – in particular varus malalignment – is performed by a variety of methods. To avoid major surgical procedures, growth modulation using temporary hemiepiphysiodesis can be employed in children with sufficient residual leg growth. Precise timing of this procedure before onset of the pubertal growth spurt is crucial to achieve sufficient correction of the deformity. Vosoritide is a new growth promoting drug for ACH, approved in 2021, enabling higher growth rate with to date no waning of treatment response. To analyze the effect of late start of vosoritide treatment on residual growth potential we analyzed 297 children with ACH (139 girls) with proven FGFR3 mutation. Onset of puberty was defined as follows: testicle volume > = 4ml, pubic stage = P2, breast stage = B2, bone age in female 11–12 or male 13–14 years (y), which was documented in 60 children (26 girls). Vosoritide treatment had been started at puberty onset in 38 out of 225 treated patients who were suitable for analysis. Puberty started in untreated girls at age 11. 0 y with mean height-SDS of -5. 1 SDS (i. e. 110. 8 cm; SD 7. 2 cm) and in untreated boys at age 12. 8 y with a mean height-SDS of -4. 6 SDS (i. e. 118. 9 cm; SD 7. 5 cm). So far, only 1st year treatment data from 16 pubertal children (5 girls) with ACH were documented. In vosoritide treated children compared to untreated ACH children a constant higher growth rate after onset of puberty of 5. 8 cm/y (SD 0. 7) vs. 4. 2 cm/y (SD 1. 1) in females and 5. 5 cm/y (SD 1. 1) vs. 4. 7 cm/y (SD 1. 1) in males was identified. In conclusion, after onset of puberty vosoritide induced an accelerated growth rate, which may be of potential benefit for effective growth modulation to correct angular deformities.

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P284

JOINT3279

Diabetes mellitus marginally impairs bone quality with chronic kidney disease

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Lately, various bone quality changes inflicted by diabetes mellitus (DM) have been linked to the elevated fracture risk with both type 1 and type 2 DM. Fracture risk is also elevated in patients with advanced chronic kidney disease (CKD), with DM being a key factor in CKD prevalence and CKD patients having an increased risk to develop DM. To decipher the contribution of bone quality parameters contributing to bone fragility, we assessed if diabetes mellitus has differential effects on bone quality in advanced CKD patients. Therefore, CKD stage 4-5D patients with (n = 11, age 58 ± 15 yrs, 10♂, 1♀) and without DM (n = 22, age 59 ± 12 yrs, 16♂, 6♀) were recruited. Double-label tetracyclines were used prior to trans-iliac bone biopsy. Quantitative bone histomorphometry was performed to determine bone turnover, mineralization, and bone structure. Bone quality was evaluated using quantitative backscattered electron imaging (qBEI) to assess bone mineral density distribution and 2D morphological analysis of the osteocyte lacunae. The osteocyte-lacunae network was visualized and quantified with Ploton silver precipitation on LR white resin sections. Additionally, bone matrix composition was analyzed using vibrational Raman spectroscopy to determine the mineral-to-matrix ratio (MMR) with a 50x objective at a laser wavelength of 785 nm. We determined that, trabecular bone volume/tissue volume (BV/TV) was lower in CKD + DM group (17. 5 (13. 9 – 19. 4) % vs. 21. 6 (18. 7 – 26. 1) %, P = 0. 02), with no differences in bone formation (BFR/BS) and bone resorption (Oc. S/BS) parameters on bone histomorphometry between the groups. Bone mineral density distribution as determined by qBEI, presented locally with lower mineral content and the presence of micropetrosis – mineralization of osteocyte lacunae. Raman spectroscopy identified a higher phosphate/amide III peak in the cortical bone in CKD + DM (1. 42 ± 0. 15 vs 1. 32 ± 0. 11 a. u., P = 0. 04), which indicates altered bone matrix composition. The results of our ongoing study point towards minor differences in bone quality between individuals with CKD with or without DM, whereby biopsies from CKD patients with DM had lower trabecular bone volume and slightly altered matrix composition. If and how these changes contribute to bone fragility will have to be explored in future studies.

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P285

JOINT168

Biochemical response kinetics in vitamin d resistant rickets (VDDR) type 1 and 2: 13-year retrospective analysis from a tertiary care centre

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Background
Vitamin D-resistant rickets (VDDR) type 1 and 2 are rare genetic forms of rickets. A few genetically proven cases have been reported from India. The pragmatic treatment responses assessed over time in literature are scarce.
Method
Retrospectively, we identified a cohort of fifteen cases of VDDR, including 6 patients of VDDR 1A, 2 patients of VDDR 1B, 7 patients of VDDR 2. The biochemical parameters, treatment and outcomes were analyzed. Data are presented as median with inter-quartile range (IQR), and mixed effect analysis for statistical analysis was used.
Result
In VDDR1A, the median age of presentation and delay in diagnosis was 12 (IQR-8-13. 5) and 26 months, whereas for VDDR2 it was 12 (IQR-6-24) and 46 months (6-58) respectively. 50% of VDDR1A patients had severe calcipenic symptoms and serum calcium improved over time from baseline- 7. 75mg/dl to 9. 3mg/dl at 1 year, and 9. 9mg/dl at 5 years, requiring a calcium dose(mg/kg/d) of 62. 5(44-128. 75), which reduced to 26. 5(18. 5-56. 25). Likewise, calcitriol dose (ng/kg/d) reduced from 40(26. 25-63. 75) to 24(12. 5-30. 75). In VDDR2, alopecia was present in 6 out of 7 patients, however only 28. 6% had severe calcipenic symptoms. Serum calcium improved over time from baseline- 7. 4mg/dl to 8. 7mg/dl at 1 year to 9. 2mg/dl at 5 years. As expected, these patients required higher doses of calcium and calcitriol. They required a calcium dose (mg/kg/d) of 138(70-160), which reduced to 100(42-200). Similarly, calcitriol dose (ng/kg/d) reduced from 75(50-100) to 62(27-100). Time to biochemical improvement was 5. 5 and 12months for VDDR1A and VDDR2 respectively. Additionally, two siblings with VDDR1B presented in their infancy, with complete biochemical response (alkaline phosphatase, serum parathyroid hormone, serum calcium) in 3 months with adequate calcium and vitamin D supplementation.
Conclusion
Timely diagnosis of VDDR is lacking, but good symptomatic and biochemical response is seen once diagnosed and appropriately treated.

		ALP	PTH	Hypocalcemia	Treatment	
VDDR1A		(duration in months)	(duration in months)		**Calcium dose(-mg/kg/-d)**	**Calcitriol dose(n-g/kg/d)**
Our study	n = 6	5. 5	5. 5	4	Baseline→ 62. 5 1 year→ 55 5 years→ 20	Baseline→ 40 1 year→ 33. 5 5 years→ 15
Manjunath H D *et al* (2021)	n = 7	12-15	12-15	3-6		
Fatma Dursun *et al* (2019)	n = 11	4-12	4-12	NA		
T Edouard *et al* (2011)	n = 7	3	3	3		Initiated Calictriol at 1ug/d
VDDR2						
Our study	n = 7	12	12	9	Baseline→ 138 1 year→ 110 5 years→ 105	Baseline→ 75 1 year→ 70 5 years→ 22. 5
Z Hochberg *et al* (1992)	n = 10	12	12	1 week-IV calcium		
Aida Al-Aqeel *et al* (1993)	n = 2	1. 5-2	1. 5-2	3 days-IV calcium		

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P286

JOINT2233

Severe short stature secondary to distal renal tubular acidosis with slc4a1 gene mutation in a nigerian adolescent

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Introduction
Renal tubular acidosis is characterized by persistent normal anion gap metabolic acidosis. It may be hereditary(primary) or secondary to disease conditions or drug use. Hereditary distal renal tubular acidosis (dRTA) is a rare genetic disease caused by mutations in either SLC4A1, ATP6VOA4 or ATP6V1B1 genes that encode the chloride-bicarbonate exchanger (AE1) or subunits of the H-ATPase pump. Affected individuals typically present with rickets, growth failure due to metabolic acidosis. This disease condition remains undiagnosed in most cases. This report is to create awareness about dRTA as a possible cause of rickets and short stature and to avoid the confusion with hypophosphatemic rickets.
Case Summary
17-year female adolescent with bony deformity first noticed in infancy presented to an orthopaedic hospital where she commenced on oral calcium and vitamin D in treatment for rickets. In view of recurrent history of fractures following minimal impacts despite use of calcium and vitamin D, she was referred to paediatric endocrinology clinic for possible vitamin D resistant rickets. There was no history suggesting autoimmune diseases or chronic drug use. She attained menarche at 15years but menstrual cycles stopped. Her weight was 19kg; length was 106cm -(minus)8. 5, and body mass index was 16. 9kg/m^2 -(minus)1. 71. Upper to lower segment ratio was 0. 95:1. Musculoskeletal system examination revealed telephone shaped deformity of the long bones and fork deformity of the wrist. Serum calcium was normal; 2. 41 mmol/l (2. 10 -2. 55), serum phosphate was 0. 51 mmol/l ↓ (0. 97 -1. 68), 25 hydroxyvitamin D was 56. 5 nmol/l (normal), Alkaline phosphatase was elevated at 692μ/l (79-370), parathyroid hormone was remarkably low < 1. 2 pg/ml (18. 50 – 88. 0). Serum electrolytes showed acidosis and hypokalemia with a normal anion gap. Urinalysis showed specific gravity of 1. 050, pH:8, low urine calcium (0. 59 mmol/l) phosphate (4. 8 mmol/l). On evaluation for vitamin D resistant rickets, FGF23 was normal. Whole genome sequencing returned positive for de novo heterozygous pathogenic variants in SLC4A1 of distal renal tubular acidosis with autosomal dominant mode of inheritance. There was an improvement with acidosis and hypokalemia on commencement of baking powder, phosphate and potassium therapy. She is also on calcitriol and calcium.
Conclusion
Rickets and growth failure are established presentations of dRTA. Serum electrolytes and urinalysis check in evaluation of a child with features of hypohosphatemic rickets are necessary to rule out dRTA.
Keywords: Distal renal tubular acidosis, children, Nigeria, Fractures, Short stature.

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P287

JOINT938

Localization imaging and postoperative outcomes in primary hiperparathyroidism (phpt): is less enough?

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Background/Aims
Surgery is the first-line established treatment for pHPT; the performance of preoperative localization techniques (LT) increases the probability of a successful parathyroidectomy. Our aim was to characterize the use of two different LT (neck ultrasound (US) and ^{99m}Tc-sestamibi scintigraphy (Sci)) and their impact on postoperative outcomes.
Methods
Retrospective study including patients with sporadic pHPT diagnosed and submitted to parathyroidectomy between january 2003 and october 2023 at a tertiary center. Patients with normocalcemic pHPT, without preoperative LT records or whose pHPT was an intraoperative finding were excluded.
Results
119 patients were included, most of whom were females (86. 6%; n = 103). At diagnosis, median age was 62. 0 (IQR=51. 0-70. 0) years and median ionized calcium (iCa), serum calcium (sCa), and PTH levels were 1. 41 (IQR=1. 37-1. 51) mmol/l (reference 1. 14-1. 29); 11. 3 (IQR=11. 0-12. 0) mg/dL (reference 8. 6-10. 5) and 178. 1 (IQR=143. 3-275. 7) pg/mL (reference 18. 0-80. 0), respectively. US was performed in all patients and Sci in 117 patients (98. 3%). US and Sci located abnormal parathyroid(s) in respectively 75. 6% (n = 90) and 90. 6% (n = 106) of patients; when both were performed, 26. 5% of patients (n = 31) presented positive localization in only one of the techniques. Neck CT and ^{18}F-fluorocholine-PET-CT were additionally performed in 17. 0% (n = 19) and 1. 7% (n = 2) of patients, respectively. Postoperative complications were documented in 16. 8% of patients (n = 16), in which 2. 1% (n = 2) presented iatrogenic hypoparathyroidism. Surgery success rates among all patients globally, patients with positive US only, positive Sci only, both US/Sci positive, both US/Sci negative and one positive with the other negative were 98. 3% (116/118); 87. 5% (7/8); 96. 0% (24/25); 100% (84/84); 50. 0% (1/2) and 93. 5% (29/31), respectively. No statistically significant differences were found between patients with one positive vs two positive LT regarding postoperative complications (18. 5% vs. 16. 7%; P = 1. 000) and calcium levels normalization (96. 9% vs. 100%; P = 0. 276). Additionally, no statistically significant differences were documented between patients with positive US only vs positive Sci only regarding the same outcomes (16. 7% vs. 19. 0%, P = 1. 000; 100% vs. 96. 0%, P = 1. 000).
Conclusion
In this study, the performance of US vs Sci demonstrated no differences regarding postoperative complications or calcemia normalization. Additionally, our results also suggest that one positive imaging exam might be enough to ensure parathyroidectomy success with no differences in the evaluated postoperative outcomes, thus reducing futile use of more preoperative localization techniques.
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P288

JOINT2210

Management of osteoporosis in a pediatric case of severe osteolysis

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Introduction
Autosomal recessive genetic osteolysis disorders include Multicentric osteolysis nodulosis arthropathy (MONA), Winchester syndrome, Torg syndrome, infantile systemic hyalinosis and mandibulo-acral dysplasia. Winchester syndrome (WS), first described in 1969, is a rare disorder characterized by short stature, coarse facial features, corneal opacities, generalized osteolysis, progressive JOINT destruction, osteoporosis and debilitating painful arthropathy. It is due to a missense mutation in *MMP14*, encoding the membrane-bound matrix metalloprotease 14. Due to the rarity of WS, evidence-based guidelines for managing osteoporosis in pediatric osteolytic syndromes are not well defined. Here we present the case of a 2-year-old girl with clinical and radiological features suggestive of likely Winchester syndrome managed with intravenous bisphosphonate for osteoporosis and immunomodulation for inflammatory arthritis.
Case: The patient, first child of consanguineous parents presented to our center for evaluation of a probable osteoporotic fracture of the left ulna diaphysis after the parents observed left wrist swelling. She had an uneventful antenatal and postnatal history and developmental milestones included delayed walking and speech delay. Chronic bilateral hand and finger swelling with pain upon tactile pressure was reported since infancy. On physical examination the anterior fontanelle was open, normal sclera and dentition, fingers of both hands had flexion deformities. Investigation revealed a normal biochemical bone profile. Radiographic findings included severe carpotarsal and phalangeal osteolysis, diffuse osteopenia with near total loss of mineralization of the scaphoid, lunate, triquetrum and pisiform bones. Thoracolumbar spine imaging revealed collapse of the T6 vertebral body. MRI of the bilateral wrists showed advanced osteolysis with necrosis like infarcts in the left wrist, synovitis, tenosynovitis and JOINT effusion indicating ongoing inflammation in the right wrist. Initial management with analgesia was minimally effective in reducing the bone pain. In view of the vertebral collapse, she was given a dose of intravenous Zoledronic acid followed by second dose 6 months later. Immunomodulation with Adalimumab was initiated for coexisting arthritis and tenosynovitis leading to decreased hand pain. She has not developed further fractures after 2 doses of Zoledronic acid. The provisional diagnosis of WS in this case was based on characteristic osteolysis, osteoporosis and arthropathy with differential diagnoses including MONA and Torg syndrome. Whole exome sequencing has been done for the child and the parents and results are awaited. This case underscores the challenges of managing osteoporosis in rare osteolytic syndromes. It highlights the importance of multidisciplinary care and need for genetic confirmation for a definitive diagnosis.
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P289

JOINT2162

Hereditary and acquired phosphopenic rickets: from childhood to adulthood

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Introduction
Phosphopenic rickets (FPR) is a group of disorders characterized by renal phosphate loss due to hereditary or acquired causes, leading to impaired bone mineralization. It affects both children and adults. This study presents the clinical data of patients diagnosed with FPR from a single center.
Patients and Methods
We present the clinical and genetic characteristics of pediatric (index) patients evaluated for hypophosphatemia and their subsequently diagnosed relatives between 2004 and 2024.
Results
A total of 33 cases (M:F = 21:12) from 26 families were identified. The median (range) age at diagnosis was 3. 9 (0. 6–31) years, serum phosphate (sP) was 2. 6(0. 5–3. 8) mg/dL, and the mean ± SD TmP/GFR 1. 7 ± 0. 9 mg/dL. Sixteen (48. 5%) had fibroblast-growth-factor-23 (FGF23)-dependent hypophosphatemic rickets (HPR) (14 hereditary, 2 acquired – both infants with liver failure), 10 (30%) from 8 families had vitamin D-dependent-rickets-(VDDR) [type 1 ($n = 8$)/type 2 ($n = 2$)], and 7(21%) had FGF23-independent-renal-tubular-dysfunction (RTD). In hereditary HPR, the age at diagnosis was 4. 8 (2-31) years, follow-up 14. 1(6. 6-21. 8) years. All patients had short stature, genu varum, and/or dental abnormalities. The Thacher score was 6. 1(5–8). While 4(28%) had enthesopathy, nephrocalcinosis was detected in 2(14%). Eight(57%) had corrective surgery, 2(%14) had history of fractures. Two(14%) were treatment naive while 6(42%) discontinued in adulthood. *PHEX* variant was identified in 4(28%). One was started on burosumab aged 10 years, resulting in significant improvement in genu varum. In VDDR age at diagnosis was 1. 6(1. 3-4) years. Nine(90%) presented with delayed walking and 9 had consanguineous parents. Wrist widening was observed in all, while genu varum was present in 7(70%). Height SDS at presentation was -2. 0(-0. 5/-4. 5) and sP 2. 9 mg/dL(1. 7-3. 3). In type 1 VDDR, *CYP27B1* variant was found in 6/8 (homozygous $n = 5$; compound heterozygous $n = 1$) while in type 2 VDDR a homozygous pathogenic variant in *VDR* was found in one. In RTD, age at diagnosis was 7(3-14. 3) years, height SDS -3. 5(-0. 6/-4. 3), sP 2. 6 mg/dL(0. 5-2. 9), and TmP/GFR 1. 7(0. 2-2. 5)mg/dL. Diagnosis included cisplatin toxicity (CT)($n = 1$, Pearson syndrome $n = 1$, cystinosis $n = 2$, and RTD $n = 3$. All but one (CT) had skeletal anomalies. In one with RTD, a pathogenic variant in the *SLC34A3* gene was identified.
Conclusion
These results highlight the wide range of clinical and genetic characteristics of patients with hypophosphatemia. Elucidation of etiology will enable early and correct diagnosis but delay causes severe morbidity. Burosumab, an FGF23 inhibitor, targeted therapy for X-linked hypophosphatemia improves skeletal deformities and growth in children, enhances fracture healing, reduces pain, and boosts physical activity in adults.

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P290

JOINT1090

Parathyroid washout's role in accurate adenoma localisation and diagnostic cut-offs

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Purpose
Accurate adenoma localisation is necessary for the application of minimally invasive surgery, which is preferred in the treatment of primary hyperparathyroidism. This study aimed to determine appropriate cut-off values for the parathormone-washout(PTH-WO) method.

Table 1: The demographical and biochemical parameters of the patients.

Parameters	n	Value
Age (years)	339	54. 00 (19. 00-81. 00)
Calcium (mg/dl)	339	11. 00 (8. 90-14. 90)
Corrected Calcium (mg/dl)	339	10. 60 (8. 30-14. 70)
Phosphorus (mg/dl)	339	2. 70 (1. 40-4. 70)
Alkaline phosphatase (U/l)	315	106. 09 ± 42. 09
Creatinine (mg/dl)	339	0. 74 ± 0. 14
Glomerular filtration rate (ml/min)	339	97. 00 (60. 00-134. 00)
Serum Parathormone (ng/l)	339	154. 00 (81. 00-738. 00)
24-hour urinary calcium (mg/day)	339	298. 50 (80. 00-947. 00)

Table 2. Locations of the parathyroid adenomas of the patients.

	Right	Left	Level VII lymph node compartment	Overall
Superior	11 (3.13%)	18 (5.12%)	N/A	29 (8.26%)
Inferior	149 (51.20%)	142 (40.45%)	N/A	291 (82.90%)
Intrathyroidal	16 (4.55%)	12 (3.41%)	N/A	28 (7.97%)
Level VII lymph node compartment	N/A	N/A	3 (0.85%)	3 (0.85%)
Overall	176 (50.14%)	172 (49.00%)	3 (0.85%)	351 (100.00 %)

Design
A total of 402 PTH-WO assays from 339 patients were included in the study. The diagnostic accuracy of the test was assessed by accepting as a positive result a PTH-WO result higher than the serum PTH level [PTH-WO/serum PTH(PTH ratio) > 1]. In addition, a cut-off value for the test was established by evaluating the PTH washout results obtained in comparison with postoperative histopathology. Undiluted test results were not included to obtain a clear numerical value in this evaluation. The results of parathyroid scintigraphy and fine needle aspiration biopsy(FNAB) were compared with postoperative histopathology.
Results
While 309(76. 86%) of the PTH-WO procedures were considered positive, 93(23. 13%) were considered negative if the PTH ratio was > 1. When these results were compared with the postoperative histopathology, the test's sensitivity was 92. 51%, and the specificity was 100. 00%. In the analysis of the remaining 292 PTH-WO samples after excluding the undiluted ones, the sensitivity and specificity of the method were 92. 3% and 94. 1%, respectively, with a PTH ratio > 0. 99. With a cut-off value of 99. 5 ng/l for PTH-WO value, 93. 1% sensitivity and 94. 3% specificity were obtained. The sensitivities of parathyroid scintigraphy and FNAB were 53. 4% and 15. 3%, respectively.
Conclusion
The PTH-WO method is safe and cheap, with high sensitivity and specificity in localising parathyroid adenoma. In cases where radiological methods cannot achieve localisation with specified cut-off values, it has high diagnostic accuracy.

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P291

JOINT2412

Pubertal development in hypophosphatemic rickets: does it have an impact on growth?

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Background
Hypophosphatemic rickets (HR) is a rare disorder characterized by impaired phosphate metabolism, leading to skeletal deformities, short stature, and delayed bone mineralization. While its impact on childhood growth is well-documented, its effect on pubertal development and final height remains unclear. This study aims to evaluate pubertal progression, final height outcomes, and associated clinical factors in HR patients to provide insights into optimizing growth management strategies.
Methods
This retrospective study included HR patients diagnosed either clinically or genetically. Data including pubertal onset, progression, final height, and pubertal height gain were collected. Height SDS and BMI SDS were analyzed across different Tanner stages. Statistical analyses were performed to assess the association between pubertal onset and final height, sex-based growth differences, and predictors of target height.
Results
A total of 34 patients (F/M:18/16) were included. Genetic analysis was available for 13 patients, with mutations identified in *PHEX* ($n = 7$), *SLC34A3* ($n = 4$), *SLC34A1* ($n = 1$), and *DENT* ($n = 1$). At presentation, the mean age of the patients was 8. 4 ± 5. 2 years, and the mean height SDS was -2. 49 ± 1. 56. The mean age at pubertal

onset was 10. 6 (8. 4–13) years in females and 10. 7 (9. 4–15) years in males. The mean age at menarche was 13. 1 ± 0. 8 years, which was significantly delayed compared to the Turkish population (12. 2 ± 0. 9 years) ($P < 0.001$). The pubertal height gain was 20. 1 ± 6. 2 cmin girls and 29. 8 ± 15. 4 cm in boys, comparable to that observed in the Turkish population. The duration of puberty was 5. 3 ± 1. 0 yearsin girls and 5. 3 ± 1. 5 years in boys. Among 13 patients (F/M:6/7), who reached final height, the final height SDS (-2. 3 ± 1. 1) was significantly lower than the target height SDS (-1. 1 ± 0. 9) ($P = 0.0005$). The final height SDS was significantly higher in females compared to males (-1. 9 ± 0. 9 vs. -3. 1 ± 1. 1, $P = 0.045$).

Conclusion

Despite a normal or slightly increased pubertal height gain in females, final height remained significantly below the genetic target in both sexes. Menarche was delayed, and pubertal duration was slightly prolonged in HR girls compared to the general population. Notably, females had a significantly higher final height SDS than males, suggesting a greater growth deficit in male patients despite comparable pubertal height gain. These findings underscore the importance of early intervention, continuous growth monitoring, and individualized treatment strategies to optimize final height outcomes in HR.

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P292

JOINT1962

Pregnancy management in ectonucleotide pyrophosphatase/phosphodiesterase family member 1 (ENPP1) deficiency: a case report and considerations for maternal medicine care

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Background

ENPP1 Deficiency is a rare autosomal recessive disorder with an estimated prevalence of 1 in 64, 000 pregnancies. It results in low inorganic pyrophosphate levels, leading to excessive soft tissue calcification, neointimal proliferation, and impaired bone mineralisation. Approximately 50% of affected infants succumb to generalised arterial calcification of infancy (GACI) within the first six months. Survivors may develop hypophosphatemic rickets, hearing loss, osteomalacia, vascular calcification, and cardiac complications. Pregnancy in women with ENPP1 Deficiency remains undocumented.

Case Presentation

We present a 32-year-old woman with ENPP1 Deficiency, currently in her second pregnancy. Her past medical history includes hypophosphatemic rickets managed with Alfacalcidol and phosphate replacement, congenital cervical spine fusion (C2-C3), and minor vascular calcification. Her twin brother died at six weeks from severe GACI. She has received lifelong metabolic bone and cardiology care. Her first pregnancy was managed in a Maternal Medicine Centre (MMC) with multi-disciplinary management. Her initial bone chemistry was within normal ranges and remained stable throughout pregnancy. The bone profile was monitored closely as the placenta can produce PTHrP in variable amounts, requiring potential dose adjustments of Alfacalcidol. She remained on Alfacalcidol 1 mg and Phosphate Sandoz 4 tablets daily. Due to increased risk of hypertension, pre-eclampsia, and fetal growth restriction, she was commenced on prophylactic aspirin (150 mg/day). Obstetric cardiology assessments showed normal ECG and echocardiogram findings. Low molecular weight heparin prophylaxis was initiated after MDT discussion. At 23 weeks, she had a positive placental screen with bilateral notches and a mean placenta pulsatility index of 1. 46 and she commenced home blood pressure monitoring and fetal growth surevillance. Normal fetal growth velocity was maintained and delivered at 36 + 4 weeks via elective cesarean section due to hypertension and abnormal placental growth factor (PIGF). In her second pregnancy, also managed at MMC, initial assessment revealed hypophosphatemia with mild secondary hyperparathyroidism (PTH 7. 8 pmol/l, PO_4^{2-} 0. 73 mmol/l, Adjusted Ca^{2+} 2. 34 mmol/l). She remains on the same dose of Alfacalcidol and Phosphate Sandoz. She is 23 weeks gestation with reassuring cardiology assessments. Placental screen shows no notches and borderline raised pulsatility index indicating a lower risk of placental pathology.

Conclusion

Pregnancy in women with ENPP1 Deficiency requires multidisciplinary care at a Maternal Medicine Centre. Pre-conception counselling should address potential complications, emphasising cardiovascular risk assessment. Close monitoring for metabolic bone disease, cardiac complications, and hypertensive disorders, along with individualised management plans, is crucial to optimising maternal and fetal outcomes.

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P293

JOINT2401

"Familial hypocalciuric hypercalcemia in adolescence: diagnostic challenges and the role of genetic testing"

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Introduction

Familial hypocalciuric hypercalcemia (FHH) is a benign, autosomal dominant condition with high penetrance. Heterozygous individuals typically present with mild hypercalcemia, hypocalciuria, inappropriately normal parathyroid hormone (PTH) levels, and elevated serum magnesium levels. FHH1, the most common form, results from inactivating mutations in the calcium-sensing receptor (CaSR) gene on chromosome 3q21. 1. Distinguishing FHH from asymptomatic primary hyperparathyroidism (PHPT) is critical, as FHH rarely requires parathyroidectomy and is not resolved by it. While typical biochemical findings can differentiate the two conditions, atypical presentations pose challenges. The calcium-creatinine clearance ratio (CCCR) aids diagnosis, with CCCR < 0. 01 indicating FHH and > 0. 02 suggesting PHPT. However, values between 0. 01–0. 02 create diagnostic uncertainty, and some PHPT cases may also present with CCCR < 0. 01, as reported by Moore *et al*. This report presents a 14-year-old girl diagnosed with FHH despite a CCCR > 0. 01, emphasizing the role of genetic testing in cases with overlapping biochemical features.

Case Presentation

A 14-year-old girl was referred for incidentally detected hypercalcemia during a routine evaluation. She had no history of polyuria, abdominal pain, weight loss, or bowel changes. Her clinical examination was normal, with no family history of hypercalcemia at initial assessment. Growth parameters were within normal limits (height: 163. 2 cm, weight: 58. 6 kg).

Investigations

- Adjusted Calcium: 2. 97–3. 20 mmol/l (elevated) (NR: 2. 20 – 2. 70)
- PTH: 7. 0–10. 1 pmol/l (unsuppressed in presence of hypercalcemia) (NR: 1. 3 – 9. 3)
- CCCR: 0. 0158
- Magnesium: 0. 89–0. 90 mmol/l (normal) (NR: 0. 7 – 1. 0)
- Vitamin D: 54 nmol/l (normal) (NR: 50 – 200)

Renal ultrasound showed no nephrocalcinosis. Normal neck ultrasound as well as Sestamibi scintigraphy scan ruled out parathyroid adenoma. Genetic testing identified a heterozygous pathogenic missense variant in the CASR gene, confirming FHH1. Following this, patient's father was also found to have asymptomatic hypercalcemia, and his genetic test results for the identified mutation are pending.

Discussion

FHH shares biochemical overlap with PHPT but is typically benign, with low urinary calcium excretion and a CCCR < 0. 01. Unlike PHPT, FHH does not lead to complications like osteoporosis or kidney stones.

Conclusion

This case underscores the importance of genetic testing in distinguishing FHH from PHPT, especially when CCCR results are inconclusive. A correct diagnosis ensures appropriate management, avoiding unnecessary procedures and anxiety.

Reference

1. Moore, E. C., Berber, E., Jin, J., and Siperstein, A. (2020) 'Calcium-Creatinine Clearance Ratio is not helpful in differentiating primary hyperparathyroidism from familial hypocalciuric hypercalcemia: A study of 1, 000 patients', *Surgery for Obesity and Related Diseases*.

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P294

JOINT2424

"A diagnostic odyssey: camurati - engelmann syndrome presenting as childhood onset leg pains and stiffness"

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A 10-year-old girl was referred to the paediatric rare bone disease service by neurology for persistent leg pain, stiffness, and an undiagnosed condition despite extensive evaluation. Born at term following an uneventful pregnancy, she met early milestones and walked independently at 12 months. Symptoms began at 2 years of age with unsteadiness and frequent falls. By 3 years of age, she struggled with running and fatigued easily. By 6 years of age, she had difficulty climbing stairs, used a one-foot-at-a-time approach, and could not jump. Her dystonia primarily affected her lower limbs, with no family history of similar conditions. Brain and spine MRIs were normal. At age 7, she was referred to the complex movement disorder service, initially suspected of primary dystonia. Extensive metabolic, neuromuscular, and genetic tests were inconclusive, and nerve conduction studies were normal. Due to needle phobia, sedation or general anaesthesia was required for testing. Multiple dystonia medications, including L-Dopa, clonazepam, and gabapentin, failed and caused side effects like anxiety, mood disturbances, and suicidal ideation. She was also enrolled in the 100, 000 Genomes Project. By age 9, her condition worsened; she developed a waddling gait with foot clawing and required a wheelchair for long distances. A paediatric neurologist questioned the dystonia diagnosis, and deep brain stimulation was not pursued. Following referral to rare bone disease service, radiographs and MRI of the lower limbs were obtained and these revealed cortical thickening, Erlenmeyer flask deformity of the femora, and bone marrow oedema, suggesting Camurati-Engelmann disease (CES). Whole genome sequencing confirmed a de novo heterozygous pathogenic TGFB1 missense variant, confirming CES. Her current management includes physiotherapy, hydrotherapy, regular analgesia, heat pads, and activity pacing. NSAIDs help control pain, with prednisolone or losartan as potential options. She is growing well and has entered puberty without issues. Audiology, ophthalmology, and DEXA scans remain normal, with a lumbar spine and Total Body Less Head BMD z-score of -0. 3. CES is a rare autosomal dominant disorder caused by TGFB1 mutations, leading to progressive diaphyseal dysplasia with bone pain, muscle weakness, and waddling gait due to cortical thickening of long bones. Skull thickening can cause CNS complications such as increased intracranial pressure, headaches, optic nerve compression, and cranial nerve dysfunction. CES should be considered in children with unexplained limb pain and stiffness, particularly with radiological features like cortical thickening, Erlenmeyer flask deformity, and bone marrow narrowing. Early diagnosis prevents unnecessary investigations and ineffective treatments.

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P295

JOINT267

Bone health index (BHI) in children with osteogenesis imperfecta: is it an accurate tool for predicting fracture risk?

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Introduction
Bone Health Index (BHI) is calculated from hand-wrist X-rays using BoneXpert® software: it assesses the average cortical thickness of the three middle metacarpal bones, adjusted for bone width and length. The software also provides a standard deviation score (BHI SDS) that allows comparison with healthy children with the same bone age. BHI has shown a significant correlation with fracture risk in a healthy pediatric population[1]; however, its correlation with fractures in OI has not been evaluated. We hypothesise that BHI would correlate with fracture risk in Osteogenesis Imperfecta (OI) and thus be helpful in the assessment of bone fragility.
Methods
The National OI service at Great Ormond Street Hospital (London, UK) currently looks after 276 children with OI and maintains a detailed and accurate record of fractures. We retrospectively reviewed their first hand-wrist X-rays, fracture history in the one-year window before and after hand-wrist X-ray was performed, lateral spine X-rays, and DXA scans. All selected patients underwent hand-wrist X-rays and DXA scans on the same day, with X-rays analyzed using BoneXpert® version 3. 0 or later. The 132 cases previously analyzed with earlier software versions are currently being reanalyzed using the latest version and are not included in this preliminary analysis.
Results
A statistically significant negative correlation was observed between BHI SDS and the total number of vertebral and non-vertebral fractures within the year before and after BHI assessment ($r = -0.702$, $P = 0.0001$). This correlation was particularly strong for vertebral fractures ($r = -0.759$, $P = 0.00002$). A statistically significant positive correlation was observed between BHI and DXA BMD absolute values ($r = 0.610$, $P = 0.0461$), but no correlation between BHI SDS and DXA SDS values was observed. Interestingly, no significant correlation was found between lumbar DXA measurements (BMD, BMD SDS and BMAD SDS) and fracture incidence, even when analyzing vertebral and non-vertebral fractures separately. Post-pubertal patients showed higher BHI values than pre-pubertal patients. Additionally, patients with an Asian geographical background had lower BHI scores and sustained more fractures compared to patients with a Caucasian and African background
Conclusion
This preliminary analysis suggests that, unlike DXA, BHI correlates more closely with fracture risk, particularly for vertebral fractures. BHI may offer a feasible, cost-effective tool for identifying OI children at higher fracture risk.
Reference
1. Prijatelj V *et al*. Bone health index in the assessment of bone health: The Generation R Study. *Bone* 2024

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P296

JOINT3731

Clinical and laboratory characteristics of genetic rickets: a single-center experience with long-term outcomes

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Background
Rickets is a metabolic bone disease characterized by inadequate mineralization of growing bone tissue due to deficiency of calcium, phosphorus, vitamin D or resistance to vitamin D. Genetic causes of rickets are rare and accounts for 13% of all rickets cases. Genetic rickets can be divided into two groups: vitamin D-dependent rickets and hypophosphatemic rickets (HR). All of them present similar clinical manifestations of hypocalcemia and/or rickets. This study aimed to evaluate the clinical, laboratory and genetic features and long-term follow-up of the patients diagnosed with genetic rickets.
Materials and Methods
The study included patients diagnosed with genetic rickets between 2010 and 2024 in our clinic. Relevant data were collected retrospectively from medical records. The patients were evaluated in terms of clinical, laboratory, and genetic characteristics.
Results
Fifteen patients were included in the study. Eight of the patients (53. 3%) were male, and seven (46. 7%) were female. Of the patients, six had Vitamin D-dependent rickets type 1 (VDDR1), two had Vitamin D-dependent rickets type 2 (VDDR2), and seven had Hypophosphatemic Rickets (HPR). The most common presentation was leg deformities; followed by delayed walking, growth retardation, alopecia, delayed dental development and bone pain. The mean age at presentation was 3.5 ± 3.1 years. Physical examination findings included JOINT widening (40%), genu varum (33. 3%), short stature (33. 3%), genu valgum (26. 7%), rachitic rosary (26. 7%), caput quadratum (6. 7%), pectus carinatum (6. 7%), and frontal bossing (6. 7%). The diagnosis of all the cases with VDDR1 was confirmed by demonstration of the variant in the *CYP27B1* gene. One of the VDDR2 cases showed a variant in the *VDR* gene, while genetic analyses could not be performed in the other. Six patients with HPR had variants in the *PHEX*, and one had variant in the *CLCN5*. The mean follow-up period for the patients was 77. 9 months. The mean final height of the four patients, who reached final height, was 142.07 ± 11.19 cm (129-155 cm). No complications were observed in any of the patients during long-term follow-up.
Conclusion
This study provides valuable insights into the clinical and laboratory characteristics, as well as long-term follow-up outcomes, of 15 patients diagnosed with genetic rickets. The findings are important for expand the knowledge and increase the awareness of this rare condition and for encouraging further research in this area.

Keywords: genetic rickets, *CYP27B1, VDR, PHEX, CLCN5*
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P297

JOINT2150

A novel case of macroprolactinoma in a patient with phenylketonuria

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Introduction

Phenylketonuria (PKU) is an autosomal recessive disorder that impairs phenylalanine (Phe) metabolism to tyrosine. We present a case of macroprolactinoma in a patient with PKU and explore potential mechanisms linking the conditions.

Case

A 36-year-old man with neonatal-diagnosed classical PKU (compound heterozygous *PAH* variants) presented to the endocrine clinic with fatigue, low mood, and erectile dysfunction. He had low lumbar spine BMD (Z-score -2. 5), managed with bisphosphonates. Phe concentrations were often above the 600 umol/l target, typically ranging from 550–800 umol/l. Examination showed BMI 32 kg/m^2, bilateral gynaecomastia, and sparse body hair. Labs confirmed secondary hypogonadism: total testosterone 6. 3 nmol/l, free testosterone 0. 15 nmol/l, LH 1. 23 IU/l, FSH 2. 3 IU/l. Prolactin was elevated at 11, 649 mIU/l (RR 73–407), with macroprolactin excluded. Remainder of pituitary function and calcium concentrations were normal. Family history was negative for pituitary disease. MRI revealed a 17 mm right-sided pituitary macroadenoma. Following initiation of Cabergoline 0. 25 mg weekly, prolactin declined to 1, 421 IU/l at four weeks and 590 IU/l at three months. Total testosterone rose to 10. 3 nmol/l after six months, with symptomatic improvement.

Discussion

Patients with PKU may have impaired neurotransmitter production due to low plasma and brain tyrosine. Elevated Phe levels further deplete brain tyrosine by competing for blood-brain barrier transport, reducing dopamine synthesis. PET studies confirm reduced dopamine production in PKU, even with mildly elevated Phe. Since dopamine inhibits prolactin secretion, low levels result in increased prolactin. Therefore, suboptimal metabolic control in PKU is typically associated with modest prolactin elevations (~1, 500 mIU/l). However, the marked hyperprolactinemia in this case suggests the alternative pathology of prolactinoma. Dopamine is thought to inhibit lactotroph proliferation, and animal models link chronic dopamine deficiency, possibly via reduced D2 receptor stimulation, to pituitary tumorigenesis. However, human data are lacking, necessitating further research on whether PKU-related dopamine deficiency could increase pituitary tumour risk. Bone health is an important concern in PKU. While PKU patients generally have lower BMD Z-scores than controls, most remain within the normal range. However, around 10% have a Z-score below -2, suggesting low BMD. These cases warrant further evaluation for secondary causes.

Conclusion

While mild hyperprolactinemia is common in PKU, markedly elevated prolactin levels should prompt further investigation. This case also highlights the importance of investigating low BMD in PKU, as its underlying causes may be multifactorial. Further research is needed to explore the link between PKU-related dopamine deficiency and pituitary tumorigenesis.

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P298

JOINT2047

Trabecular bone score and risk of vertebral fracture in systemic lupus erythematosus children and adolescent who treated with glucocorticoids

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Background

Glucocorticoid-induced osteoporosis (GIO) is a common consequence in children and adolescents with systemic lupus erythematosus (SLE). Vertebral fractures (VFs), which are typically asymptomatic, occur in 4-28 percent of these patients, emphasising the importance of close monitoring. While bone mineral density (BMD), assessed by dual-energy X-ray absorptiometry (DXA), is the gold standard for evaluating bone health. its limitations are evident as many children with VFs show normal BMD Z-scores. Trabecular bone score (TBS) offers insight into bone quality and has been linked to fracture risk. Despite its potential, limit studies have explored TBS's role in identifying prevalent VFs among SLE children treated with glucocorticoids therapy.

Purpose

To evaluate the TBS in glucocorticoid-treated SLE children and adolescents with and without VF and the correlation between the TBS and BMD data.

Methods

The retrospective cohort study included 48 patients with SLE who had been treated with systemic glucocorticoids (GCs) for over three months. Both TBS and BMD were assessed between January 1, 2017 and December 31, 2024, at the Pediatric Department of Phramongkutklao hospital. TBS was analyzed using iNsight software (version 3. 0. 2. 0) and TBS Z-scores as well as BMD Z-scores were calculated using established reference values for children and adolescents. Patients were classified into two groups: VF and non-VF according to the Genant semi-quantitative method. A comparison of TBS Z-scores between the VF and non-VF groups was done.

Results

At baseline, the mean age (11 years [10. 5-14]), BMI (21. 49 kg/m^2 [18. 2-25. 99]), cumulative GCs dose (8, 083. 75 mg [5, 105-12, 800]) showed no significant differences between two groups. TBS L1-L4 and TBS L1-L4 Z-scores were lower in the VF group than in the non-VF group, although not significantly: [1. 16 (1. 14-1. 40) vs. 1. 36 (1. 30-1. 42), P 0. 117; 0. 05 (-2. 12 to 0. 38) vs. 0. 09 (-0. 6 to 0. 5), $P = 0.370$]. Both VF and non-VF groups had L1-L4 BMD Z-scores above -2: -1. 04 (-2. 57 to 0. 4) vs. 0. 26 (-1. 04 to 1. 02), P 0. 12. TBS L1-L4 Z-scores showed a moderate positive correlation with L1-L4 BMD Z-scores (r 0. 477, P 0. 001). TBS L1-L4 also exhibited moderate positive correlations with L1-L4 BMD (r 0. 686, $P < 0.001$) and BMAD L1-L4 Z-scores (r 0. 488, $P < 0.001$).

Conclusion

Lower TBS may indicate compromised bone microarchitecture, providing additional insight beyond BMD alone in childhood and adolescent patients with SLE.

Keywords: SLE, Adolescents, Glucocorticoid, Trabecular bone score

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P299

JOINT2014

Hypercalcaemia from primary hyperparathyroidism and CYP24a1 pathogenic variant: a coincidence or an underlying mechanism?

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The *CYP24A1* gene encodes the enzyme 24-hydroxylase, which plays a crucial role in the catabolism of 1, $25(OH)_2D_3$ and 25-hydroxyvitamin D [$25(OH)D_3$]. A deficiency in this enzyme results in elevated circulating levels of both $25(OH)D_3$ and 1, $25(OH)_2D_3$, leading to enhanced vitamin D activity. This, in turn, increases serum calcium levels due to heightened intestinal calcium absorption and renal calcium reabsorption. Biallelic pathogenic variants in this gene are responsible for infantile idiopathic hypercalcemia, whereas heterozygous individuals may either maintain normocalcemia or develop mild hypercalcemia. To date, only six cases of patients with a heterozygous CYP24A1 variant and primary hyperparathyroidism (PHPT) has been documented in the literature. Here, we present the cases of two unrelated patients evaluated at our outpatient clinic. The first patient is a man with a history of recurrent nephrolithiasis since the age of 16. At 26, he was referred to our clinic for evaluation after presenting with a serum calcium level of 12. 5 mg/dL (reference range: 8. 6–10. 2), PTH of 24 pg/mL (10–40), 25(OH)D of 72. 8 mg/dL, 1, $25(OH)_2D_3$ 64. 9 mg/dL and 24-hour urinary calcium of 558 mg/24h. Suspecting PHPT, a SPECT/CT scan revealed a hyperfunctioning parathyroid gland, leading to parathyroidectomy (PTx) with histological confirmation of a parathyroid adenoma. Six months postoperatively, the patient continued to have persistent hypercalcemia (10. 8 mg/dL) and suppressed PTH (7 pg/mL), raising suspicion for PTH-independent hypercalcemia. Genetic analysis revealed a heterozygous variant c. 1226T>C, p. (Leu409Ser) in the *CYP24A1* gene. The second patient is a 59 years-old woman who presented with severe hypercalcemia (14. 3 mg/dL), PTH of 47 pg/mL and 25(OH)D of 30. 9 mg/dL. Suspecting PHPT, she underwent PTx of the left lower and upper glands, with histological confirmation of parathyroid adenomas. Four years later, after missing follow-up appointments, she was admitted to the emergency department with nausea

and vomiting due to severe hypercalcemia (19 mg/dL) and an elevated PTH of 227 pg/mL. She was treated with hemodialysis, zoledronic acid, cinacalcet, and, subsequently, underwent PTx of the right lower parathyroid with histological confirmation of adenoma. Six months later, despite persistent hypercalcemia (10. 4 mg/dL) and suppressed PTH (7 pg/mL), genetic analysis revealed compound heterozygosity for the c. 428_430del, p. (Glu143del) and c. 245A > G, p. (Gln82Arg) variants in the *CYP24A1* gene. These two cases illustrate the clinical presentation of PHPT in patients with CYP24A1 mutations, showing that these individuals can develop severe hypercalcaemia challenging-to-manage hypercalcemia. Whether this association is just by chance or depends on specific mechanisms remains to be explored.

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P300

JOINT2132

Effect of long-term treatment with teriparatide and vitamin k on bone density and bone markers, glucose metabolism and body composition in severe osteoporotic patients

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Osteocalcin (OC) is emerging as a hormone regulating metabolic/endocrine functions including glucose metabolism and energy homeostasis. OC displays different carboxylation status modulated by vitamin K with different biological activities. Here, we investigated the role of carboxylated (γ_3OC) and uncarboxylated (γ_0OC) osteocalcin using a human model of severe osteoporotic patients treated with teriparatide (TPT) and randomized to supplementation with metaquinone (MK-7) 375 microg/die. Sixty-five normoglycemic patients (60 females, 5 males, aged 73. 9 ± 6. 0 years, BMI 24. 2 ± 3. 8 kg/m^2, mean ± SD) were enrolled, treated with 20 microg TPT daily sc and reevaluated after 18 months. Forty-three patients concluded the study, including 11 women supplemented with MK7 (TPT + MK-7). All patients experienced at least one fragility fractures (n = 3. 4 ± 1. 9), while during the follow up incident vertebral morphometric deformities occurred just in one patient. TPT increased the circulating bone formation markers γ_3OC, γ_0OC, bone-specific alkaline phosphatase (BALP), as well as the bone resorption markers C-terminal telopeptide of type 1-collagen (β-CTX-I) and tartrate-resistant acid phosphatase 5b (TRACP5b), while TPT reduced sclerostin. Of note, in patients treated with TPT + MK-7, circulating γ_3OC levels, but not γ_0OC, after 18 months were higher than those in non-supplemented patients (21. 1 ± 13. 1 vs 12. 7 ± 3. 7 ng/ml, P = 0. 0651; Δ + 94. 1 ± 0. 7% vs + 34. 5 ± 0. 5%, P = 0. 0313). TPT treatment significantly increased lumbar T-scores, with any difference in the amount of increase between the two groups (Δ17. 0 ± 14. 0% vs 18. 3 ± 15. 0%), while no changes were detected at neck and hip levels. By contrast, TPT + MK-7 induced a higher T-score Δ at hip level than TPT (22. 2 ± 0. 5% vs 0. 4 ± 0. 2%, P = 0. 0374). Long-term TPT as well as TPT + MK-7 did not prevent skeletal muscle mass reduction, evaluated as appendicular skeletal muscle index (ASMI; 5. 76 ± 0. 82 vs 5. 51 ± 0. 74 kg/m^2; P = 0. 0018; Δ − 3. 9% per year) and lean mass/height^2 (LMH; 14. 2 ± 1. 6% vs 13. 9 ± 1. 6%, P = 0. 0156) by DXA, as well as muscle strength loss by handgrip test (17. 5 ± 5. 8 vs 15. 7 ± 3. 9 kg, P = 0. 0715). Besides, the trunk/limb fat mass ratio increased, though circulating leptin levels decreased. Finally, TPT treatment induced a significant increase in insulin sensitivity evaluated by oral glucose tolerance test (OGIS index, 427. 7 ± 82. 7 vs 474. 0 ± 81. 4 μmol/min/m^2, P = 0. 0102). In Conclusions, long-term TPT increases γ_3OC and γ_0OC circulating levels and lumbar T-scores and prevents new fractures, improves peripheral insulin sensitivity and decreases leptin levels; however, it does not protect from aging-related loss of muscle mass and strength. MK-7 supplementation amplifies the TPT-induced increases of circulating γ_3OC levels and hip T-scores, but it does not affect glucose metabolism as well as body composition in normoglycemic severe osteoporotic elder patients.

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P301

JOINT3580

Prevention and treatment of hypocalcaemia in children undergoing total thyroidectomy

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Background
Hypocalcaemia due to hypoparathyroidism is one of the most common complications of total thyroidectomy in the paediatric population. Early screening and postoperative monitoring are crucial to minimise long-term complications.
Aim
To evaluate the incidence of hypocalcaemia in paediatric patients submitted to total thyroidectomy, to identify associated risk factors, and to improve the screening protocol implemented at our centre since 2020.
Methods
Retrospective cohort study including all children submitted to total thyroidectomy, at our centre, from 1st January 2020 to 30th June 2024, without any conditions affecting calcium homeostasis and with a minimum follow-up period of 6 months after surgery. Demographic, clinical, surgical and laboratory data were collected from the patient's medical records. A comparative statistical analysis was subsequently performed between children who developed hypocalcaemia and those who did not, using SPSS®, with a significance level set at $P < 0.05$. Transient hypocalcaemia (< 8. 5mg/dL) was defined as resolved within 6 months post-surgery.
Results
A total of 19 paediatric patients underwent total thyroidectomy, 68. 4% of whom were female, with a median age of 15. 2 years (IQR 3. 3). Indications for surgery included malignant neoplasm (n = 8), hyperthyroidism (n = 5), multinodular goitre (n = 3), and prophylactic thyroidectomy due to genetic risk of neoplasia (n = 3). The median hospital stay was 5 days (IQR 1. 25). Only 8 children had blood samples taken in the recovery room 60 minutes post-surgery, and only 8 received vitamin D supplementation at least one week prior (ranging from 10 to 435 days). Hypocalcaemia occurred in 68. 4% of the cases (n = 13), all within the first 24 hours post-surgery. Three patients developed paresthesia. Hypocalcaemia was transient in 9 cases (4 resolving during hospitalisation) and permanent in 4. Patients with hypocalcaemia had significantly lower preoperative vitamin D levels (19 vs 31 ng/mL, P = 0, 033) and a greater decrease in baseline calcium levels (-1. 3 vs -0. 8 mg/dL, P= 0, 046). ROC curve analysis to predict hypocalcaemia demonstrated an AUC of 0. 929 (P = 0. 040) for preoperative vitamin D (with an optimal cut-off using Youden Index of 25. 5 ng/mL) and 0. 788 (P = 0. 048) for calcium drop (cut-off of -1. 15 mg/dL).
Conclusion
The importance of screening and managing for post-total thyroidectomy hypocalcaemia is emphasised. This includes vitamin D supplementation for all children prior to elective surgery and monitoring calcium and PTH levels in the postoperative period, beginning in the recovery room, in order to identify at-risk patients early. We recommend multicentre studies to confirm these findings and enhance the intervention protocol.

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P302

JOINT3977

X-linked hypophosphatemic rickets in children and adolescents - single centre expertise in romania

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Introduction
XLH is a rare, genetic, chronic, progressive, lifelong musculoskeletal disorder characterised by renal phosphate wasting caused by excess FGF23 activity. It has biological and clinical consequences since early childhood: hypophosphatemia, low active vitamin D, craniosynostosis, rickets, bone deformity, short stature, and nephrolithiasis. The inheritance pattern of XLH is X-linked dominant, and the total incidence of XLH (paediatrics and adults) is 1 in 20, 000. There are two main therapeutic options: conventional therapy (phosphate supplements and active vitamin D) and biological therapy (Burosumab, a specific antibody against FGF23, EMA approved since 2018).
Subjects and Methods
Between 2018 and 2024, 13 children (7 girls) (median age = 4. 1 years, 1. 8-6. 8 years) and 1 adolescent girl were diagnosed and treated for XLH in a tertiary centre of pediatric endocrinology. Clinical, biological and radiological parameters were measured every 3-6 months: height, bone deformity, cranial circumference, 6MWT, serum calcium, phosphate and alkaline phosphatase, serum 25 OHvitamin D, PTH, TRPh, rickets severity score (RSS) and mechanical and anatomical axis of the lower legs.
Results
The children were first treated with conventional therapy and then switched to biological treatment after a median time of 4. 2 years. The main reasons for therapeutic alternatives were unimproved short stature and low leg deformity needing orthopaedic correction. None of the children on conventional therapy developed nephrolithiasis. After a median time of 2. 3 years (0. 5-3. 5 years), Burosumab treatment (median dose 1 mg/kg) showed a clear improvement of the clinical, biological and radiological data: an average 0. 425 SDS at week 96 improvement of Z-score for height, a constant increase of serum phosphorus to low normal levels, a constant decrease of alkaline phosphatase. Minor local reactions at injection sites or flu-like symptoms were described in the first doses but without clinical significance. None of the children needed orthopaedic correction. None of the children developed hyperparathyroidism.
Conclusions
Although a rare disease, XLH can be easily identified, evaluated, and treated by multidisciplinary teams from specialised bone disorders children's centers.

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P303

JOINT3998

From highs to lows: the challenge of hypocalcemia after parathyroid carcinoma surgery

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Background
Parathyroid carcinoma is a rare but aggressive cause of primary hyperparathyroidism (PHPT), accounting for <1% of cases. Its delayed diagnosis often results in severe phosphocalcic imbalance, leading to marked hypercalcemia, skeletal destruction, and end-organ damage. Surgical resection is the only curative treatment, but postoperatively hungry bone syndrome (HBS) frequently complicates recovery, prolonging hypocalcemia due to excessive mineral uptake by bones.
Case Presentation
A 36-year-old underweight female (body mass index = 16. 4 kg/m^2) with facial dysmorphia and feeding difficulties, presented after four years of progressive, uninvestigated right mandibular and left maxillary swellings, found to be large (10 cm) brown tumors with maxillary sinus invasion on cone beam computed tomography. Laboratory findings revealed severe hypercalcemia (Calcium = 14. 2 mg/dL), markedly elevated parathormone (PTH) (780. 8 pg/mL), and hypercalciuria (779 mg/24h), confirming PHPT. Ultrasonography identified a 1. 52 × 1. 74 × 4 cm hypoechoic, inhomogeneous left superior parathyroid lesion, with intense Technetium -99m MIBI uptake, highly suspicious for malignancy. PHPT complications included forearm osteoporosis and bilateral nephrocalcinosis with stage 3 chronic kidney disease. She underwent emergency total en bloc thyroidectomy with removal of three parathyroid glands. Histopathology confirmed parathyroid carcinoma (pT2N0L0V1Pn1) in the left superior gland, with hyperplasia in the left inferior and right superior glands. Despite preoperative vitamin D supplementation, intensive hydration, andavoiding bisphosphonates, severe HBS developed (Calcium=5, 1 mg/dl; Magnesium=1, 7 mg/dl; Phosphorus=2. 3mg/dl; Alkaline Phosphatase = 467 U/l, after the PTH postsurgical drop (2, 4 pg/ml). She required prolonged high-dose IV and per os calcium (up to 2500 mg calcium element daily), high doses of calcitriol, and magnesium supplementation with multiple dose adjustments for three months. MEN syndromes were excluded. A six-month follow-up is scheduled to assess brown tumor regression and determine if surgical correction for skeletal damage is necessary. Lifelong multidisciplinary follow-upwill monitor forrecurrence, phosphocalcic balance, and end-organ damage.
Conclusion
Delayed diagnosis led to severe pre- and postsurgical phosphocalcic imbalance and severe skeletal and renal complications. Identifying risk factors for malignancy guided the choice of an optimal surgical approach. However, despite close monitoring and intensive management, metabolic rebalancing was prolonged. Long-term multidisciplinary follow-up is essential for bone recovery, and recurrence monitoring.

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P304

JOINT2437

Biochemical ratios for predicting primary hyperparathyroidism: revisiting simple yet powerful diagnostic tools

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Background
The differentiation of primary hyperparathyroidism (PHPT), normocalcemic primary hyperparathyroidism (NPHPT), and vitamin D deficiency-associated secondary hyperparathyroidism (VDSHPT) remains a diagnostic challenge. This study evaluates the diagnostic performance of biochemical markers in distinguishing these conditions.
Methods
This cross-sectional study included 437 participants categorized into PHPT (n = 161), NPHPT (n = 97), VDSHPT (n = 89), and control (n = 90) groups. Serum calcium (Ca), phosphate (P), chloride (Cl), parathyroid hormone (PTH), and vitamin D levels were analyzed, along with biochemical indices such as Cl/P, Ca/P, Ca × Cl/P ratios, and the PF Index (Ca × PTH/P). Patients with chronic kidney disease, malignancy, or medication use affecting calcium and PTH metabolism were excluded. Receiver operating characteristic (ROC) curve analysis was used to determine diagnostic accuracy.
Results
Calcium levels were highest in PHPT (2. 73 ± 0. 17 mmol/l, P < 0. 001), while phosphate levels were lowest (0. 70 ± 0. 19 mmol/l, P < 0. 001). PTH levels were significantly elevated in PHPT (164. 9 ± 73. 4 pg/mL), NPHPT (126. 0 ± 40. 4 pg/mL), and VDSHPT (134. 9 ± 49. 2 pg/mL) compared to controls (43. 2 ± 14. 0 pg/mL, P < 0. 001). The Ca/P ratio was highest in PHPT (4. 17 ± 1. 21), significantly differing from other groups (P < 0. 001). The Ca × Cl/P ratio was also significantly elevated in PHPT (448. 5 ± 133. 6) compared to controls and other hyperparathyroidism subtypes (P < 0. 001). No significant differences were observed between NPHPT and VDSHPT for Ca/P (P = 0. 63) and Ca × Cl/P (P = 0. 74) ratios. The Ca × Cl/P ratio exhibited the highest diagnostic accuracy for PHPT (AUC: 0. 876, 95% CI: 0. 834–0. 917), with a specificity of 89. 2% and PPV of 82. 2%. The Ca/P ratio had the highest sensitivity (77. 6%) and an NPV of 86. 6%. The PF Index (AUC: 0. 851, 95% CI: 0. 816–0. 886) and Cl/P ratio (AUC: 0. 766, 95% CI: 0. 711–0. 820) showed moderate accuracy. In contrast, all markers showed high sensitivity (100%) but extremely low specificity (1. 6–23. 2%) in NPHPT, with poor PPV (<27%) despite maintaining an NPV of 100%.
Conclusion
The Ca × Cl/P and Ca/P ratios demonstrate strong diagnostic value for PHPT, while biochemical markers have limited specificity in NPHPT. These findings highlight their role in screening but emphasize the need for additional diagnostic approaches.
Keywords: Primary hyperparathyroidism, Normocalcemic hyperparathyroidism, Vitamin D deficiency, Biochemical markers, ROC analysis, Parathyroid function index

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P305

JOINT3771

Bone marrow stem cells derived exosomes for osteoporosis treatment

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Introduction
Osteoporosis is a systemic bone metabolic disorder caused by reduced bone formation and increased bone resorption. Currently, there are several anti-resorption drugs and osteosynthesis drugs that are effective in the treatment of osteoporosis, but their use is limited due to contraindications and side effects. In regenerative medicine, the unique repair ability of mesenchymal stem cells (MSCs) has gained significant attention from researchers. The exosomes secreted by MSCs possess signal transduction and molecular delivery mechanisms, which may have therapeutic effects.
Methods
MSCs were initially isolated from human bone marrow. After the surface antigen of MSCs was identified using flow cytometry, MSC-derived exosomes (MSC-Exo) were extracted. The osteogenic and adipogenic differentiation abilities of BMSCs were assessed using alizarin red staining and oil red O staining, respectively. Quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) was employed to analyze the mRNA expression of various genes. The cell viability of osteoblasts was determined using the Cell Counting Kit-8 (CCK-8) assay. Western blotting was used to measure the expression of specific surface markers in exosomes and the MAPK pathway-related proteins in osteoblast cells. Additionally, the cell cycle of osteoblasts was analyzed by flow cytometry.
Results
We found that surface antigens were positively expressed in MSCs, indicating a strong multipotent differentiation ability. The isolated MSC-Exo exhibited typical exosome morphology and particle size, with the detection of specific surface-labeled proteins being positive under electron microscopy. After co-culturing MSC-Exo with the osteoblast cell line, we observed that MSC-Exo could promote the proliferation of osteoblast cells. Additionally, mRNA and protein expression levels in the cells were increased, and the cell cycle was also enhanced.
Conclusion
MSCs-derived exosomes have the potential to promote osteoblast proliferation by inhibiting cell apoptosis, ultimately improving osteoporosis. We suggest that MSCs-derived exosomes could be a promising therapeutic approach for osteoporosis in the future.

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P306

JOINT3762

Jaw tumor syndrome: a rare endocrine disorder with diverse clinical manifestations

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Jaw Tumor Syndrome (JTS) is a rare, autosomal dominant endocrine syndrome caused by pathogenic variants of the **CDC73 gene**. The most common manifestation is primary hyperparathyroidism (PHPT), due to adenoma or, more rarely, parathyroid carcinoma. Other manifestations include ossifying fibromas of the jaw, renal cysts and tumors, as well as uterine conditions. However, a concomitant diagnosis of pheochromocytoma has not been identified to date. The clinical case of a 56-year-old woman is presented. She was referred to the Endocrinology department in 2004 due to hypercalcemia and bilateral kidney stones. There were no other significant personal or family medical histories. After investigation, she was diagnosed with primary hyperparathyroidism and underwent a left inferior parathyroidectomy (pathological examination confirmed it was a parathyroid adenoma), along with a left lobectomy and isthmectomy (consistent with nodular thyroid hyperplasia). About two years after the parathyroidectomy, she presented with a progressively worsening expansive lesion of the right upper jaw, causing bone destruction. She underwent surgical intervention, and the diagnosis of a cemento-ossifying fibroma was made. There were no recurrent lesions throughout imaging follow-up. Additionally, the patient had a history of endometrial and endocervical polyps and uterine fibroids (she underwent partial endometrial ablation). In 2008, due to newly developed and difficult-to-control hypertension, further studies were performed, including the measurement of plasma, urinary metanephrines and an abdominal CT scan revealed a 3. 5 cm nodule in the right adrenal gland. She underwent a right adrenalectomy, which confirmed a benign norepinephrine-producing pheochromocytoma. She remained asymptomatic until 2016 when she was hospitalized with a suspected diagnosis of MEN or hereditary pheochromocytoma/paraganglioma. A genetic study was conducted to look for mutations in the **SDHAF2, SDHB, SDHC, SDHD, MAX, TMEM127 and VHL** genes, but no relevant mutations were found. Given her personal history, a diagnosis of **JTS** was suggested. A subsequent mutational analysis of the **CDC73 gene** revealed an 8-base deletion in exon 16, resulting in the substitution of lysine with proline at position 474, leading to the appearance of a premature stop codon. Following this result, genetic testing was performed on family members, including her sister(**CDC73+ and diagnosed with a 6mm angiomyolipoma in the upper third of the left kidney**)and her mother (**negative genetic test result**). Her father passed away at very young age. Currently, the patient continues to follow up with the Endocrinology consultation, monitoring potential complications related to the syndrome. This case describes the complexity of diagnosing this rare syndrome, which should be considered in the presence of hyperparathyroidism and ossifying jaw tumors. The concomitant presence of pheochromocytoma, not described in the syndrome, made the definitive diagnosis more challenging.

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P307

JOINT1045

Heterozygous WNT1 variant causing severe, adult-onset hereditary osteoporosis

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Osteoporosis primarily affects postmenopausal women and several secondary causes may predispose to osteoporosis in premenopausal women or males < 50 years. If no secondary causes are found, possible genetic causes should be considered despite adult age. WNT1-mutation related osteoporosis, a genetic form of osteoporosis is characterized by early-onset fragility fractures in childhood and a rather mild disease course. We describe a novel family with a different phenotype, that presented at adult age with multiple fractures and severe, progressive disease. Patient 1 A 27-year-old man presented with multiple vertebral fractures and 7. 5 cm height reduction. Dual-energy absorptiometry (DXA) Z-scores in the lumbar spine, femoral neck and total hip were -4. 6, -2. 6 and -2. 9, respectively. Biochemistry including calcium, phosphate and bone turnover markers was normal. After exclusion of secondary causes, we performed a genetic analysis revealing a heterozygous pathogenic *WNT1* variant (p. Cys218Gly) in exon 4 of Chromosome 2. This variant is known to result in reduced WNT1 signaling and impaired bone mineralization. Patient 2 At the same time, a 59-year-old woman, mother of patient 1, was referred because of several years of back pain and 7 cm height reduction. At presentation, she had multiple vertebral fractures and severe kyphosis. The first vertebral fractures were diagnosed three years earlier. DXA T-scores in the lumbar spine, femoral neck and total hip were -3. 2, -2. 7 and -2. 1, respectively. Secondary causes were excluded and genetic testing revealed that she carried the same *WNT1* mutation as her son. Histomorphometry analysis of transiliac bone biopsy after tetracycline double labeling showed low bone turnover in both patients. Patient 1 was started on denosumab 60 mg twice a year. During 3 years of follow-up, he has not suffered from further fractures. Also in patient 2, denosumab was initiated. A year later, BMD had improved markedly, however, she then suffered low-energy hip and humerus fractures. Sequencing of treatments was as follows; denusomab 18

months, followed by 5 mg of zoledronic acid and, 9 months later, initiation of romosozumab. Romosozumab is an anabolic osteoporosis medication that acts via WNT-signaling. The results of 6 months of treatments are available in March 2025. In conclusion, hereditary WNT1-mutation related osteoporosis can present with an adult-onset, severe and progressive phenotype.

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P308

JOINT2997

Infantile idiopathic hypercalcemia associated with heterozygous mutation of SLC34A1: a case series

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Objective

Idiopathic infantile hypercalcemia (IIH) is a rare clinical disorder defined by hypercalcemia, typically presenting with symptoms such as failure to thrive, dehydration, vomiting, nephrocalcinosis, and elevated calcium levels. Mutations in *SLC34A1*, which encodes the sodium-phosphate cotransporter (NPT2A), lead to phosphate depletion and dysregulated production of 1, 25-dihydroxyvitamin D, resulting in subsequent hypercalcemia. Here, we present three cases of IIH associated with mutations in the SLC34A1 gene.

Methods

The clinical and laboratory findings of three patients with IIH were analyzed retrospectively.

Results

All patients were asymptomatic at presentation, and hypercalcemia was detected incidentally. The first two patients were twins, both presented with hypercalciuria and nephrocalcinosis. The third patient had hypercalciuria but did not show nephrocalcinosis. A targeted next-generation sequencing panel for nephrocalcinosis/nephrolithiasis was conducted to investigate the underlying aetiology. Genetic analysis revealed that the twins had compound heterozygous mutations in *SLC34A1* (c. 644+1G>A/c. 398C>T p. (Ala133Val)), one of which was a pathogenic variant and the other variant of uncertain significance (VUS). The third patient had a monoallelic variant in *SLC34A1* (c. 272_292del p. (Val91_Ala97del)), which was likely pathogenic (Table-1).

Table 1. Clinical and laboratory findings of patients

	Family-1		Family-2
	Patient-1	Patient-2	Patient-3
Sex	Female	Female	Male
Gestational-age, week	29+4	29+4	41+3
Birth-weight, gr	1174	1261	3445
Consanguinity	No	No	No
Family-history of renal calcification	No	No	No
Family-history of hypercalcemia	No	No	No
History of vitamin D application	600 U/day (from birth to 10w)	NA	400 U/day (from birth to 2 month)
Symptoms	Asymptomatic	Asymptomatic	Asymptomatic
Age at initial assessment, months	12	12	2
Initial assessmentAdjusted-Ca(mmol/l) (normal-range 2. 2-2. 7)	2. 91	2. 97	2. 71
Serum-Pi(mmol/l)	1. 26	1. 33	2
ALP(U/l)	192	213	1986
PTH(ng/l)(normal-range:15-63)	<3	<0. 5	10
25(OH)D3(nmol/l)	101	111	36
1, 25-dihydroxyvitamin D (pmol/l) (normal-range:48-192)	96		252
UrineCa/Cr(mmol/mmol) (normal-range:10. 05-1. 5)	2. 17	2. 33	3. 88
Renal-function Imaging-examination	Normal	Normal	Normal
Nephrocalcinosis	+	+	-
Skeletal abnormality	-	-	-
Treatment	Potassium-citrate	Potassium-citrate	None
Gene-analysis	Compound-heterozygous mutation in *SLC34A1* gene c. 644+1G>A/c. 398C>T p. (Ala133Val)		Heterozygous mutation in *SLC34A1* gene c. 272_292del p. (Val91_Ala97del)

Conclusion

In the presence of hypercalcemia accompanied by hypercalciuria, DNA analysis for mutations in the *SLC34A1* gene should be conducted. Heterozygous patients typically exhibit milder clinical symptoms compared to homozygous patients due to haploinsufficiency of NTP2A. Despite having a mild phenotype, they remain at risk for kidney damage and chronic kidney disease due to nephrocalcinosis and require close monitoring. Gaining a better understanding of the phenotypic and genotypic characteristics of this rare disease may help clarify its full spectrum over time.

Keywords: hypercalcemia, nephrocalcinosis, nephrolithiasis

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P309

JOINT4009

Analysis of symptoms in paediatric patients with familial hypocalciuric hypercalcaemia, a case series

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Background

Familial hypocalciuric hypercalcaemia (FHH) type 1 is caused by mutations in the *CASR* gene which encodes the calcium sensing receptor (CaSR). It is inherited in an autosomal dominant pattern with high penetrance. CaSR is highly expressed in parathyroid glands and kidneys and is an important regulator of calcium homeostasis. Inactivating/loss-of-function mutations in *CaSR* result in a decreased sensitivity of CaSR to serum calcium, leading to inappropriate PTH release with respect to hypercalcaemia. This PTH effect leads to an increase in renal tubular reabsorption of calcium. The net biochemical effect is of hypercalcaemia, with inappropriately normal or mildly elevated PTH and low urinary calcium. Well described symptoms of hypercalcaemia include nephrocalcinosis, gastrointestinal symptoms and fatigue. Conversely patients with FHH are often asymptomatic and this condition is usually identified incidentally. In terms of management, calcimimetic medications are allosteric agonists at CaSR. By enhancing the effect of extracellular calcium at the CaSR they consequently reduce serum calcium levels. However given the benign natural history of FHH, the necessity of these medications is controversial. Particularly in a paediatric population where safety and efficacy are not well established. We aimed to review symptomatology in our patients with FHH1 to add to the debate of whether treatment is required.

Methods

We retrospectively reviewed cases of patients with FHH1 actively attending our endocrine clinic. Patient demographics, calcium measurements and documented symptoms were collected. Data are mean $\pm$ standard deviation unless otherwise stated.

Results

11 participants were identified over the last ten years. All patients had confirmed *CaSR* heterozygous mutations. (45%) $n = 5$ patients from same kindred and remainder ($n = 7$) were unrelated. Diagnosis was made at age 5. 75 years $\pm$ 6. 07 and resulted from an incidental finding of hypercalcaemia in 72% ($n = 8$) and screening due to family history in 27% ($n = 3$). Serum calcium at diagnosis 2. 95 mmol/l $\pm$ 0. 10. Range of serum calcium over time 2. 66 to 3. 1 mmol/l. The most common symptom reported was constipation in 36% ($n = 4$). One patient reported polydipsia, all other patients ($n = 6$) were asymptomatic. All patients had normal renal ultrasound.

Conclusions

The majority of patients with FHH1 attending our service are asymptomatic of hypercalcaemia. Constipation was the only consistently reported symptom and given the prevalence of constipation in a paediatric population, causality from hypercalcaemia alone is unlikely. Given these findings, we have not considered calcimimetic medication for any of our patients. Further prospective studies to correlate calcium concentrations with symptoms is warranted for this paediatric cohort.

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Diabetes and Insulin

P7

JOINT592

Secretagogin deficiency leads to gut microbiome dysbiosis and impairs thermogenesis in age-related diabetes via reduced 12,13-diHOME

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\[Type 2 diabetes (T2D) is increasingly recognized as a global pandemic. Secretagogin (SCGN), an EF-hand calcium sensor, plays a crucial role in hormone secretion across the pancreas, enteroendocrine cells (EECs), and neural compartments. While pancreatic SCGN expression has been linked to T2D, its role in EECs remains underexplored. In this study, we show that SCGN is significantly downregulated in the intestinal epithelial cells of both T2D patients and diabetic mice. Scgn deficiency in EECs of mice leads to age-associated diabetes by impairing thermogenesis in brown adipose tissue, attributed to reduced circulating levels of 12,13-diHOME, as revealed by metabolomics. Notably, the diabetic phenotypes and impaired heat production are alleviated in germ-free mice receiving stool transplants from Scgn-deficient mice, highlighting the critical role of gut microbiota. Additionally, we find a significant correlation between circulating 12,13-diHOME levels and brown adipose tissue activity in both diabetic patients and mouse models, with 12,13-diHOME levels being substantially lower than in healthy controls. Through extensive data from T2D patient stool transplants, we confirmed the correlation between butyrate in fecal samples and 12,13-diHOME levels in plasma. Our findings suggest that butyrate-producing microbiota can restore 12,13-diHOME levels, offering a promising therapeutic strategy for T2D. In conclusion, our study highlights the role of SCGN in EECs as an important cause of intestinal hormone secretion disorders and provides new insights into the complex interplay between microbiota dysbiosis and T2D.]

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P8

JOINT381

Diabetes type 1 can induce testicular atrophy with Leydig cell hyperplasia and germ cell depletion and therefore negatively influence reproductive function in rats

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Research aim
Diabetes type 1 can negatively influence testicular function and fertility but the pathomechanisms on the testicular level remains to be elucidated. Therefore, the aim of the study was to evaluate effects of diabetes mellitus type 1 disease on testicular function.
Material and methods
BB/OKL rats developed type 1 diabetes during adolescence. One group received sufficient insulin treatment with excellent HbA1c levels, a second group insufficient amounts of Insulin and had a poor glycaemic control (8 rats per group). Leydig-, Sertoli-, and Germ-cell function was analysed on RNA and protein level. Furthermore, androgens were measured in serum samples and after extraction from testicular tissue with LC–MS/MS. Immunhistochemistry was performed and the inflammatory status and apoptosis was evaluated.
Results
After diabetes manifestation 25–33% of the rats developed testicular atrophy compared to none in the healthy control group. In the atrophic testis, we found a strong reduction of elongated and round spermatids and spermatocytes by more than 80%. Leydig cells showed a hyperplasia with a strong and significant upregulation of steroidogenic enzymes on RNA and on protein level (Star by 106%/94%, 3beta-HSD by 177%/203%, 17Beta-HSD by 276%/134%, CYP11A1 by 66%/65% and CYP17A by 1859%/2202%; all $P<0.001$). Furthermore, we measured significantly higher concentrations of androgens and INSL3 levels in the atrophic testis. In contrast, germ cells showed a depletion with a strong downregulation of DDX4 (by 78,19%/) and Crem (by 51,54%). In addition, we found a strong increase of oxidative stress, apoptosis and inflammation. SF-1 (+965%) and DHH (by 2575%) pathways were strongly upregulated in the atrophic testis and might me a possible pathomechanism.
Conclusion
Diabetes type 1 can induce testicular atrophy with germ cell depletion, apoptosis and increased inflammation. In parallel, Leydig cell hyperplasia develops with an upregulation of steroidogenic enzymes, and higher intratesticular testosterone levels. Therefore, diabetes type 1 can negatively influence reproductive function and fertility in male rats.

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P9

JOINT1924

Assessment of metabolic status in adolescents with type 1 diabetes: the utility of the SPISE index

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Background and objectives
Body mass index(BMI) has limitations in assessing metabolic status in adolescents. Insulin-based methods are not applicable in patients with type 1 diabetes(T1D). The SPISE index, calculated using BMI, HDL, and triglyceride levels, has been proposed as a potential tool for monitoring metabolic status in adolescents with T1D.This study aimed to evaluate the efficacy of the SPISE index in assessing metabolic status in this population.
Methods
A total of 83 adolescents(aged 12–18 years,Tanner stage 5) with T1D for at least one year were included. Participants were categorized into three groups: underweight(-UW:BMI SDS <-1), normal(NW: $-1<$BMI SDS <1), and overweight(OW:BMI SDS >1). Baseline anthropometric measurements, daily insulin doses, HbA1c levels, lipid profiles, and body fat percentages (BFP) by bioelectrical impedance were noted. The SPISE index(SPISE $=600 \times HDL^{0.185}/(Triglyceride^{0.2} \times BMI^{1.338})$) was also used to assess the metabolic status. Standardized diet and exercise recommendations were provided, and all parameters were re-evaluated after 12 months.
Result
The study included 24(28.9%) underweight,36(43.4%) normal,and 23(27.7%) overweight participants. The median age was 15.7(14.4;17) years, and the median duration of diagnosis was 4.1(3.1;6.1)years. The age,gender and insulin delivery mode distributions were similar between the groups. The baseline and follow-up metabolic parameters of the groups are presented in **Table 1.** Notably,BFP and triglyceride levels in the UW group were found to have significantly increased compared to the OW. The SPISE index levels significantly decreased in both UW and NW groups compared to the OW group. Despite the absence of significant differences in HbA1c and daily insulin doses, deterioration in metabolic control was observed in UW and NW groups. Finally, linear regression analysis found a significant negative correlation between the BFP and the SPISE index in ($P=0.001$, $R^2=0.26$).

	Baseline(0.month)			Control(12.month)			
	Under-weight	Normal	Over-weight	Under-weight	Normal	Over-weight	*P* value
BMI S.D.	−1.67± 0.6	0.1±0.55	1.71± 0.56	−1.4± 0.98	0.22± 0.73	1.61± 0.88	0.86
Body Fat(%)	17.86± 6.37	20.9±4.2	29.45± 6.5	19.6 ± 6.6	22.2±7.3	28.7± 8.2	**0.03**
Total Insulin (IU/kg/day)	0.87± 0.27	0.94± 0.27	1.05± 0.34	0.94± 0.29	0.99± 0.34	1.1±0.33	0.70
Basal Insulin (IU/kg/day)	0.37± 0.12	0.41± 0.12	0.46± 0.15	0.4±0.11	0.42± 0.13	0.47± 0.14	0.71
HbA1-c(%)	7.78± 1.19	8.1±1.95	8.2 ±1.7	8.1±1.58	8.5±1.9	8.5±1.64	0.40
HDL(mg/-dl)	58.6±11	58.7±13	61± 19.8	55.8± 12.6	57.4± 15.3	56.8± 12.2	0.94
LDL(mg/-dl)	89.8± 21	91±26.7	96.9± 28.5	92.8±23	89.6± 20.2	96.5± 24.3	0.78
Triglycer-ides (mg/dl)	80.5±43	84±36.3	106.8± 54.5	90 ±38	87.7±34	82.6±40	**0.04**
SPISE Index	12.3±2.1	9.44±1.8	6.5±1.4	11±2.3	8.7±1.8	6.7±1.4	**0.001**

Conclusion
Monitoring the SPISE index may provide a more comprehensive assessment of metabolic status in adolescents with T1D. However, larger longitudinal studies are needed to validate its predictive value for future complications.

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P310

JOINT341

Long-term beta-cell function and GLP-1 secretion after sleeve gastrectomy vs gastric bypass in patients with type 2 diabetes: the oseberg clinical trial

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Introduction
Bariatric surgery improves beta-cell function and insulin sensitivity in people with type 2 diabetes short-term. Comparative long-term data on the glycaemic effects of gastric bypass vs sleeve gastrectomy remain limited.
Methods
Prespecified secondary analyses of a two-armed, single centre, RCT conducted at Vestfold Hospital Trust (Norway). Adult patients with obesity and type 2 diabetes were randomised (1:1) to undergo either gastric bypass or sleeve gastrectomy and were followed for 5 years. The study assessed changes from baseline in beta-cell glucose sensitivity (modelled from c-peptide deconvolution), postprandial GLP-1 hormone profile, and intestinal absorption rate of paracetamol, using a 25g 180-minute oral glucose tolerance test (OGTT). Acute insulin response to glucose (AIRg) and peripheral insulin sensitivity (Si) were estimated with a 180- minute intravenous glucose tolerance test (IVGTT). Outcomes were assessed according to intention to treat principles utilizing generalized linear mixed models for repeated measures using identity link. Statistical analyses; Stata (version 18).
Results
A total of 109 patients were randomised to gastric bypass ($n = 54$) or sleeve gastrectomy ($n = 55$). The baseline demographic characteristics were comparable between the groups (mean age 47. 7 years [SD 9. 6], BMI 42. 3 kg/m^2 [5. 3], HbA1c 8. 1% [1. 7], and 72 [66%] were women). At 5-year follow-up, 73 (67%) participants underwent an OGTT and an IVGTT. During follow-up, beta-cell glucose sensitivity increased three-fold following gastric bypass, compared with a two-fold increase after sleeve gastrectomy, between-group difference 0. 35 pmol/kg/min/mmol (95%CI [0. 01 to 0. 70]; $P = 0. 042$). The incremental area under the curve ($iAUC_{0-180}$) for GLP-1 increased after gastric bypass only, between-group difference 797 pmol/l*min (95%CI [172 to 1422]; $P = 0. 012$). AIRg increased two- to three-fold in both surgical groups (between-group difference: -54 mU/l per min [95%CI [-144 to 36], $P = 0. 239$]), and Si approximately doubled in each group (between-group difference: 0. 3 mU/l^{-1}*min^{-1} [95% CI -0. 4 to 1. 0, $P = 0. 358$]). Paracetamol peak concentration (C_{max}) was higher, whilst time to peak concentration (T_{max}) was shorter after gastric bypass than after sleeve gastrectomy, between-group difference 57 mmol/l (95%CI [44 to 71]; $P < 0. 001$) and -27 minutes (95%CI [-36 to -18]; $P < 0. 001$) , respectively.
Discussion
The insulin secretion and peripheral insulin sensitivity improved similarly during 5 years of follow-up after both surgical procedures. However, gastric bypass was associated with higher paracetamol and GLP-1 levels, and a greater insulin response to changes in glucose levels after an oral glucose-paracetamol load. This suggests accelerated gastric emptying, and a more pronounced influence on the entero-insular axis after gastric bypass as compared with sleeve gastrectomy.

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P311

JOINT1302

Cathepsin s is elevated in pancreatic islets and plasma in new-onset type 1 diabetes and positively associates with systemic inflammatory cytokines

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BackgroundAccumulating data indicate that cathepsin proteases are implicated in the development and progression of type 1 diabetes (T1D). Several cathepsins are regulated by proinflammatory cytokines in human islets/β-cells and have functions in the β-cells. We recently showed that cathepsin S (CTSS) is induced and secreted from the β-cells during T1D, and that CTSS serum levels are elevated in children with new-onset T1D and autoantibody-positive siblings.
Aims
The aims were to investigate the pancreatic islet expression of the 15 human cathepsins during T1D and to further explore the biomarker potential of CTSS in new-onset T1D.
Methods
The cathepsin gene expressions were extracted from previously generated microarray data on laser-dissected pancreatic islets from individuals with new-onset T1D ($n = 5$) from the Diabetes Virus Detection (DiViD) study and donors with autoantibody-positivity (AAb+, $n = 12$), T1D ($n = 20$), type 2 diabetes (T2D, $n = 8$), and healthy controls ($n = 18$) from the network of Pancreatic Organ Donors (nPOD). Cathepsin expression levels were compared between the groups using one-way ANOVA and Fisher's LSD analyses. *P*-values were corrected for multiple comparisons. CTSS plasma levels were measured by ELISA at onset and 6 and 12 months after onset in a Remission cohort of children with new-onset T1D ($n = 73$) and analyzed for association with the inflammatory cytokines IFNγ, IL-1β, IL-6, IL-8, IL-10, IL-12p70, and TNFα, measured by MSD V-PLEX assays. A linear mixed effect model was used to evaluate changes between visits, and linear regression models were used to evaluate associations between CTSS and cytokines levels at the three time points. $P < 0. 05$ was considered statistically significant.
Results
Seven cathepsins were differentially expressed in islets from individuals with T1D as compared to healthy controls: *CTSD*, *CTSH*, *CTSL*, and *CTSS* in new-onset T1D, and *CTSA*, *CTSB*, and *CTSZ* after longer T1D duration (FDR-adjusted $P < 0. 05$). Only *CTSS* was induced in new-onset T1D. The CTSS plasma levels were decreased 12 months after onset compared to at onset ($P < 0. 05$) and 6 months after onset ($P < 0. 01$), after adjusting for age and sex. CTSS was positively associated with IFNγ (6 months, $P < 0. 001$), IL-10 (baseline, $P < 0. 05$; 12 months, $P < 0. 05$), and TNFα (baseline, $P < 0. 05$), after adjusting for age.
Conclusions
Several cathepsins are differentially expressed in the pancreatic islets during T1D. CTSS is elevated in both the islets and plasma in new-onset T1D and shows potential as an early biomarker of islet inflammation and T1D progression.

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P312

JOINT1985

Challenges in managing MODY 12: a case report

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Introduction
Maturity-onset diabetes of the young (MODY) comprises a heterogeneous group of monogenic diabetes often misclassified as type 1 or type 2 diabetes. We describe a case of ABCC8-Mody with an atypical course and unexpected non-responsiveness to high-dose sulfonylurea therapy.
Case description
A 12-year-old girl initially presented at 8 years of age with polyuria, polydipsia, and weight loss. She had normal weight (10th percentile), and a BMI of 12 kg/m^2 with early puberty (Tanner stage II) and no signs of insulin resistance. Laboratory tests revealed severe hyperglycemia (29 mmol/l), normal pH (7. 37), mild-to-moderate ketonuria (+1–2), and HbA1c of 14%. She was diagnosed with new-onset type 1 diabetes (T1DM) and started intensive insulin therapy. During follow-ups, her diagnosis was reconsidered as a detailed family history uncovered early-onset diabetes in three maternal uncles and her grandmother, along with

hyperinsulinism in her younger brother—who had a confirmed ABCC8 mutation and underwent near-total pancreatectomy. Her insulin requirements were lower than expected (0. 6 – 0. 7 unit/kg/day at 10 months post-diagnosis) with an HbA1c of 8. 3%. Further evaluation showed mild positive insulin autoantibodies (0. 7 U/ml, cutoff <0. 4) while glutamic acid decarboxylase, zinc transporter 8, and islet cell antibodies were negative. Whole exome sequencing confirmed a pathogenic heterozygous autosomal dominant ABCC8 mutation, consistent with MODY 12. Given the typical sulfonylurea responsiveness in ABCC8-MODY, an inpatient trial of high-dose glibenclamide was initiated and titrated over 8 days to 2 mg/kg/day. However, she continued to require frequent insulin corrections (up to 1 unit/kg/day). After 3 days at the maximum dose, the trial was deemed unsuccessful. Over the subsequent year, her insulin needs increased to 1. 8 IU/kg/day (65% basal) amid factors such as pubertal insulin resistance, menarche, and insulin omission from diabetes burnout and psychosocial challenges. Her glycemic control deteriorated with HbA1c reaching to 10. 5%, compounded by an episode of severe diabetic ketoacidosis due to insulin omission. Emerging evidence supporting GLP-1 receptor agonists in ABCC8-MODY prompted a trial of liraglutide, which improved her time in range by 60% and allowed insulin dose reduction within 6 weeks. Gastrointestinal side effects led to a switch to weekly Semaglutide. Repeat autoantibody testing returned negative.

Discussion

This case underscores the management complexities of ABCC8-MODY in the presence of autoimmune positivity. The failure of sulfonylurea therapy suggests that autoimmunity may alter the therapeutic response, while GLP-1 receptor agonists show promise as an adjunct therapy in such complex cases.

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P314

JOINT547

Gut microbiota-derived indole-3-propionic acid alleviates diabetic kidney disease through its mitochondrial protective effect via reducing ubiquitination mediated-degradation of SIRT1

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Objective

Diabetic kidney disease (DKD) has a complex pathogenesis, and current therapies offer limited benefits. Gut-derived metabolites, particularly indole-3-propanoic acid (IPA), a deaminated derivative of tryptophan produced by gut bacteria, may play a role in DKD. This study aimed to assess serum metabolic alterations in DKD and explore the effects of IPA on glomerular endothelial cells (GECs) and mitochondrial function.

Methods

Untargeted metabolomics was employed to identify differentially expressed metabolites in DKD mouse serum, followed by validation in DKD patients using UHPLC-MRM-MS/MS. IPA supplementation was tested in high-fat diet combined with STZ-induced DKD mice to evaluate its effects on kidney morphology, glomerular filtration barrier integrity, fibrosis, and albuminuria. *In vitro*, high glucose-stimulated GECs were used to investigate IPA's impact on mitochondrial function, the PGC-1α pathway, and SIRT1 protein degradation.

Results

Metabolomics revealed significant alterations in tryptophan metabolism and its metabolites, including IPA. UHPLC-MRM-MS/MS analysis confirmed reduced IPA levels in DKD patients, which were negatively correlated with fasting blood glucose, HbA1c, and UACR, and positively correlated with eGFR. In DKD mice, IPA supplementation improved kidney structure, reduced fibrosis, enhanced glomerular filtration barrier integrity, and decreased UACR. IPA also alleviated mitochondrial abnormalities in GECs, increasing mitochondrial quantity and ATP, while reducing oxidative stress markers such as malondialdehyde (MDA). *In vitro*, IPA reduced ROS and MDA in GECs, improved mitochondrial membrane potential and ATP levels, and upregulated mtTFA and SOD2 expression. Additionally, IPA inhibited SIRT1 degradation via the ubiquitin-proteasome pathway, leading to increased SIRT1 levels and activation of the SIRT1/PGC-1α pathway, which enhanced mitochondrial biogenesis and antioxidant defense.

Conclusions

IPA, a gut-derived metabolite, is reduced in DKD and correlates with UACR. IPA supplementation alleviates albuminuria in DKD by improving mitochondrial function, reducing oxidative stress, and activating the SIRT1/PGC-1α signaling pathway. These findings suggest that IPA is a potential therapeutic target for DKD, offering new insights into renal protection through enhanced mitochondrial biogenesis and antioxidant capacity.

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P315

JOINT2974

Leukocyte telomere length as a potential indicator of early kidney dysfunction in persons with type 2 diabetes

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Background

Leukocyte telomere shortening can occur as a result of both natural age-related changes in the body and various damaging factors. The study of laboratory indicators reflecting age-related changes in chronic kidney disease (CKD) patients serves as an important tool for assessing disease progression and predicting future risk. The search for new markers of kidney damage and factors influencing CKD progression remains highly relevant. Recently, increasing research attention has been given to the role of leukocyte telomere length in various pathological conditions, including systemic inflammation, atherosclerosis, complications of infectious diseases, apoptosis, and aging processes.

Aim

In our study, we examined the relationships between early markers of kidney damage and relative leukocyte telomere length (RTL) in individuals with type 2 diabetes (T2D).

Methods

Our study involved 86 individuals with T2D, who were categorized into two groups on the basis of their estimated glomerular filtration rate (eGFR): Group I ($n = 21$) with an eGFR < 60 ml/min/m^2 and Group II ($n = 65$) with an eGFR ≥ 60 ml/min/m^2. The standardized method proposed by Cawthon *et al*. was used to measure RTL.

Results

The analysis of RTL in relation to the eGFR revealed a significant difference between the patient groups (1. 10 (0. 97–1. 18) vs 1. 18 (1. 06–1. 41) in group I and group II, respectively; $P = 0. 031$). A significant positive correlation between RTL and eGFR was observed only in the reduced eGFR group ($r = 0. 44$; $P = 0. 042$). In the multivariate logistic analysis, RTL, albumin-to creatinin ratio in daily urine, and T2D duration were found to be independent predictors of decreased eGFR (< 60 ml/min/m^2). The AUROC of the model was 0. 79 (95% CI 0. 684 - 0. 897; p <0. 001), with a sensitivity of 71. 4% and a specificity of 73. 8%.

Conclusion

RTL shortening, a longer duration of T2D, and the presence of albuminuria are early prognostic factors independently associated with a decline in renal function in patients with diabetic kidney disease (DKD). Early detection of DKD and an understanding of the predictors of eGFR impairment progression can help reduce the risk of severe complications that significantly impact patients' quality of life. Timely diagnosis can prevent or substantially slow irreversible changes in the eGFR and enable the initiation of treatment in the early stages of DKD.

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P316

JOINT555

Effect of semaglutide vs placebo on HbA1c, weight, mental health and SF-36: a randomized clinical trial in people with pre-diabetes, obesity and schizophrenia

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Background
Individuals with schizophrenia face a 10 to 20-year reduction in life expectancy, primarily due to cardiovascular disease (CVD) and obesity-related type 2 diabetes (T2D). These risks may be exacerbated by treatment with second-generation antipsychotics (SGAs), which may cause obesity and thereby diminish quality of life (QoL). Semaglutide, a GLP-1 receptor agonist approved for obesity has demonstrated significant efficacy in promoting weight loss, and reducing the prevalence of T2D and risks for CVD. Therefore, this trial evaluated whether once-weekly semaglutide improves HbA1c, reduces weight, and enhances mental health and QoL in prediabetic, overweight/obese SGA-treated patients with schizophrenia.
Methods
We conducted a double-blind, randomized, placebo-controlled trial involving 154 adults, aged 18-60 years, with BMI $\geq$27 kg/m^2, SGA-treated schizophrenia, and prediabetes (HbA1c: 39–47 mmol/mol). Participants were randomized (1:1) to receive once-weekly semaglutide or placebo, titrated to 1. 0 mg or maximally tolerated dose, over 30 weeks.
Outcomes
In total, 151 participants completed randomization (semaglutide group: 74; placebo group: 77). Intention-to-treat analysis demonstrated that semaglutide reduced HbA1c by 5. 07 mmol/mol (95% CI: -6. 05 to –4. 09) and body weight by 9. 21 kg (95% CI: -11. 68 to -6. 75) compared to placebo. Furthermore, 81% in the semaglutide group vs. 19% in the placebo group obtained an HbA1c $<$39 mmol/mol ($P < 0.001$). The semaglutide group improved physical QoL scores (SF-36) by 3. 6 points (95% CI: 1. 4 to 5. 8), but changed neither mental QoL scores nor psychiatric symptoms outcomes. Finally, the semaglutide group had higher incidence of gastrointestinal symptoms, but experienced no worsening in somatic or mental serious adverse events.
Interpretation
Semaglutide appears safe as adjunct therapy for SGA-treated patients with schizophrenia, prediabetes, and overweight/obesity. During 30 weeks, semaglutide significantly improved glycemic control, promoted weight loss, and enhanced physical QoL without adversely affecting mental health. These findings highlight its potential role in mitigating cardiometabolic risks in this high-risk population.

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P317

JOINT2428

Cardiorespiratory fitness and cardiovascular risk in youth with type 1 diabetes

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Introduction
In 2022, type 1 diabetes (T1D) prevalence in youth was estimated at 1. 52 million, listing it among the most common pediatric chronic conditions. The T1D pediatric population has been identified to be at higher risk of cardiovascular morbidity and mortality. Lower cardiorespiratory fitness (VO_2 peak) has been associated with higher cardiovascular mortality in the adult population. However, no studies have examined the effect of VO_2 peak on early markers of cardiovascular disease in youth with type 1 diabetes.
Objective
To assess the association between VO_2 peak and early markers of CVD in adolescents with and without T1D and determine differences across groups.
Methods
This is a cross-sectional study conducted in the CARDEA cohort consisting of adolescents (14-18 years of age) with T1D ($n = 100$) and without T1D ($n = 97$). VO_2 peak was measured on an electromagnetic bicycle during an incremental exercise test. The morphological cardiac outcomes were assessed using cardiac magnetic resonance imaging. For vascular outcomes, flow-mediated dilation was used to evaluate endothelial function, and arterial stiffness was estimated using pulse-wave velocity. Multivariable linear regressions were adjusted for age, sex, ethnicity, diabetes, household income, physical activity (accelerometry), and heart rate. Differences between groups were tested using an interaction term between T1D status and VO_2 peak.
Results
In comparison to the control group, adolescents with T1D had a lower VO_2 peak, MVPA and familial income, while they had higher daily screen time. A higher VO_2 peak was associated with higher left ventricle (LV) papillary mass (0. 04 g; 95% CI: 0. 01; 0. 06) and LV end-systolic volume (0. 37 mls; 95% CI: 0. 07; 0. 67) . In contrast, higher VO_2 peak was associated with a lower LV wall thickness (-0. 10 mm; 95% CI: -0. 19, -0. 01). There were no meaningful associations between VO_2 peak and endothelial function or arterial stiffness. No differences in associations were found between T1D participants and controls.
Conclusion
Overall, adolescents with T1D had lower cardiorespiratory fitness and poorer lifestyle habits compared to controls. Our results indicate that higher cardiorespiratory fitness is linked to favorable cardiac morphology but not vascular function, irrespective of T1D status.

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P318

JOINT2673

Parental perception on immunotherapy for children at risk of type 1 diabetes and islet cell transplantation/stem cell therapy for children with type 1 diabetes

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Aim
This study aims to evaluate parental perception on immunotherapy to delay onset of diabetes for siblings at risk of type 1 diabetes (T1D), as well as examine parents' viewpoints on islet cell transplantation and stem cell therapy for children with established T1D. Understanding these viewpoints is essential for integrating novel treatments into clinical practice locally.
Method
A survey was administered to parents of children diagnosed with T1D at the Hong Kong Children's Hospital from October to December 2024. 9 questions assessing their awareness of these treatments, willingness to consent for their use, as well as concerns regarding long term safety were included.
Results
34 parents were surveyed in the study period. The mean age of their children (53% male) was 11. 7 and mean diagnosis duration was 5. 3 years. 70. 6% were on multiple daily injections while the rest were on insulin pump therapy. 73. 5% showed readiness for autoantibody screening for siblings, despite awareness on potential impact on insurance coverage. 47% of the parents were aware of immunotherapy for predisposed siblings, with 59% expressing readiness to consent to administration for their child if they were found to be at risk. Reasons for not considering immunotherapy included concern on side effects (71. 4%), unknown long-term side effects (71. 4%), inadequate knowledge about the therapy (35. 7%), doubts about its effectiveness (35. 7%), logistical issues related to time and transportation (21. 4%), and concern on required treatment duration of 14 days (21. 4%). Regarding novel methods of beta cell replacement, 55. 9% and 64. 7% of the respondents were aware of islet transplantation and stem cell therapy respectively. 67. 6% of the parents accepted these treatments for their child with diabetes. Reasons for not considering these therapies included safety concerns (60%), doubts about the effectiveness (60%),

inadequate knowledge about these options (50%) and a preference for lifelong insulin injections over immunosuppressant (40%).
Conclusion
Our findings showed that local parents had a moderate awareness on novel therapies for diabetes. While majority accepted these treatments, safety and efficacy profile were most concerning for them. These findings highlighted the importance of integrating parental perspectives into the development of treatment protocols for T1D. Future research should focus on creating targeted educational initiatives that empower parents in navigating innovative treatment options for their children.
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P320

JOINT1956
Can diabetes self-management applications replace continuous glucose monitoring in low-resource environments?"
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Background
The "Rightest" app connected to Right test glucose meter via Bluetooth, helps to set blood glucose target and customize measurements. The app is provided with ketone alert when BG is $\geq$ 240 mg/dl.
Aim of the Work
To assess the role of the rightest app in improving glycaemic control as well as quality of life in a 6- month interval of its usage.
Patients and Methods
A case- control study included 40 participants with type 1 diabetes, mean age 14. 3 ± 1. 42 years and diabetes duration of 4. 5 ± 3. 6 years regularly following up at Diabetes Unit. Rightest app was installed on the participants' smart phone on enrollment and 6 months later. Assessment of the glycemic control was done by HbA1c and time in range. Results collected from app Quality of life (PedsQL) and user experience (UEQ) Questionnaires were applied at the end of the study.
Results
Using smartphone app yielded a significant reduction in mean BG level (-17. 64%, $P = 0.012$) that decreased HbA1c (-10.63%, $p = 0.000$). Increase of SMBG frequency was observed ($P = 0.04$). This is reflected on a 20 % increment time in range generated by app (P-value = 0. 002) and lower time above range (TAR > 180mg/dl, -18. 75%, $P = 0.001$) in intervention group compared to control. However, the number of hypoglycemic events ($P = 0.71$) or DKA($P = 0.59$) did not differ between groups. PedsQL questionnaire total score has improved (P-value = 0. 010) in favor of intervention group with good experience with app indicated by UEQ. The pragmatic total score (1. 425) of UEQ was above average while the hedonic total score was good (1. 250) and overall score was good (1. 338). The higher score of UEQ was inversely correlated with mean BG ($r = -0.414$, $P = 0.008$) and positively correlated to glycemic control ($r = 0.644$, $P = 0.002$).
Conclusion
Using mobile apps as an alternative for CGM in low resource settings can help improve glycemic control and quality of life for those who don't have access to diabetes. technology services because of unavailability or unaffordability.
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P321

JOINT2870
Comparison of moderate intensity atorvastatin and ezetimibe with high intensity atorvastatin on cardiovascular events and diabetes in patients with angina pectoris
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Background
The beneficial effect of moderate-intensity statin with ezetimibe combination therapy compared to high-intensity statin monotherapy in patients with angina pectoris undergoing percutaneous coronary intervention (PCI) remains unclear. We aimed to investigate the effect of moderate-intensity atorvastatin with ezetimibe combination therapy in patients with angina pectoris in real-world practice.
Methods
This retrospective cohort study used Korean National Health Insurance Database. A total of 6, 784 patients underwent PCI between 2015 and 2018 and received either moderate-intensity atorvastatin (10 and 20 mg) and ezetimibe 10mg ($n = 4, 682$) or high-intensity atorvastatin (40 and 80 mg; $n = 2, 102$). The primary outcome was a composite event of cardiovascular death, myocardial infarction, coronary revascularization, and stroke. The secondary outcome was newly developed diabetes. Subgroup analyses were performed based on baseline comorbidities.
Results
During the mean follow up of 4 years, the incidence rates of the primary outcome were 70. 14 vs. 62. 05 per 1, 000 person-years in the moderate-intensity atorvastatin and ezetimibe group and the high-intensity atorvastatin group, respectively. There were no significant differences in the risk of primary outcome between the moderate-intensity atorvastatin and ezetimibe group and the high-intensity atorvastatin group [hazard ratio (HR): 0. 99, 95% CI: 0. 90-1. 10]. The risk of new onset diabetes was not different between the two-treatment groups (HR: 0. 99, 95% CI: 0. 88-1. 13). However, in patients with underlying chronic kidney disease (CKD), moderate-intensity atorvastatin with ezetimibe combination therapy was associated with lower risk of primary outcome compared to the high intensity atorvastatin therapy (HR: 0. 40, 95% CI: 0. 18-0. 86).
Conclusion
In real-world cohort study, there was no significant difference in the cardiovascular outcome and new onset diabetes between moderate-intensity atorvastatin with ezetimibe combination therapy and high-intensity atorvastatin monotherapy in patients with angina pectoris undergoing PCI. Moderate-intensity atorvastatin with ezetimibe combination therapy may be beneficial particularly in patients with CKD.
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P322

JOINT138
To study the effect of medical nutrition therapy on school-time hyperglycemia and the glycemic outcomes in childeren with type 1 diabetes mellitus
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Background
In resource-limited settings, poor support and non-compliance for school-time insulin, coupled with carbohydrate-rich breakfast and school-snacks, school-time is the most vulnerable period for hyperglycemia. Thus, appropriate nutritional intervention is a practical solution to the aforementioned problem. Medical nutrition therapy (MNT) in type 1 diabetes (T1D) is associated with improved glycemic outcomes. Hence, this study examines the effect of MNT on the glycemic outcomes in school going children with T1D.
Aim
The aim of this open-label randomized controlled trial was to determine the effectiveness of MNT in the form of appropriate carbohydrate and calorie containing breakfast and school-snacks, on the glycemic control during school hours, in children with T1D.
Methods
At the baseline, for a total of 60 children and adolescents with T1D, glycemic parameters were recorded using a continuous glucose monitoring system (CGMS) for 14 days along with the dietary records. In the RCT, the intervention group ($n = 30$) received carbohydrate content of 45-55% during breakfast and school-snacks whereas, the control group practiced the routine diet, for four weeks and reassessed with CGMS for 14 days with dietary analysis. The CGMS derived glycemic variables for the school-time and the whole day as well, were analyzed along with the dietary analysis for average dietary records, during the 14 days of CGMS. The primary outcome was to determine the difference in the time in range (TIR) between the intervention and control group.
Results
After the dietary modification provided in the intervention group, the carbohydrate content reduced significantly from 59. 9% to 50. 1% ($P = 0.01$) in the breakfast, and from 65. 5% to 52. 1% ($P = 0.002$) in the mid-morning snacks during the school-hours. The TIR significantly improved ($P = 0.018$) whereas, the time above range (TAR) significantly reduced ($P = 0.039$), in the intervention group. The TIR showed

significant improvement in the 24-hour CGMS profile as well ($P = 0.037$). Multivariate regression showed insulin requirement and change in carbohydrate percentage in the midmorning snacks had significant association with TIR. The intervention was safe as there was no significant increase in time below range (TBR) and no episode of severe hypoglycemia was recorded in the intervention group.

Conclusion

An appropriate reduction in carbohydrate content in breakfast and midmorning snacks improves TIR and reduces TAR during school hours in children with T1D who do not administer pre-snack insulin at school, with benefits extending to 24-hour profile. The MNT intervention was very effective in improving the overall glycemic outcomes and was safe as well.

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P323

JOINT3802

The impact of regulatory-approved and open-source automated insulin delivery systems on glycemic control: real-world data from a heterogeneous population

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Background

Type 1 diabetes leads to absolute insulin deficiency and necessitates lifelong insulin therapy. Despite advancements in diabetes care, achieving optimal glycemic control remains challenging. Automated insulin delivery (AID) systems are a breakthrough in diabetes management, improving glycemic outcomes and quality of life. While regulatory-approved systems are available, open-source systems—developed by patients for self-installation—offer an alternative that requires technical expertise and active engagement with support networks. This study uniquely evaluated the efficacy and safety of both systems in a real-world, heterogeneous population, including patients with limited technological literacy and restricted internet access— groups assumed to benefit less from open-source AID systems.

Methods

This cross-sectional study was conducted at Shaare Zedek Medical Center and involved children with type 1 diabetes. Glycemic control was assessed while the children were using an AID system, compared to a sensor-augmented pump. The change in glycemic control following the transition to the automated system was compared between two systems: the regulatory-approved Medtronic G780 and an open-source system (Android APS).

Results

Sixty-one children were included in the study- 30 using the approved system and 31 using the open-source system. Both groups showed significant improvements in glycemic control, including an increase in time in range and reduction in mean blood glucose, estimated HbA1c/Glucose Management Indicator (GMI) and time spent in hypo and hyperglycemia. A trend toward greater reduction in mean blood glucose and estimated HBA1C/GMI was observed in the regulatory approved system group. No significant differences in rates of severe hypoglycemia or diabetic ketoacidosis were observed between the two systems and before and after the transition to an AID system.

Conclusions

Real world data from a heterogeneous population demonstrates significant improvement in glycemic control with both regulatory-approved and open-source AID systems, with an acceptable safety profile. Notably, even patients with limited technological literacy achieved meaningful improvements using open-source systems. These findings highlight the adaptability and effectiveness of AID systems across diverse patient populations, emphasizing the importance of preserving patient autonomy in choosing the system that best suits their needs. However, the observed trend favoring the regulatory-approved system warrants further evaluation in larger trials.

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P324

JOINT2892

Can insulin level measured by oral glucose tolerance test be a guide in the diagnosis of prediabetes?

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Background

In our study, we aimed to show the role of insulin level obtained by oral glucose tolerance test (OGTT) and insulin resistance in indicating dysglycemia and their correlation with HbA1c level.

Material and methods

The data of the cases who administered OGTT in our clinic between 2014 and 2024 were examined retrospectively. For OGTT, 1. 75 g/kg (maximum 75 g) dextrose was administered perorally and serum glucose and insulin levels were measured at 0. and 120. minutes. Insulin resistance was defined in those with serum insulin level >75 mU/l at 120. minutes. Results were presented as mean$\pm$standard deviation or median (25-75p) depending on the normality of the distribution.

Results

Of the 512 patients included in the study [median age 13. 7 (12 – 15. 5) years], 53. 9% were female and 93. 9% were pubertal. When the OGTT results of the patients were examined, insulin resistance was detected in 58% ($n = 297$). While the HbA1c level didn't show a significant difference when the cases were grouped according to obesity or insulin resistance ($p>0.05$), it was significantly higher in those with impaired glucose tolerance ($P < 0.001$). HOMA-IR, 0. and 120. minute insulin levels were found to be higher in obese patients, those with impaired glucose tolerance and those with insulin resistance than those without ($P < 0.05$). Impaired glucose tolerance was detected in 8. 2% of the group with normal HbA1c. For the diagnosis of insulin resistance, when the basal insulin level is taken as 23. 4 mU/l; It was found to have 80% sensitivity and 74% specificity (AUC$=0.829$, $P < 0.001$). When the 0. minute HOMA-IR upper limit for the diagnosis of insulin resistance is taken as 5. 6; it was observed that it had 78% sensitivity and 73% specificity (AUC$=0.817$, $P < 0.001$), and when the 120th minute HOMA-IR upper limit was taken as 19, it had 96% sensitivity and 94% specificity (AUC$=0.985$, $P < 0.001$). There was no significant relationship between HbA1c and insulin levels at 0. or 120. minutes ($p>0.05$).

Conclusion

In this study, we showed that the insulin level measured by OGTT isn't guiding in the diagnosis of prediabetes. Additionally, we found that the upper limit of basal fasting serum insulin level, which is used for insulin resistance especially in the pubertal period, can be lowered to less than 30 mU/l, but HbA1c isn't compatible with OGTT for the definition of insulin resistance. We evaluated that HOMA-IR can be used with high specificity and sensitivity in the definition of insulin resistance in children.

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P325

JOINT1236

HDL Lipidome remodeling is linked to diabetic kidney disease progression independent of albuminuria severity

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Background and Aims

Diabetic kidney disease (DKD) is associated with alterations in lipid and lipoprotein metabolism, worsening kidney function and increasing cardiovascular disease (CVD) risk. Changes in HDL composition, proteomics, and functionality have been reported in DKD. This study analyzed HDL lipidome in non-dialysis DKD patients, categorized by estimated glomerular filtration rate (eGFR) and urinary albumin excretion rate (AER), to identify potential biomarkers for DKD progression and CVD risk.

Methods

DKD patients were classified into three groups: EA1A2 (early-stage DKD, AER A1–A2, eGFR ≥ 45; $n = 21$), AA1A2 (advanced DKD, AER A1–A2, eGFR < 45; $n = 9$), and AA3 (advanced DKD, AER A3, eGFR < 45; $n = 24$). Age-matched controls (C; eGFR > 60, AER < 30; $n = 7$) were included. The study was approved by the local ethics committee, and all participants provided written informed consent. HDL was isolated by ultracentrifugation ($D = 1.063$–1.21 g/mL) and analyzed via high-performance liquid chromatography-mass spectrometry (HPLC-MS). Lipidomic data were processed using MetaboAnalyst 6. 0, with statistical analyses conducted via Student's t-test, ANOVA, and Kruskal-Wallis test.

Results
The study population comprised 61% men and 39% women. Baseline characteristics, including age, body mass index, total cholesterol, LDL-C, HDL-C, and triglycerides (TG), were comparable across groups. No significant differences were observed in diabetes duration or glycated hemoglobin levels among DKD groups. Among 480 lipid species identified in HDL, six showed significant reductions across four groups, including four sphingomyelins (SM), one lysophosphatidylcholine (LPC) and one phosphatidylcholine (PC). Compared to controls, EA1A2 exhibited a reduction of 21 lipid species, primarily from the lipid core (cholesteryl esters, sterols and TG). AA1A2 and AA3 exhibited reductions in 132 and 86 lipid species, respectively, compared to controls, predominantly affecting surface lipids, including SM, PC, LPC and ceramides (Cer). Only four lipid species differed significantly between AA3 and AA1A2, whereas 70 species (41. 4% SM, 30% PC, 11% Cer, 7. 1% free fatty acids, 4. 3% plasmalogens, 2. 8% LPC, and 2. 8% prenol) were consistently reduced in advanced DKD, irrespective of albuminuria severity.
Conclusion
DKD progression is associated with extensive remodeling of the HDL lipidome, characterized by early reductions in core lipids and progressive depletion of surface lipids in advanced stages. These changes, independent of albuminuria, may impair HDL functionality and exacerbate cardiovascular risk. Further research is warranted to assess their potential as biomarkers for DKD progression and CVD risk stratification.

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P326

JOINT597

Relevance of PFKP lysine lactylation in coupling glycolytic adaptation and mitochondrial respiration in diabetic proximal tubules

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Synopsis
Diabetic kidney disease (DKD) is a major burden and a predictor of mortality in diabetes, characterized by clinical heterogeneity. Hyperglycemia enhances glycolysis-driven pyruvate-to-lactate conversion in the proximal tubules. Lysine lactylation (Kla), a novel post-translational modification induced by intracellular lactate, may contribute to this heterogeneity. Here, we used lactylome analysis and experiments to explore its impact on biological processes with redirection of glycolytic flux.
Purpose
DKD is associated with altered metabolic patterns. Enhanced glycolysis and pyruvate-to-lactate conversion are common early adaptive features in the proximal tubules. Here we investigate the metabolic consequences and present a global lactylome profiling of lactate dehydrogenase(LDH) inhibition to characterize the landscape of lactylation in the human renal proximal epithelial tubular cell line(HK-2) under hyperglycemic conditions.
Methods
HK-2 cells were treated with 25 mM high D-glucose(HG) for 7 days, followed by 40 mM oxamate, the LDH inhibitor, for 24 hours. This induced metabolic reprogramming without affecting cell growth[1]. Global lactylome analysis using 4D label-free proteomics identified differentially lactylated proteins. Co-immunoprecipitation(Co-IP)and site-directed mutagenesis were used to verify modification sites. Respiratory measurements using Seahorse assay, alongside fluorescent probes, western blot, qPCR and cross-species sequence comparisons were performed.
Results
Integrative lactylome and proteome analysis identified 1, 149 Kla sites and 83 differentially expressed (DE) modified sites. Notely, three glycolytic enzymes contained DE sites: ATP-Dependent 6-Phosphofructokinase, Platelet Type (PFKP), Alpha-enolase (ENO1) and Aldolase (ALDOA). PFKP was the second most down-regulated DE site with P-value $= 4.86\times10^{-5}$and log2FC $= -0.66$, and only one lactylated lysine residue in PFKP (K688) was identified (modified sequence: NFGTK(1)ISAR). Subsequently, the lactylation modification of PFKP was verified by Co-IP, while neither those of ENO1 nor ALDOA. The modification site of PFKP (K688) was further confirmed by site-directed mutagenesis. The modification level of PFKP (K688) was downregulated by oxamate. During this process, mitochondrial membrane potential significantly increased, while the oxygen consumption rate revealed a decrease in ATP-linked respiration, a reduction in maximum respiration, and an increase in proton leak. Cross-species sequence comparison reveals both the conservation and diversity of the PFKP gene across various organisms, with the K688 site being highly conserved throughout evolution.
Conclusion
PFKP lactylation revealed a feedback loop among glycolysis, lactate, and lactylation in hyperglycemic proximal tubular cells. The high conservation of the PFKP K688 site, along with its dynamic modifications, coupled with glycolytic reprogramming and their impact on mitochondrial respiration in diabetic proximal tubules, may provide valuable insights into the study of heterogeneity in DKD.

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P327

JOINT1819

Alpelisib therapy for patients with congenital hyperinsulinism

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Background
Congenital hyperinsulinism (CHI) is a disorder of unregulated insulin secretion, leading to severe and persistent hypoglycemia. Current medical treatment options include Diazoxide, octreotide, nifedipine, and sirolimus. However, most patients with K_{ATP} channel gene (ABCC8 and KCNJ11) mutations do not respond to these medications and require a near total pancreatectomy. We previously described the adjunct use of Alpelisib therapy in a three-month-old patient with CHI avoiding the need for a near total pancreatectomy (N Engl J Med. 2024;390(4):379-380).
Aims
We describe our observations in two additional patients with severe CHI treated with Alpelisib therapy, which resulted in the complete discontinuation of all existing treatments and the normalization of feeding.
Case studies
Two children (aged 3 and 4 years) with severe CHI (homozygous *ABCC8* and *KCNJ11* mutations) who were unresponsive to all the conventional therapies were treated with Alpelisib. The 3-year-old patient was on continuous gastrostomy feeds, received four-weekly long-acting octreotide injections, and was on diazoxide. The 4-year-old was also on continuous gastrostomy feeds overnight and 2 hourly bolus feeds during the day As well as on four-weekly long-acting octreotide. Treatment was initiated at 12. 5mg daily of Alpelisib, with gradual dose adjustments based on clinical responses. Outcome measures included blood glucose variability, frequency of hypoglycemic episodes, need for supplemental feeding, and treatment safety. In both cases, Alpelisib significantly improved glycemic control, reducing the frequency of hypoglycemic episodes. This allowed for the tapering and discontinuation of other medications (diazoxide and octreotide) and facilitated a transition to bolus gastrostomy-tube/oral feeding. No significant adverse effects were reported in either patient.
Conclusions
Alpelisib therapy shows promise as both an adjunctive and primary therapy for CHI, improving glucose control and reducing dependence on continuous feeding and other medications. Randomized controlled trials are needed to assess its long-term safety and efficacy for CHI.

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P328

JOINT1790

Hyperinsulinemic hypoglycaemia in small for gestational age neonates: clinical characteristics, biochemical features, treatment, and clinical outcome

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Introduction
Hyperinsulinemic hypoglycaemia(HH) is a common cause of persistent hypoglycaemia in neonates. Risk factors for transient HH include small for gestational age(SGA) newborns, perinatal asphyxia, intrauterine infections,

preeclampsia, and maternal diabetes. In neonates with HH and SGA, hypoglycaemia frequently has good response to diazoxide despite persisting for several months.
Objective
to review a cohort of patients diagnosed with HH in the neonatal period with a history of SGA.
Patients and Methods
Descriptive and retrospective study conducted at a tertiary hospital.
Inclusion criteria
Newborns with SGA (birth weight or length ≤-2 SD Carrascosa 2010) and HH: glucose <50 mg/dL with detectable insulin and/or C-peptide, and/or low free fatty acids(<1800 µg/dL) and carbohydrate requirements >12 mg/kg/min.
Exclusion criteria
Neonates with infection or syndromic hypoglycemia. Medical records were reviewed. Genetic testing included the *ABCC8, AKT2, CACNA1C, FOXA2, GCK, GLUD1, HADH, HK1, HNF1A, HNF4A, INSR, KCNJ11, SLC16A1, UCP2, and PGM1* genes.
Results
Twenty patients met inclusion criteria and none of the exclusion criteria. Thirteen(65%) were male. The mean gestational age was 34. 8±2. 9 weeks, with 14(70%) being preterm. Birth anthropometry(Mean±SD): weight Z-score -1. 9±0. 6 and length Z-score -1. 7±1. The mean age at hypoglycaemia onset was 1. 3±0. 7 days. **Biochemical parameters during hypoglycaemia**(Mean±SD)**:** glucose 37. 3±11. 6mg/dL, cortisol 16±15. 8µg/dL, insulin 6. 8±8mU/l, and C-peptide 1±0. 8ng/mL. Five patients(33%) had prematurity-related complications. Three(15%) had left ventricular hypertrophy(LVH) on echocardiography, one with a patent foramen ovale(PFO) and one with an intraventricular communication.
Treatment
All patients required initial intravenous glucose and continuous nasogastric feeding, with an average carbohydrate intake of 18. 1±3. 6mg/kg/min. Seventeen(85%) needed additional enteral supplementation with dextrin-maltose with maximum concentration of 5±1. 1%. Fourteen(70%) were treated with diazoxide, with a mean dose of 10±4. 4mg/kg/day. Thirteen patients responded well except for one with partial response. Diazoxide was discontinued after a mean of 5. 1±3 months. Two preterm patients experienced complications from diazoxide: Reopening of the ductus arteriosus with no previous cardiopathy and pulmonary hypertension with previous PFO and LVH. The mean age to treatment (enteral and pharmacological) discontinuation was 5. 2±5. 4 months.
Genetics
NGS was performed in ten patients, with one showing heterozygous VUS variant in *UCP2*(c. 127-1G>T). The Array CGH and exome sequencing were normal in the two and three patients tested, respectively.
Conclusions
In our cohort of SGA patients, HH resolved in average of five months. Most responded well to diazoxide. Two preterm presented complications. Genetic studies might be not necessary in the first six month of live if there is clinical resolution of hypoglycaemia.

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P329

JOINT2347

Predictive markers of insulin resistance and dysglycemia in children and adolescents with overweight or obesity before and after the COVID-19 pandemic

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Objective
Childhood obesity is a major global health concern, closely linked to insulin resistance, dysglycemia, and increased cardiometabolic risk. The COVID-19 pandemic has further exacerbated these issues, leading to a higher prevalence of obesity-related metabolic disorders. This study aimed to assess the predictive ability of fasting glucose, fasting insulin, HOMA-IR, HOMA-β, and HbA1c for insulin resistance and dysglycemia in children and adolescents with overweight or obesity before (BPD, 2019) and after (APD, 2021) the pandemic.
Methods
A total of 392 patients (146 BPD, 246 APD) aged 5–18 years underwent oral glucose tolerance tests (OGTT). Insulin resistance and dysglycemia were defined based on OGTT Results The 90th and 97. 5th percentiles for fasting glucose, fasting insulin, HOMA-IR, and HOMA-β, as established by Hammel *et al*., were evaluated as predictors of insulin resistance and dysglycemia. ROC analysis was conducted to determine optimal cut-off values for these markers.
Results
Insulin resistance was detected in 74. 7% of BPD and 83. 3% of APD patients, while dysglycemia was observed in 11. 6% and 19. 1%, respectively. We demonstrated that the 90th and 97. 5th percentiles for fasting insulin, HOMA-IR, and HOMA-β, as established by Hammel *et al*., effectively predict insulin resistance, while fasting glucose is an effective predictor of dysglycemia in youth with excess body weight. Additionally, an HbA1c level of ≥5. 7% was a reliable predictor of dysglycemia detected by OGTT. ROC analysis revealed optimal cut-offs for fasting insulin (13. 65–25. 05 µU/mL), HOMA-IR (3. 35–5. 30), and HOMA-β (156. 34–318. 41) in detecting insulin resistance, while fasting glucose (89. 50–94. 50 mg/dL) and HbA1c (≥5. 61%) were effective in identifying dysglycemia.
Conclusion
Fasting glucose, fasting insulin, HOMA-IR, HOMA-β, and HbA1c serve as valuable non-invasive markers for predicting insulin resistance and dysglycemia in children and adolescents with overweight or obesity. Their consistency before and after the pandemic highlights their clinical utility and potential as alternatives to OGTT for early detection. Integrating these markers into routine clinical practice could facilitate timely intervention and personalized management strategies, particularly in resource-limited settings, to address the growing burden of obesity-related metabolic disorders in pediatric populations.

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P330

JOINT2966

Co-designing a multicentre quality improvement initiative for hypoglycaemia: the dekode model

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Background
Effective hypoglycaemia management requires adherence to standardized guidelines, yet implementation remains inconsistent across healthcare settings[1]. A structured monitoring system can improve compliance, but its success depends on user acceptability and integration into clinical workflows[2]. Codesigning such systems with end-users enhances usability and adoption, ultimately supporting better patient care[3].
Aims
This study aimed to develop and implement a multicentre, standardised data collection system co-designed with end-users, assessing its feasibility, scalability, and sustainability.
Methods
This multicentre observational study was conducted from October 2023 to July 2024 and involved nine hospitals across three NHS trusts. An online Google Form was created through collaboration between clinical experts, medical students, and resident doctors. The form was piloted by diverse team members to ensure its appropriateness and robustness. Data collection focused on various factors involved during the management of hypoglycaemia, with a two-tier system ensuring data security. The system was scaled across the hospitals, with regular training and quality control measures in place.
Results
The co-designed data collection system, iteratively refined based on end-user feedback, was implemented consistently through structured training. Overall, we collected data on 1, 881 hypoglycaemic episodes across nine hospitals in 10 months. The system was scaled across varied IT environments, making it a sustainable tool in continuous data collection by new cohorts of medical students and ensuring ongoing implementation. Users found the system easy to use, with seamless accessibility and robust data security.
Conclusion
The study successfully developed a scalable, sustainable, and standardised data collection system for hypoglycaemia management, addressing a critical gap in UK healthcare. Its sustainability across various IT environments highlights its long-term feasibility. Further refinement of the system through AI-driven analytics and real-time data integration could enhance its predictive capabilities

and clinical decision-making support. Future efforts should focus on expanding the system to additional healthcare settings and evaluating its impact on clinical outcomes and patient safety.

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P331

JOINT578

Prevalence of MASLD in children and adolescents with type 1 diabetes assessed by transient elastography

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Aims
To evaluate the prevalence of liver steatosis, fibrosis, and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) in children and adolescents with type 1 diabetes using transient elastography, and to identify associated clinical variables.
Material and Methods
Cross-sectional study including 192 children and adolescents aged 6–18 years with type 1 diabetes for at least 12 months, recruited from Pediatric Diabetes Departments across Eastern Denmark between May 2022 and June 2024. Transient elastography was used to measure controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) to assess steatosis and fibrosis, respectively. MASLD was defined as the presence of steatosis or fibrosis in addition to at least one metabolic risk factor, such as overweight/obesity, insulin resistance, impaired glucose tolerance, low HDL cholesterol, elevated blood pressure, or high triglycerides. Moreover, alanine aminotransferase and aspartate aminotransferase levels were measured, and screening for celiac disease was performed.
Results
The prevalence of steatosis (CAP > 90th percentile) was 2%, fibrosis (LSM > 90th percentile) was 8%, and MASLD was 4%. Higher CAP values were associated with higher BMI z-scores ($P = 0.012$) and lower glucose time-in-range ($P = 0.029$). Fibrosis was more prevalent in males ($P = 0.0003$). None of the participants with steatosis, fibrosis or MASLD had elevated alanine aminotransferase and aspartate aminotransferase levels or celiac disease.
Conclusion
The prevalence of steatosis, fibrosis, and MASLD in children and adolescents with type 1 diabetes was low. Steatosis was associated with higher BMI and poorer glycemic control, while fibrosis was associated with male sex.

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P332

JOINT2728

Portosystemic shunt as a cause of alternating ketotic hypoglycemia and hyperinsulinism in patients with associated anomalies

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Background
Congenital porto-systemic shunt (CPSS) between the portal vein and the inferior vena cava is a very rarely described cause of alternating pathological fasting ketotic hypoglycemia (pKH) and hyperinsulinemic hypoglycemia (HH).
Methods
Case reports.
Results
In two male patients aged 14. 9y, and 7. 0y, respectively, a CPSS was identified. Patient 1 was diagnosed with fasting pKH age 5y. Glucose did not increase after i. m. glucagon. Unsuppressed serum insulin during hypoglycemia and chronic zink deficiency were recorded. Ammonia was persistently elevated (80-120 mcM); other liver counts were only slightly affected. Plasma amino acids indicated liver affection with increased tyrosine and methionine. IgF-1 and IgF-BP3 were low despite normal growth hormone (GH) stimulation test and IgF1 only increased to 120 mg/l upon IgF1 stimulation test. Synacthen test showed low cortisol response with low ACTH. MRI of the pituitary and related structures was normal. Other hormonal, extensive metabolic, and expanded genetic studies returned normal. Treatment variably included extended release cornstarch, diazoxide, long-acting somatostatin analogue, GH and hydrocortisone. Repeat abdominal ultrasound showed discrete hepatic changes. MRI and contrast CT identified an intrahepatic CPSS. Radiological shunt closure at the age of 15 y led to normalization of blood glucose, ammonia, zink deficiency and hormonal disturbances without further treatment. Patient 2 was diagnosed with pKH age 3y with later diagnosis of mild hyperinsulinism. Except for slightly decreased coagulation factors II-VII-X, liver biochemistry was normal including ammonia. He had persistent, unexplained iron deficiency anemia, refractory to oral supplementation. He had prominent veins on the anterior truncus and a tendency to declive edema. Blood pressure and echocardiography were normal. Synacthen test was flat with low ACTH. IgF1 and IgF-BP3 were low with low IgF1 response upon IgF1 generation test. GH stimulation tests, other hormonal tests, MRI of the brain and pituitary and intensive metabolic and genetic investigations were normal. Treatment included extended release cornstarch, diazoxide, GH, hydrocortisone and iron. Abdominal ultrasound identified a very narrow portal vein and an extrahepatic CPSS was diagnosed by contrast CT. A first trial of radiological shunt balloon occlusion was unsuccessful due to reduced portal venous flow with unacceptable elevation of pressure in the hepatic vein.
Conclusion
CPSS should be suspected in children with alternating pKH and HH, liver affection and variable other manifestations. Ultrasound followed by contrast CT of the abdomen is diagnostic. The hypoglycemia, low IgF1 and IgF-BP3 and blunted ACTH-cortisol axis can normalize after shunt closure.

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P333

JOINT492

Disparities in diabetes incidence and prevalence among koreans under 30 in 2008–2021: a greater burden on socioeconomically disadvantaged populations

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Background
The burden of diabetes mellitus is increasing globally, with significant implications for younger populations. This study evaluated temporal trends in the incidence and prevalence of type 1 (T1DM) and type 2 diabetes mellitus (T2DM) among Korean individuals aged <30 years from 2008 to 2021.
Methods
Data from the National Health Insurance Service in South Korea were analyzed to assess trends by sex and age group. Sex- and socioeconomic status (SES)-adjusted rate ratios (aRRs) were calculated to evaluate annual changes in incidence and prevalence rates.
Results
For T1DM, incidence per 100, 000 persons increased from 3. 02 (95% CI, 2. 78–3. 27) in 2008 to 3. 75 (95% CI, 3. 45–4. 06) in 2021 (aRR: 1. 017, $P < 0.0001$). This increase was significant in the 0–14 age group (from 2. 65 to 5. 28, aRR: 1. 041, $P < 0.0001$), while the 15–29 age group showed no significant change (from 3. 32 to 2. 70, aRR: 0. 997, $P = 0.5069$). Females consistently had higher incidence than males (aRR: 1. 176, $P < 0.0001$). Prevalence increased from 21. 83 (95% CI, 21. 17–22. 49) in 2008 to 46. 42 (95% CI, 45. 34–47. 50) in 2021 (aRR: 1. 058, $P < 0.0001$), with increases observed across all age groups and sexes. For T2DM, incidence escalated from 27. 61 (95% CI, 26. 87–28. 36) in 2008 to 60. 45 (95% CI, 59. 22–61. 69) in 2021 (aRR: 1. 083, $P < 0.0001$). A sharp rise was observed in the 0–14 age group (from 4. 94 to 17. 59, aRR: 1. 105, $P < 0.0001$) and nearly doubled in the 15–29 age group (from 46. 05 to 89. 81, aRR: 1. 075, $P < 0.0001$). Females consistently had lower incidence than males

(aRR: 0. 800, $P < 0.0001$). Prevalence increased dramatically from 73. 30 (95% CI, 72. 09–74. 51) in 2008 to 270. 39 (95% CI, 267. 79–272. 99) in 2021 (aRR 1. 104, $P < 0.0001$), with higher rates among males (from 75. 51 to 298. 61, aRR: 1. 111, $P < 0.0001$) and the 15–29 age group (from 124. 99 to 430. 37, aRR: 1. 098, $P < 0.0001$). Significant SES-related disparities were evident, with lower SES individuals having higher incidence (T1DM: aRR 1. 483; T2DM: aRR 2. 282, $P < 0.0001$) and prevalence (T1DM: aRR 2. 861; T2DM: aRR 3. 699, $P < 0.0001$).

Conclusion

The rising incidence and prevalence of diabetes, particularly among younger age groups, underscore an urgent need for public health interventions to mitigate the growing diabetes burden among Korean youth and young adults.

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P334

JOINT3013

Influence of SARS-CoV-2 virus and COVID-19 pandemic on course of type 1 diabetes in children during the first year of disease

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Objectives

After several medical centres, including Children's Clinical University Hospital (CCUH) in Latvia, had reported increase in type 1 diabetes (T1D) incidence in children during COVID-19 pandemic, our aim was to analyse influence of SARS-CoV-2 and pandemic itself on the control and course of T1D during the first year of disease.

Materials and Methods

Patients were included prospectively from August 2022 till January 2024, retrospectively from January 2017 until August 2022 and further divided depending on previous COVID-19 history: exposed to SARS-CoV-2 before T1D and unexposed patients. Data about initial manifestation and compensation measures 3, 6 and 12 months after diagnosis were gathered via interviews and medical records. Partial remission (PR) was defined by insulin doses <0.5 IU/kg/day and HbA1c $<7\%$. Complete remission (CR) was referred in patients with no requirement of insulin. Metabolic compensation (HbA1c) was also compared between pandemic and non-pandemic periods.

Results

In total, 277 patients were included in this study: 122 (44%) in exposed group (53. 3% boys, median age 9. 54 (IQR_{1-3} 5. 98-13. 27)), 155 (56%) in unexposed group (56. 8% boys, median age 10. 58 (6. 67-13. 42)). Initial manifestation of T1D was significantly more severe in patients previously exposed to SARS-CoV-2 (pH 7. 29 (7. 13-7. 37) vs pH 7. 33 (7. 19-7. 39)), $P = 0.02$. SARS-CoV-2 exposed patients needed higher doses of insulin initially (0. 74 (SD $\pm$ 0. 27) IU/kg/day vs 0. 66 ($\pm$0. 27) IU/kg/day), $P = 0.02$, but in 3-, 6- and 12-months requirement for insulin was similar in both groups. During the first year of T1D, PR was observed in 48 (39. 7%) exposed patients and 50 (33. 8%) unexposed patients, showing no significant difference ($P = 0.58$). 2 patients in both groups had CR period. Overall patients who initially presented with diabetic ketoacidosis (DKA), had significantly lower prevalence of remission period during the first year (26. 1% vs 48. 9%, $P = 0.001$). There was significantly higher frequency of DKA during one-year period in patients previously exposed to SARS-CoV-2 (6. 1% vs 0. 7%, v = 0. 02). Comparison analysis of follow-up visits (3, 6 and 12 months after diagnosis) between pandemic and non-pandemic periods showed slightly higher HbA1c levels during COVID-19 pandemic, but results did not reach statistical significance.

Conclusion

New-onset T1D patients previously exposed to SARS-CoV-2 have more severe initial manifestation, but insulin dosages, prevalence of remission and HbA1c levels reach similar levels 3, 6 and 12 months after diagnosis. However, cause of significantly higher prevalence of DKA in SARS-CoV-2 exposed group during the first year of diabetes should be further analysed.

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P335

JOINT140

Correlation between visceral fat and estimated disposal glucose rate in patients with type 1 diabetes

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Introduction

Metabolic syndrome (MS), closely associated with visceral fat, is a growing global health concern that also affects individuals with type 1 diabetes (T1D). The estimated glucose disposal rate (eGDR) is a simple and validated tool for predicting MS in patients with T1D. This study aimed to assess the correlation between visceral fat and eGDR.

Methods

We conducted a cross-sectional study including 68 patients with T1D. The study subjects were young adults, aged between 18 and 45 years. Each patient underwent a physical examination (anthropometric parameters and blood pressure), a fasting biological sample collection for the measurement of HbA1c, and lipid parameters and an evaluation of body composition by DXA Scan to measure the visceral fat mass (VFM). Visceral fat mass proportion (%VFM) was calculated by the formula: [VFM (g)/Weight (g)] x 100. High visceral fat mass (HVF) was defined by a %VFM >1, 1 in men and >0, 7 in women. MS was diagnosed according to the International Federation of Diabetes (IDF) criteria.

Results

The study population consisted of 29 men (42. 6%) and 39 women (57. 4%). The mean age was 29. 4 $\pm$ 7. 23 years. MS was observed in 14 patients with T1D (20. 6%). HVF was present in 15 patients (23, 4%). The mean eGDR score was 8. 31 $\pm$ 1. 72 mg/kg/min, ranging from 2. 81 to 11. 8 mg/kg/min. T1D patients with HVF had lower eGDR (7, 06 $\pm$ 2, 01 *vs* 8, 80 $\pm$ 1, 31, $P < 0,001$). eGDR was negatively correlated with %VFM ($r = -0,516$, $P < 0,001$). Using ROC curve analysis, we evaluated the relationship between eGDR and HVF. The area under the curve (AUC) was 0. 775 ($P = 0.001$), indicating that an eGDR value below 8. 41 mg kg^{-1} min^{-1} was associated with HVF in individuals with T1D, with 71% sensitivity and 73% specificity.

Conclusion

Our study demonstrated that eGDR, with a cut-off value of 8. 41 mg kg^{-1} min^{-1}, is a reliable marker for estimating visceral fat and can serve as an alternative to DXA scans, especially in situations where DXA is unavailable.

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P336

JOINT1008

Screening of first-degree relatives of children with type 1 diabetes: preliminary results

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Objective

To screen first-degree relatives of individuals with type 1 diabetes (T1D) for diabetes-related autoantibodies(AAs), identify individuals at increased risk for T1D, and evaluate the psychological impact of screening on both children and their parents.

Methods

This multicenter study targeted the inclusion of 400 children and adolescents aged 2-18 years who were first-degree relatives of individuals diagnosed with T1D. Thus far, 262 participants were enrolled, and screening was completed for 176. Venous blood samples were tested for four autoantibodies (IAA, GAD, IA-2, ZnT8). Psychological assessments were performed using the Screen for Child Anxiety Related Emotional Disorders(SCARED) for children and the State-Trait Anxiety Inventory(STAI-I and STAI-II) for parents, before and after the disclosure of screening Results SCARED scores ≥ 30 indicated clinical anxiety, 25-30 mild anxiety, and <24 normal. STAI scores >41(state) and >44(trait) signified heightened anxiety.

Results
The mean age of the 176 individuals was 10. 1 ± 0. 34 years, with a gender distribution of 79(44. 9%) females and 97(55. 1%) males. Autoantibody positivity was detected in 17 participants(9. 7%), with one autoantibody identified in 9 individuals(5. 1%), three autoantibodies in 4 individuals(2. 3%), two autoantibodies in 3 individuals(1. 7%), and four autoantibodies in 1 individual (0. 6%). ZnT8 was positive in 13 individuals(7. 39%), anti-GAD in 11(6. 25%), IA-2 in 6(3. 41%), and anti-insulin in 1(0. 57%). SCARED assessment was completed in 61 patients. Anxiety levels increased by 100% in autoantibody-positive children(from 25 to 37, $p < 0.001$), while 72% of autoantibody-negative children showed a significant decrease(from 25 to 18, $p < 0.001$). The STAI was completed by 53 mothers and 8 fathers. In the autoantibody-negative group, both state(from 38 to 31, $p < 0.001$) and trait anxiety(from 39 to 37, $P = 0.007$) decreased significantly in parents. In the autoantibody-positive group, state anxiety in parents increased significantly(from 35 to 46, $p < 0.001$), while trait anxiety anxiety changed slightly(from 36 to 39, $P = 0.353$). Mothers had higher STAI scores than fathers for both state(38 vs. 35) and trait anxiety(35 vs. 28, $P = 0.245$).
Conclusion
Among 176 individuals, 4. 54% had two or more positive autoantibodies, which is consistent with findings reported in the literature. This is the first multicenter T1D autoantibody screening in Turkey. Psychological evaluations conducted before and after screening revealed significant anxiety reduction among autoantibody-negative children and their parents, while autoantibody-positive individuals experienced marked increases in anxiety levels. Findings highlight the need to educate at-risk individuals and provide psychological support.
Keywords: Type 1 Diabetes, Autoantibody Screening, Diabetic Ketoacidosis, Psychological Impact
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P338

JOINT3159

"Urinary c-peptide to creatinine ratio (UCPCR) as a marker of insulin secretion: impact of glucose load and sex differences"

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Background
Insulin resistance and prediabetes are growing risk factors for metabolic and cardiovascular sequelae in many populations worldwide. Early risk detection could be based on biochemical and functional biomarkers for individual diagnosis and monitoring. Therefore, the urinary C-peptide to creatinine ratio (UCPCR) is an emerging diagnostic approach based on a noninvasive tool for assessing and monitoring insulin secretion. This study aims to investigate changes in UCPCR values before and after a defined oral glucose tolerance test (OGTT) and explore potential differences between men and women.
Methods
This study investigated a subgroup of 169 volunteers from the BioPersMed cohort (Biomarkers in Personalized Medicine), with 1022 participants overall. A regular OGTT was performed, with spot urine samples taken before and after the glucose load. In parallel, glucose, insulin, and C-peptide measurements in blood serum or plasma were taken at baseline, 30, 60, and 120 minutes, and a large number of parameters related to metabolic and cardiovascular risk were measured.
Results
Our findings indicate a significant increase in UCPCR following the OGTT compared to fasting values, suggesting that the test induces a measurable change in insulin secretion. We observed no statistically significant difference in UCPCR values between men and women at baseline before the OGTT (P-value 0. 250). However, a notable difference in UCPCR values was found between genders after the OGTT, with women showing higher UCPCR values than men based on the Mann-Whitney U test (P-value <0. 001). Further analyses are ongoing.
Conclusion
These results highlight the dynamic nature of insulin secretion in response to glucose intake and suggest that gender influences UCPCR findings after an OGTT. Further studies in the larger BioPersMed cohort will refine the clinical potential of UCPCR as a biomarker for insulin secretion.
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P339

JOINT1379

Single-cell analysis reveals plasticity of pancreatic β-cells during pregnancy and postpartum in mice

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Background
During pregnancy, the pancreatic β-cell mass expands to meet the increased metabolic demands, and it subsequently regresses in the postpartum period as maternal glucose homeostasis returns to normal. The transcriptional changes underlying these adaptations remain unclear. This study seeks to explore the heterogeneity of pancreatic beta cell populations at various stages of pregnancy and postpartum involution, focusing on the molecular mechanisms driving their adaptive plasticity.
Methods
Islets were isolated from non-pregnant mice, pregnant mice at day 14. 5, and postpartum mice at day 4. Single-cell RNA sequencing (scRNA-seq) was performed to analyze the transcriptomic features of the β-cells. Bioinformatics analyses were conducted to identify heterogeneity within these cells. SCENIC analysis was employed to identify the transcription factors most active in proliferating β-cells. Immunofluorescence assays revealed that Pbx4 positivity significantly increased in pancreatic islets of pregnant mice and returned to baseline levels postpartum. *In vitro* functional assays were conducted on mouse β-cell lines to validate the role of Pbx4 in regulating the expression of cell cycle-related proteins, thereby promoting β-cell proliferation.
Results
Our single-cell transcriptomic analysis identified five functionally distinct β-cell subpopulations. We focused on three dynamically regulated clusters that exhibit stage-specific heterogeneity during gestational adaptation and postpartum recovery, we observed:A polyhormonal subpopulation co-expressing Gcg (glucagon), Sst (somatostatin), and Ppy (pancreatic polypeptide), indicative of endocrine plasticity, decreases during pregnancy and recovers in the postpartum. This suggests that the increased metabolic stress during pregnancy may drive this cell population to differentiate into mature beta cells. A pregnancy-enriched cluster marked by acinar-to-β cell transdifferentiation, with expression of Ctrb1 and Prss2, suggests that acinar cells transdifferentiate into β-like cells during pregnancy to alleviate insulin insufficiency; and a proliferative population marked by Mki67, potentially regulated by the transcription factor Pbx4. Overexpression of Pbx4 in mouse β-cell lines has demonstrated that Pbx4 can upregulate the expression of cyclins, thereby promoting β-cell proliferation.
Conclusion
Using single-cell RNA sequencing, we revealed transcriptomic changes of distinct β-cell subpopulations, including polyhormonal cells, acinar-like clusters, and a proliferative β-cell subset during pregnancy and postpartum. Our analysis reveal novel mechanisms of β-cell adaptation to metabolic challenges during pregnancy-related changes.
Keywords: Pancreatic β-cells, Single-cell RNA-seq, cellular plasticity, Pbx4
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P340

JOINT1347

Influenza vaccine coverage and factors associated with vaccination in adults with type 1 diabetes - a danish register-based study

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Background
20% of all confirmed influenza cases are admitted to hospitals in Denmark. Underlying conditions such as type 1 diabetes (T1D) can lead to increased risk of severe complications from influenza. In Denmark, influenza vaccination is recommended to all adults with T1D, and the World Health Organization (WHO) recommends an influenza vaccination coverage (IVC) of 75% in high-risk groups. This register-based, repeated cross-sectional study aims to investigate IVC among individuals with T1D and identify subgroups susceptible to non-vaccination.
Methods
Using nationwide Danish registers, we compiled a cohort of adults in Denmark aged 19-64 with T1D during influenza seasons 2015/16-2022/23. Vaccination status was assessed prior to every influenza vaccination season. We investigated associations between non-vaccination and gender, region of residence, age at T1D onset, T1D duration, hemoglobin A1c, socioeconomic status and events of severe hypoglycemia and/or ketoacidosis using robust Poisson regression to compute adjusted relative risk (RR).
Results
IVC was low in the 2015/16 season (IVC 17. 99%, 95% confidence interval (CI) (17. 44%, 18. 54%)), and increased slightly throughout seasons 2016/17-2020/21. In 2021/22, IVC increased significantly to 41. 13% (95% CI (40. 45%, 42. 18%)). Male sex was associated with not receiving influenza vaccination (RR 0. 75, 95% CI (0. 73, 0. 77)). Age at onset and T1D duration was also associated with vaccination status: As these increase, so does the likelihood of vaccination. Individuals with HbA1c $>$ 53 mmol/mol had a reduced RR of vaccination (RR 0. 97, 95% CI (0. 95, 0. 99)). Region of residence and socioeconomic factors were strongly associated to RR of vaccination. Diabetic ketoacidosis prior to season start showed a significant decrease in RR of vaccination by 12% (RR 0. 88, 95% CI (0. 83, 0. 92)).
Conclusions
This study reveals that IVC among individuals with T1D is suboptimal and does not meet the recommendations set by the WHO. Although IVC seems to be increasing, more intense and tailored vaccination strategies are needed to increase it further. We have identified several factors that are associated with non-vaccination, revealing specific subgroups that healthcare providers should prioritize in vaccination efforts.

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P341

JOINT573

Continuous glucose monitoring in paediatric residents with normal glucose metabolism: correlations to 24-hour duty schedule

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Intoduction
Glucose values in healthy humans are influenced by many factors like dietary habits, stress and hormonal signaling, lack of adequate sleep.
Aim
To quantify glucose fluctuations in healthy paediatric residents with the use of commercial continuous glucose monitoring systems (CGMS).
Methods
Eligibility criteria for participation in the research were: a)participation as a paediatric resident in the full on-call duty schedule of a Paediatric department in a teritiatory hospital, b)age: 25-40 years, c)absence of chronic disease or receiving treatment affecting glucose metabolism and d)willingness to participate in the study after providing signed consent.
Results
Fifteen sensors were placed in 13 residents (8 females). A total of 35 days of 24-hour duty shift in outpatient basis were covered. Additionally, 35 days were stratified as days after a 24-hour outpatient duty and 114 days were classified as being away from 24-hour outpatient duty shift. In the whole study group, mean glucose values were 99. 69 $\pm$ 20. 31 mg/dl, 97. 67 $\pm$ 19. 28 mg/dl and 97. 14 $\pm$ 16. 99 mg/dl on 24h outpatient duty days, on days after 24h outpatient duty and on days away from 24h outpatient duty respectively ($P < 0.001$). Males showed significantly higher glucose values on 24h outpatient duty days in compared to females (101. 22 $\pm$ 19. 42 mg/dl vs 99. 17 $\pm$ 20. 57mg/dl, $P = 0.006$), while on the days after and away from 24h outpatient duty shift, males displayed significantly lower glucose values compared to females (97. 25 $\pm$ 19. 24 mg/dl vs 97. 85 $\pm$ 19. 30 mg/dl, $P = 0.002$ and 96. 57 $\pm$ 15. 95 mg/dl vs 97. 12 $\pm$ 17. 60 mg/dl, $P < 0.001$). The analysis of the data per person individually, showed that the majority of participants significantly increased levels of glucose on the 24h outpatient duty shift (with the exception of 1 male and 1 female resident). Lower glucose values during the night compared to the whole 24 hours for the away from the 24h outpatient duty shifts, were recorded for the majority of participants with the exception of 1 male and 2 3 female participants. On the contrary, higher glucose values were recorded in the night compared to the whole 24 hours in 8 participants (4 males and 4 females) during the 24h outpatient duty shift.
Conclusions
24h outpatient duty shifts for Paediatric residents have shown that significantly affect glucose values. The stressful environment, lack of sleep and poor and unhealthy dietary habits contribute to this glucose disturbances. Further studies are warranted to confirm and further extent these preliminary data.

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P342

JOINT3952

Acceptance of artificial intelligence by clinicians: a study on adoption and integration in medical practice

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Aim
This study aims to evaluate the acceptance of artificial intelligence (AI) technologies by clinicians, focusing on factors influencing adoption, perceived benefits, challenges, and the impact on clinical decision-making and patient care.
Materials and Methods
A cross-sectional survey was conducted among 200 clinicians from various medical specialties across India. The survey included questions on familiarity with AI tools, perceived usefulness, ease of integration into clinical workflows, and concerns regarding AI's role in medical practice. The Technology Acceptance Model (TAM) was used as a framework to assess clinicians' attitudes and intentions to adopt AI. Data were analyzed to identify trends and correlations between clinician demographics, specialties, and AI acceptance levels.
Results
The study revealed that 68% of clinicians expressed a positive attitude towards adopting AI in their practice, citing improved diagnostic accuracy and efficiency as key benefits. However, 45% of respondents reported concerns about the reliability of AI tools and the potential for reduced clinical autonomy. Younger clinicians and those in tech-savvy specialties, such as radiology and pathology, showed higher acceptance rates compared to their peers. Additionally, 52% of clinicians indicated that lack of training and integration challenges were significant barriers to AI adoption.
Conclusion
While there is a growing acceptance of AI among clinicians, several barriers, including concerns about reliability, loss of autonomy, and insufficient training, hinder widespread adoption. Addressing these issues through targeted education, robust AI tool validation, and seamless integration into clinical workflows can enhance acceptance and utilization. The findings underscore the need for collaborative efforts between technology developers and healthcare professionals to ensure AI tools effectively support clinical practice and improve patient outcomes.

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P343

JOINT2313

Postprandial glucose response to a novel low-sucrose chocolate spread in adults with type 1 diabetes: a randomized, double-blinded, cross-over, controlled trial

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Aims
Controlling postprandial glucose excursions remains a challenge for people with Type 1 diabetes (T1D). Novel advances in food technology enable the production of foods with significantly reduced sucrose without the use of additives. We aimed to test the postprandial glycemic response of subjects with T1D to a novel sucrose-reduced chocolate spread, as well as its acceptance and palatability.
Materials and Methods
A randomized, double-blind, crossover, active-controlled trial comparing the glycemic response to two test-meals: 20 grams of the sugar-reduced spread (8% sugar; 1. 6 grams sucrose), and 20 grams of control chocolate spread, (56% sugar; 11 grams sucrose) in people with T1D.
Results
Thirty adults (50% males), aged 18–28 years (mean 23. 0 ± 3. 0), mean HbA1C of 7. 2 ± 0. 9 % were recruited. Postprandial glucose excursions were significantly lower following consumption of the study spread compared to the control spread: pre-meal to peak glucose difference (mean 25. 8 ± 34. 9 mg/dL lower, $P < 0.001$), postprandial CGM iAUC (mean 2271 ± 3789 min × mg/dL, $P = 0.003$). Median time in range was higher for the study vs control spread (100% and 64. 6%, respectively, $P = 0.030$). In the sweetness scale questionnaire, the study spread rated higher than the control, with a "right degree of sweetness" 53. 3% and 26. 7% respectively, $P < 0.001$.
Conclusion
The study product with 80% less sucrose and 50% less carbohydrates showed a more favorable glycemic response, without compromising sweetness. This new technology could be a significant contributor to the ongoing effort to produce healthier, sugar-reduced foods, both for people with diabetes, and for the general population.

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P344

JOINT3673

Advance glycation end-products in diabetic persons with and without retinopathy during the first and second year of the project EEA-RESEARCH-60 "perdire"

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Prolonged hyperglycemia results in the formation and accumulation of complex and heterogeneous groups of compounds - advanced glycation end-products (AGEs) that increase oxidative stress and induce inflammatory reaction, which exacerbate the occurrence and progression of diabetic complications. The project "Integrated model for personalized diabetic retinopathy screening and monitoring using risk-stratification and automated AI-based fundus image analysis – PerDiRe" involved data on type 1 diabetes (T1D) and type 2 diabetes (T2D) patients from four countries - Latvia, Lithuania, Estonia, and Norway, on two consecutive annual visits. The project was funded by EEA-RESEARCH-60 grant. The objective of this substudy was to assess the relationship between AGE levels and diabetic retinopathy (DR) course in patients with diabetes across all four countries.
Methods
410 patients with diabetes attended the initial visit, and 226 patients returned for the 1st year follow-up. At both visits, the patients with diabetes underwent full ophthalmological and diabetes-specific clinical examinations. The patients were stratified according to the DR status as follows: no retinopathy, non-proliferative (simple) retinopathy, proliferative retinopathy, and diabetic macular edema. AGEs were measured non-invasively using an *AGE Reader* device (DiagnOptics Technologies B. V., SN 00010604, Netherlands). AGE z-scores were calculated with the formula: AGE z-score = AGE mean-(0. 024*age, years + 0. 83).
Results
During the initial visit, 47. 3% ($n = 194$) of the patients had some form of DR. By the second visit, 52. 2% ($n = 118$) presented with DR ($P = 0.23$). 9. 3% of the study subjects experienced progression to a more severe stage of DR ($P < 0.05$). A significant change in DR severity from first to second visit was found only within the T2D group ($P < 0.05$). During both visits, T2D patients had significantly higher median AGE values and z-scores, compared to T1D ($P < 0.001$). Patients with T1D exhibited a statistically significant increase in median AGE values and z- scores at the second visit compared to the first one ($P < 0.05$ for both measures). Conversely, patients with T2D showed no significant change in either AGE values or AGEs z-scores between the two visits. In both groups combined, marginal means of AGE values and z-scores increased significantly with progression of DR stages during both visits (general linear models' $P < 0.001$).
Conclusions
The results indicate a notable change in the distribution of DR stages between the first and second visits, especially in T2D. AGE levels were significantly higher in T2D patients and were directly related to more advanced stages of DR.

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P345

JOINT2898

Randomized controlled trial on the effectiveness and usability of interactive diabetes management application: a multi-centre study

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Introduction
Emerging trends insmartphone usage have led to integration of smartphone technologies in diabetes management via mobile application. Ideally, a newly-developed application should be evaluated in terms of its effectiveness and usability to ensure patients' and continuous engagement. However, majority of the applications are not evaluated on the effectiveness in improving in health outcomes.
Objective
We aimed to evaluate the effectiveness and usability of complementary interactive automated data entry diabetes management tool vs standard physician care.
Methods
Diabetes mellitus patients treated with insulin were randomly assigned to intervention (standard of care plus interactive mobile application) or control arms (standard physician care without mobile application). Every patient was provided with bluetooth-enabled glucometer and strips as well as blood pressure measuring set. Blood glucose and blood pressure data were automatically synced to the mobile application for the intervention arm and pharmacists monitored the patients remotely every month in addition to standard physician care. Meanwhile, patients in the control arm who received only standard physician care, recorded the glucose and blood pressure monitoring manually. Demographic data, haemoglobin A1c (HbA1c), systolic and diastolic blood pressure readings, insulin doses, hypoglycaemic episodes and usability of the interactive mobile application via questionnaire were collected at baseline and 3 months post-intervention.
Results
A total of 112 patients (63. 4% female, mean age 53. 1 years, mean duration of diabetes 16. 3 years) with similar baseline characteristics for intervention and control arms completed the study. Glycaemic control improved significantly, in the intervention arm as compared to control arm with HbA1c -1. 22 ± 1. 36% (95% CI -1. 59, -0. 84) and -0. 23 ± 1. 04% (95% CI -0. 50, 0. 04) respectively ($P < 0.001$). Blood pressure improved significantly in the control arm with systolic and diastolic blood pressure reduced by 6. 72 ± 17. 26 mmHg ($P = 0.005$) and 2. 95 ± 8. 97 mmHg ($P = 0.016$) respectively. There was no difference in insulin doses in both arms but hypoglycaemic episodes reduced significantly in the intervention arm, $P = 0.016$. Most of the patients (87. 8%) in the intervention arm reported good usability and were satisfied with the interactive mobile application.

Conclusion
The interactive diabetes management tool with automated glucose and blood pressure data entry improved glycaemic control and reduced hypoglycaemic episodes significantly with high satisfaction among users. This application has proven to be an effective tool for remote monitoring by healthcare professionals, providing timely oversight and serving as a valuable alternative for patient monitoring especially in the rural areas.
Keywords: interactive diabetes application, glycaemic control, blood pressure, usability, glucose monitoring
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P346

JOINT554
JAK/STAT and TRAIL signaling in latent autoimmune diabetes in adults: findings from single-cell transcriptomics
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Goal
Latent Autoimmune Diabetes in Adults (LADA) exhibits a hybrid autoimmune-metabolic phenotype, sharing features of both type 1 and type 2 diabetes. However, the molecular mechanisms underlying its slower β-cell decline remain poorly characterized. We aimed to clarify the role of two key immune signaling pathways, JAK/STAT (Janus Kinase/Signal Transducer and Activator of Transcription) and TRAIL (TNF-Related Apoptosis-Inducing Ligand), in shaping the autoimmune landscape of LADA compared to classic type 1 diabetes mellitus (T1DM).
Methods
Peripheral blood mononuclear cells (PBMCs) were collected from 15 individuals with LADA, 21 with T1DM, and 22 healthy controls. Single-cell RNA sequencing (10x Genomics platform) provided 5'single-cell transcriptomic profiling (scRNA-seq) of immune subsets (T-cells, B-cells, NK-cells, and monocytes). After quality control and batch-correction, pathway-centric analyses (PROGENy-based scoring) assessed relative JAK/STAT and TRAIL pathway activities across these groups, focusing on T- and NK-cell subpopulations.
Results
In T1DM, JAK/STAT showed robust hyperactivation across CD4+ and CD8+ T-cell subsets, often reaching 10- to 20-fold higher scores than in healthy controls. Concomitantly, TRAIL activity was markedly reduced 2- to 5-fold, suggesting a diminished apoptotic checkpoint against hyperreactive lymphocytes. This imbalance likely contributes to the rapid β-cell destruction typically observed in T1DM. LADA, however, demonstrated more moderate JAK/STAT activity 2- to 6-fold, consistently lower than T1DM but slightly above healthy levels. Notably, TRAIL signaling scores were significantly elevated in LADA 2- to 3-fold compared with T1DM. This pattern implies that, while JAK/STAT-driven inflammation persists, enhanced TRAIL-mediated apoptosis selectively eliminates the most aggressive immune clones. Hence, LADA appears to adopt an attenuated autoimmune response that slows β-cell decline. NK-cells (CD56dim) mirrored these findings, showing intense JAK/STAT upregulation in T1DM but a tempered response in LADA. TRAIL in LADA NK-cells was consistently higher than in T1DM, reinforcing the idea of apoptotic regulation limiting full-blown cytotoxicity. Collectively, these pathway-level distinctions align with LADA's milder clinical progression relative to T1DM.
Conclusion
Our single-cell profiling indicates that LADA's immunopathology is shaped by an interplay of moderately elevated JAK/STAT signaling and heightened TRAIL-mediated apoptosis. This contrasts sharply with T1DM, where excessive JAK/STAT activation and insufficient TRAIL-related cell death of autoregressive T-cells foster a more aggressive β-cell attack. These findings suggest that targeting JAK/STAT hyperactivation or enhancing TRAIL-mediated apoptosis may provide novel therapeutic strategies to modulate LADA's autoimmune trajectory and preserve β-cell mass. Pharmacological modulation of these pathways warrants further exploration as a potential strategy for LADA management.
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P347

JOINT2641
Assessment of insulin-releasing and glucose-lowering effects of Piper guineense extracts in cellular and animal models of type 2 diabetes
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Aim
Piper guineense is a plant used traditionally for the management of diabetes in many countries across West Africa. However, mechanisms underlying its actions are poorly understood. This study assessed phytochemical composition, insulin-releasing effects of aqueous extracts of the plant extract
Methods
The screening for common flavonoids and phenolic compounds in *P. guineense* was carried out. Actions of *P. guineense* extracts (0–1000μg/ml) on insulin release, cell viability and markers of cytotoxicity in BRIN-BD11 cells and in mice fed with a high-fat diet were assessed. The involvement of the ATP-dependent pathway in the actions of the plant extract was also assessed.
Results
Aqueous extract of *P. guineense* had total phenolic and flavonoids content of 1. 84±0. 18GE/g and 1. 72±0. 16QE/g respectively. The extract stimulated non-toxic insulin release from BRIN-BD11 cells at all concentrations tested (0. 01 – 1000μg/ml, 1. 2- to 2. 3-fold, $P < 0.05$ to $P < 0.001$). The observed insulinotropic effects was glucose-dependent (1. 8-fold, $P < 0.001$ at 1. 1mM to 5. 6mM; 1. 5-fold, $P < 0.01$ at 5. 6mM to 16. 7mM). Effects of *P. guineense* increased in the presence of KCl (30mM, 1. 5-fold, $P < 0.01$). Reduced effects were observed in the presence of verapamil (50nM, 43%, $P < 0.001$), diazoxide (300μM, 53%, $P < 0.001$) and absence of extracellular calcium (48%, $P < 0.01$). *P. guineense* improved glucose tolerance (24. 7 – 38. 4%, $P < 0.01$-0. 001 at 150 - 300mg/kg bw) and plasma insulin levels (1. 6 - 2. 8-fold, $P < 0.01$ at 150 - 300mg/kg bw) in high fat fed mice in a dose-dependent manner.
Conclusions
Observed anti-diabetic actions provide a basis for further research of the therapeutic potential of *P. guineense* extract as an anti-diabetic agent.
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P348

JOINT3813
Liver androgen receptor knockout fails to prevent high-fructose diet-induced glucose dysregulation in female mice
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The liver androgen receptor (AR) plays a crucial role in metabolic regulation, particularly under dietary stress. This study examined the impact of a high-fructose diet (HFrD) on glucose metabolism in male and female liver androgen receptor knockout (LivARKO) mice. LivARKO and wild-type (WT) mice were fed either an HFrD or a control diet, and glucose tolerance and insulin sensitivity were assessed over two months. In female mice, LivARKO did not prevent HFrD-induced glucose intolerance, as LivARKO-HFrD females exhibited similar impairments in glucose tolerance as their WT counterparts. While insulin sensitivity improved slightly in LivARKO females at later time points, they displayed significant hyperinsulinemia relative to controls. In contrast, male LivARKO mice experienced exacerbated glucose intolerance and heightened hepatic insulin resistance under HFrD conditions, suggesting sex-specific effects of hepatic AR loss on metabolic function. These findings indicate that liver AR knockout does not protect against HFrD-induced metabolic dysfunction in females and may worsen glucose homeostasis in males, highlighting the differential role of AR in diet-induced metabolic dysregulation.
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P349

JOINT121
Experience with the use of dapagliflozin in patients with ckd of various etiologies
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Background and Aims
Multiple trials have reported that SGLT2 inhibitors reduce the risk of its primary composite outcome of kidney disease progression or cardiovascular death in a wide range of patients with CKD. Our aim was to compare effects on kidney outcomes among the different types of kidney diseases.
Method
Eligible patients with eGFRs ≥30-45, or ≥45-90 ml/min/1. 73 m2 with a urinary albumin-to-creatinine ratio of ≥300 mg/g, and receiving renin angiotensin system inhibitor, where indicated and tolerated were randomized to dapagliflozin 10 mg once daily vs placebo. Kidney disease progression was defined as a sustained ≥30% eGFR decline from randomization or to <10 mL/min/1. 73 m2, start of maintenance dialysis or receipt of a kidney transplant, or renal death, and the effects of dapagliflozin were analyzed using a pre-specified Cox model. Testing for heterogeneity of effect between pre-specified kidney disease subgroups was performed, including exploratory analyses by specific glomerular disease etiologies.
Results
362 participants were followed for a median of 2. 0 years. 90 (24. 8%) had diabetic kidney disease, 126 (34. 8%) had glomerular disease, 94 (26%) had hypertensive or renovascular disease, and 52 (14. 4%) had other or unknown causes. Overall, dapagliflozin reduced the risk of kidney disease progression by 34% (dapagliflozin 29/178 vs placebo 48/184; hazard ratio 0. 62, 95% CI 0. 51-0. 78). This relative risk reduction appeared broadly similar in subgroup analyses by primary cause of kidney disease and by different types of glomerular disease.
Conclusion
Our study with a few numbers of patients with diabetic and non-diabetic causes of CKD showed that dapagliflozin reduced risk of kidney disease progression with relative risk reductions that were broadly similar across the different CKD etiologies.

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P350

JOINT2878

Accuracy and cost saving using haemoglobin A1c and lipid profiles point-of-care testing: a multicentre study

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Introduction
Measurement of glycosylated haemoglobin (HbA1c) and lipid profiles have been the standard monitoring for diabetes control and cardiovascular disease management respectively. Point-of-care testing (POCT) offers quick results with little blood sample needed compared to standard laboratory testing that requires additional time to hospital or health clinic.
Objective
We aimed to compare HbA1c and lipid profile POCT accuracy to the standard hospital laboratory testing and evaluate the potential cost savings from the patients' perspective.
Methods
Venous blood sample obtained from the diabetes mellitus patients were sent for standard laboratory testing. Simultaneously, capillary blood samples were collected for HbA1c and lipid profiles POCT using Quo-Lab® and PixoTest® respectively. Demographic data, time taken for blood tests, patients' salary, cost of travelling including distance from hospital, and absenteeism cost were collected. Intraclass correlation coefficient (ICC) and correlation coefficient analyses were employed.
Results
Seventy-three patients (mean age 53. 8±12. 4, 60. 3% female) were included. Patients spent median 5(IQR 4) hours for blood taking. HbA1c POCT using Quo-Lab® showed excellent correlation [ICC 0. 984 (95% CI 0. 975, 0. 990), rho=0. 97, $P < 0.001$] to the standard laboratory test. However, lipid profiles POCT using PixoTest® showed moderate correlation with the ICC for total cholesterol, triglycerides, low-density-lipoprotein cholesterol and high-density-lipoprotein cholesterol (0. 652, 0. 597, 0. 743 and 0. 704 respectively). POCT translated to cost saving from patients' perspective was RM61. 65 (IQR RM53. 55) or USD13. 70 (IQR USD11. 90) [1USD =RM4. 50].
Conclusion
The HbA1c POCT showed high reliability while the lipid profiles POCT had moderate reliability as compared to standardised laboratory testing. POCT is a cost saving alternative option for patients who have difficulty to travel or having to miss work for routine blood tests.

Keywords: point-of-care, HbA1c, lipid profiles, cost saving, accuracy
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P351

JOINT2868

CGM as a useful tool providing deeper insights into the glucose metabolism of patients with transfusion dependent b-thalassemia

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Background
The iron overload occurring in patients with transfusion-dependent B-thalassemia causes a wide range of endocrine disorders, one of the most common being glucose dysregulation. Both insulin deficiency and resistance are reported in these patients. Current recommendations require assessment of glucose abnormalities by testing fasting blood glucose (BG) and performing oral glucose tolerance tests (oGTT) annually after a certain age. A new promising method for determining glucose disorders is the use of continuous glucose monitoring system (CGM).
Case reports
We present three cases of patients with transfusion-dependent B-thalassemia (TDT) with high ferritin levels (above 1000 ng/mL despite of the chelating therapy) and glucose dysregulation. Fasting blood glucose and extended oGTT were conducted to evaluate the glucose homeostasis along with the calculation of HOMA-IR. CGM (Dexcome One) was applied to each of them for a period of one week. MRI was conducted to evaluate the iron overload in the liver and pancreas. The first patient (14 years, male) had normal HOMA-Ir = 0. 88, but oGTT showed pronounced hyperinsulinism and impaired glucose tolerance – BG at 120'- 9. 2 mmol/l. CGM data showed postprandial glucose elevation up to 15. 3 mmol/l and mean BG 6. 2 mmol/l. The second patient (14 years, female) had insulin resistance according to HOMA-Ir = 3. 16, and normal BG and insulin levels during oGTT but the CGM showed postprandial BG up to 12. 5 mmol/l and mean blood glucose 8. 01 mmol/l. The third patient (8 years, female) had normal HOMA-Ir = 0. 7 and insulin levels during oGTT, no hyperglycemia. Three symptomatic episodes of hypoglycemia were observed with BG 3. 1, 2. 5 and 2. 0 mmol/l – two of them during the oGTT and one later the same day. CGM data showed postprandial glucose elevation up to 13 mmol/l, mean BG 6. 1 mmol/l.
Conclusions
The use of CGM seems to be more useful for diagnosing glucose dysregulation in patients with TDT than fasting BG and oGTT alone. More investigations and a longer follow up are needed.

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P352

JOINT1237

KARLOTTA 2. 0 (kids + adolescents research learning on tablet teaching aachen) – study results of a digital educational app for pediatric patients with type 1 diabetes

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Objectives
Improvement of disease-specific knowledge in pediatric patients with type 1 diabetes using a digital app and individualized teaching.
Methods
We developed the KARLOTTA app (Kids + Adolescents Research Learning on Tablet Teaching Aachen), a game with knowledge-quiz and mini-games, designed for use before outpatient clinic appointments. The app provides immediate feedback on answers, mirrored for caregivers. The quiz-content is based on established educational programs in Germany. In our randomized-controlled pilot study, 57 patients were included to evaluate acceptance, transition-readiness, and changes in behavior and glycemic control (HbA1c). Of the 57, 27 were in the intervention group and 30 in the control group. The mean age at diagnosis was similar in both groups (8. 37 Intervention, 9 Control), as was the mean duration of T1D (5. 19/5. 05 years). The gender distribution, insulin therapy type, and HbA1c values were comparable between the two groups. We analyzed 26 patients in the intervention group and 24 in the control group. The intervention group used the game 3 times over 6 months, with 3-month intervals. They completed quality of life (Qol), satisfaction, and transition questionnaires before and after the intervention. The control group filled out the same

questionnaires at their first and final visits after 6 months. The median time between visits in the intervention group was 101. 5 days (IQR 91-111), $n = 50$. The average time between the first and last visits was 210 days (SD 27), $n = 25$. The 26 intervention group patients completed a satisfaction questionnaire after the last game, with 15 multiple-choice, 2 open-ended, and 1 transition question for adolescents over 16. Responses were analyzed descriptively using the Likert scale. The analysis of the feedback Questionnaire indicated that patients learned from using the App. The App encouraged them to pay more attention to their blood sugar levels and improve insulin bolus administration. Patients reported increased openness in discussing their therapy with our diabetes team and a greater overall concern for their condition. They enjoyed the game feature and planned to continue using it. Both groups (Intervention and Control) showed improved HbA1c levels. Evaluation of our Qol and transition questionnaire will be reported.

Conclusion

Individualized teaching is essential for managing chronic diseases like T1D, particularly for children and adolescents who require intensive communication and ask for modern and age-adequate tools. The KARLOTTA app identifies knowledge gaps, offers customized teaching, and is easily implementable in outpatient settings. Further studies are planned in multi-centric and international settings.

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P353

JOINT1913

Incidence trends and seasonal variation of new cases of type 1 diabetes in lithuanian children in 2001-2022

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Introduction

Type 1 diabetes (T1D) incidence is rising globally, with significant regional variation, ranging from low rates in Asia (2. 4-3. 2 per 100, 000 person-years) to the highest in Scandinavia and Sicilia (up to 65 per 100, 000 person-years). Despite extensive research, the contributing factors — climate, genetic, environmental, or lifestyle-related, remain unclear. Therefore, data from highly homogeneous populations, such as Lithuanian, may contribute to a better understanding of these factors. This study examines 21-year trends in childhood T1D incidence and seasonal patters in Lithuania.

Methods

The current study relied on the incidence data sourced from the T1D Database of Lithuanian children, while population data were procured from the Lithuanian Department of Statistics. The annual incidence rates for more than two decades were computed utilizing established methodologies (per 100, 000 person-years in children aged 0-14 years (*from this point onward per 100, 000 person-years*). The study included 2, 472 (1221 boys) patients with T1D diagnosis before the age of 15, permanent residents of Lithuania.

Results

During 2001-2022, the mean standardized incidence rate (IR) was 24. 09 per 100, 000 person-years (95% CI 20. 89, 27. 28). The IR scaled from 11. 4 to 40. 8 per 100, 000 person-years, with the lowest in 2001-2002, reaching its peaks in 2017 (36. 3 per 100, 00 person-years), 2021 (40, 8 per 100, 000 person-years) and 2022 (34 per 100, 000 person-years). Analysis of the trends in age subgroups, showed the most rapid increase in young teenagers (10-14 years), with more steadily increasing incidence in younger groups (0-4 years and 5-9 years). No significant disparity in incidence trends was noticed between male and female cohorts. The boys-to-girls ratio varied from 0. 7 to 1. 53 during the study period, however, the overall ratio was 1. 00. The majority of new T1D cases (54, 5%) were diagnosed from October to March, and the lowest incidence rate was during late spring and summer months (May-July).

Conclusion

This study demonstrates arapidly increasing incidence of T1D in Lithuanian children over a 21-year period, with the incidence peaking at 40. 8 cases per 100, 000 person-years in 2021, rating Lithuania among the top three European countries. The seasonal distribution of new cases, with the majority occurring during the darker months of the year, suggests a potential role of reduced sunlight exposure and lower vitamin D levels, as well as increased school related stress and viral infections during autumn and wintermonths. However, additional contributing factors are likely involved, underscoring the need for further research to elucidate the underlying mechanisms driving this trend.

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P354

JOINT1822

Pilot screening program for early detection of type 1 diabetes in first-degree relatives in saudi arabia (VISION-T1D)

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Background

Type 1 Diabetes (T1D) is a growing global health concern, with a notable rise in incidence in Saudi Arabia. Despite the potential benefits of early detection through screening programs, such initiatives are currently lacking in Saudi Arabia and other Arab countries.

Objectives

To evaluate the feasibility, acceptability, and cost-effectiveness of a T1D screening program targeting high-risk individuals, specifically children with a first-degree relative diagnosed with T1D.

Methods

The VISION-T1D program is a prospective cohort study focused on the early detection of pre-symptomatic T1D by screening children aged 2–18 years. The primary screening method involves testing for islet autoantibodies, including insulin autoantibodies (IAA), glutamic acid decarboxylase autoantibodies (GADA), IA-2 autoantibodies (IA-2A), and Zn-transporter 8 (ZnT8) autoantibodies. Optional genetic testing, including HLA phenotyping and the Genetic Risk Score (GRS), is offered. Outcomes include the feasibility of the screening process, prevalence of early-stage T1D, psychological impacts, educational interventions effectiveness, progression rates to Stage 3 T1D, and the economic viability.

Results

The VISION-T1D program began in May 2024. As of December 2024, 210 families have been enrolled with 430 children. Data collection will continue until April 2025.

Conclusions

The VISION-T1D study provides a practical approach to T1D screening tailored to the healthcare landscape of Saudi Arabia. The insights gained from this pilot program will inform the development of a national, population-based screening initiative designed to reduce diabetic ketoacidosis (DKA) at diagnosis, improve long-term outcomes, and alleviate the economic burden of T1D. The VISION-T1D initiative could also serve as a scalable and sustainable model that can be adopted internationally, contributing to global efforts to manage and prevent T1D.

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P355

JOINT796

Impact of sex and BMI on A1C trajectory amongst children and adolescents with type 1 diabetes

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Introduction

Glycemic control in type 1 diabetes is known to worsen significantly during adolescence and young adulthood. Female sex is known to be a risk factor for this worsening glycemic control, but the mechanisms of this are unclear. We hypothesized that body mass index (BMI) may be a factor that facilitates worsening A1C in female youth.

Methods

We have previously established the British Columbia Pediatric Diabetes Registry (BC-PDR). Using this registry, we graphed the trajectory of A1C by age according to sex. We conducted this same analysis stratifying by BMI categories: underweight/normal weight, overweight, and obese. Using regression modelling, we compared average A1C between the sex-BMI categories for each age, adjusting for total daily dose of insulin and presence of chronic comorbidities. Missing data was addressed with multiple imputation.

Results
There were 674 patients with type 1 diabetes diagnosed in childhood and adolescence from the BC-PDR who were included in this study (299 females and 375 males). At recruitment, 35. 5% of females and 31. 7% of males were in the overweight or obese BMI category. At age 7, the average A1C of underweight/normal weight males was 7. 53%, which was not significantly different compared to the average A1C of overweight males, obese males, and females of any BMI category. However, by age 17, there were significant differences in average A1C between the different sex-BMI categories. At this age, the average A1C of underweight/normal weight males was 8. 16%, but average A1C was 0. 84% lower (95% CI -1. 10, -0. 59, $P < 0.001$) in overweight males and 0. 94% lower (95% CI -1. 21, -0. 68, $P < 0.001$) in obese males. The average A1C of underweight/normal weight females was not significantly different from that of underweight/normal weight males (+ 0. 15%, 95% CI -0. 04, 0. 34, $P = 0.118$), but was 0. 78% higher (95% CI 0. 53, 1. 03, $P < 0.001$) in overweight females and 0. 35% higher (95% CI 0. 15, 0. 55, $P = 0.001$) in obese females.
Conclusions
There appears to be a differential effect of sex and BMI on A1C amongst adolescents with type 1 diabetes. Average A1C is highest amongst adolescent females who are in the overweight and obese BMI categories. These findings suggest that weight management (e. g. including the use of weight loss adjuncts), particularly in overweight and obese post-pubertal females, may be an important treatment modality for adolescents with type 1 diabetes. Further study is needed to determine the factors and mechanisms, whether biological or psychological, that contribute to elevated A1C amongst female youth living with type 1 diabetes.

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P356

JOINT2112

Incidence and burden of childhood diabetes in china from 1990 to 2021: findings from the global burden of disease study 2021

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Background
Diabetes is emerging as a significant threat to human health in 21st-century China. Accurate data on diabetes prevalence, incidence, associated mortality, and life expectancy are crucial for informing public health policy, yet such data remain scarce, particularly among children in China.
Methods
Data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021 were used to estimate the incidence, trends, disease burden, and regional distribution of type 1 and type 2 diabetes among children in China from 1990 to 2021. Children aged 0 to 19 years with diabetes were included in the analysis.
Results
In 2021, the national incident cases of diabetes in children were 342, 121 (95% uncertainty interval [UI], 265, 699-426, 246), with 204, 118 being male (60•0%) and 138, 003 being female (40•0%). The incidence was 102. 34 per 100, 000 (95% UI 79•48-127•50) for diabetes mellitus, 4•09 per 100, 000 (95% UI 2•82–5•64) for T1DM, and 98•25 per 100, 000 (95% UI 75•11-123•44) for T2DM. The incidence of T1DM in males was lower than in females (3•96 per 100, 000 vs. 4•24 per 100, 000), while the incidence of T2DM in males was higher than in females (110•30 per 100, 000 vs. 84•42 per 100, 000). From 1990 to 2021, the incidence of diabetes mellitus, T1DM, and T2DM in children increased by 156•5%, 24•68%, and 168•31%, respectively. T1DM-associated DALYs in children decreased by 70•23%, whereas T2DM-associated DALYs increased by 51•08%. Over the past 30 years, the number of diabetes-associated deaths in children decreased by 75%.
Interpretation
The growing trend of childhood diabetes in China, particularly type 2 diabetes, requires significant attention. Future measures should focus on reducing the incidence of type 2 diabetes and its complications in areas with high obesity rates.

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P357

JOINT2260

Elevated alanine aminotransferase predicts the risk of prediabetes/-diabetes and NAFLD in obese children: a cross-sectional retrospective study

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Background
The obese children and adults, NAFLD is associated with type 2 diabetes or prediabetes. However, it is unrealistic to have all obese children willing to complete all assessment items.
Objective
To detect the association of type 2 diabetes and prediabetes in obese children with MRI-PDFF proved NAFLD and assess useful screening factors for predicting obese children without NAFLD and prediabetes.
Method
We recruited a cohort of 149 Chinese children/adolescents who finished OGTT test, and 108 children/adolescents with MRI-PDFF evaluated liver fat content. The diagnosis of prediabetes and type 2 diabetes was based on either hemoglobin A1c, fasting plasma glucose or 2 h post-load glucose concentrations.
Result
The prevalence of prediabetes and type 2 diabetes in children/adolescents with obesity was 26. 17% and the OR increased with increasing serum GGT and morning cortisol. There was no significant difference in glucose concentrations at 0 and 120 min in both the prediabetic and non-prediabetic groups with different NAFLD grades. Among factors screened in the comparison between subgroup of NAFLD with prediabetes and subgroup without NAFLD and prediabetes, BMISDS/P90, PLT, ALB, UASDS, ALT, cortisol and HOMA-IR were included for logistic regression analysis. the OR for both NAFLD and prediabetes in obese children increased with increasing serum ALT and PLT. ROC analysis shows ALT lower than 18. 5IU/l had a sensitivity of 85% and specificity of 72. 7% for detecting patients without prediabetes and NAFLD in obese children (ROC AUC 0. 857).
Conclusion
Although prediabetes is highly prevalent among children/adolescents with obesity but was not consistent with the grades of NAFLD. ALT lower than 18. 5IU/l might be useful in deciding not to conduct OGTT test or liver MRI-PDFF after basic examination for children with obesity.

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P358

JOINT1152

Giving the child with diabetes a clear voice: what matters the most to children with type 1 diabetes attending a pediatric diabetes clinic? A substudy in the ProKidsDia project

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Background
Previously, Patient-Reported Experience Measures (PREMs) for children with type 1 diabetes (CwD) were developed in cooperation with parents and clinicians alone. This resulted in a lack of knowledge concerning children's experiences in meeting the health care system. It is a challenging task to obtain this information from children, who do not read and write. There exists no animated PREMs for CwD and their parents, teachers and health care professionals (HCP). Our overall aim is to develop an animated, diabetes specific Patient Reported Outcome Measures (PROMs) and PREMs instrument for CwD aged 4-12 years old. This work builds on the animated Child Health Rating Inventories (CHRIS) PROMs questionnaire.
Aims
The specific aims of this study were 1) To obtain the perspectives of CwD, parents, teachers and HCP on needs and experiences, when attending an outpatient pediatric diabetes clinic in Denmark and 2) To establish a minimal set of PREM domains as the first step in developing an animated PREMs questionnaire.
Materials and Methods
COSMIN guidelines for developing Patient reported Outcome measures (PROMs) were used. Three participatory design workshops were executed in

two regions in Denmark in the period August 2023 – April 2024. Relevant stakeholders partook in the workshops: 16 CwD, 36 Parents, 7 Teachers and 19 HCP and 27 facilitators. Play-based communication and storytelling tools were used to enable and engage CwD to participate in the workshop. All participants (but HCP) were systematically encouraged to describe what is of personal value in daily life with diabetes and also describe bio-psycho-social challenges and needs in the PREMs context. All workshops were video- and audio recorded, transcribed, and thematically analyzed.

Results

Four main PREM domains were identified. 1) Diabetes-specific expertise, where trust in the HCP's expertise played an important role. 2) The hospital environment, in which the consultation rooms were perceived as clinical and not child-friendly, resulting in children being more passive during the consultation. 3) The diabetes team's family-centered approach with emphasis on establishing and maintaining a relationship while considering the child's interests and developmental stage. 4) The family's preparation and planning prior to outpatient visits, which was described as important to create a more positive experience for the child.

Conclusion

This study describes four important PREM domains for a CwD, parents and HCPs attending an outpatient pediatric clinic. The next study is to develop animated PREM items specific to these four PREM domains in order to develop a PREM questionnaire.

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P359

JOINT1710

Use of portable elastomeric pump for home-based continuous enteral carbohydrate administration through gastrostomy in children with congenital hyperinsulinism or ketotic hypoglycemia

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Background

Continuous enteral glucose infusion through gastric tube may be useful in patients with congenital hyperinsulinism (CHI) or pathological ketotic hypoglycemia (pKH). Home-based enteral treatment with infusion pump is, however, limited by impracticalities for patients and their caregivers.

Methods

We developed the novel use of enteral portable elastomeric pump (ePEP) therapy to deliver home-based continuous enteral carbohydrates through gastrostomy. The first pilot results of this novel treatment modality are presented.

Results

Ten pediatric patients (girls, $n = 7$) were enrolled. Six patients had pKH with unknown background ($n = 4$); Russel-Silver syndrome ($n = 1$), or clinical glycogen storage disease with digenic heterozygous *PYGL* and *GBE1* DNA variants ($n = 1$). Four patients had diffuse CHI with biallelic *ABCC8* mutations ($n = 2$), activating *GCK* mutation ($n = 1$), or CHI with associated organ malformations of unknown cause ($n = 1$). Prior surgical treatment for ABCC8-CHI included near-total or partial pancreatectomy ($n = 2$). All patients had a gastrostomy. Prior or concomitant treatment included continuous i. v. glucose ($n = 7$), continuous i. v. glucagon ($n = 3$) , diazoxide ($n = 8$), octreotide ($n = 8$) long-acting somatostatin analogue ($n = 5$), sirolimus ($n = 3$), dietary cornstarch ($n = 9$), extended-release cornstarch ($n = 9$), protein supplementation ($n = 8$), and/or overnight gastrostomy tube feeding with liquid full-dietary products ($n = 9$), glucose ($n = 8$), or maltose ($n = 8$). Home-based ePEP therapy with home-blended glucose 10-40% was initiated at the median (range) age of 5. 4 (0. 3-15. 1) years. Maltose or apple juice was used alternatively in two for shorter periods. The median (range) duration of ePEP was 1. 25 months (4 hours to 26 months). Three patients aged 1. 8 y (ABCC8-CHI), 5. 4 y (GCK-CHI) and 13. 9 y (pKH) still use ePEP therapy at present after 7, 19 and 26 months, with high satisfaction in terms of improved glucose control and ease of daily living. One patient (8. 7 y; pKH) reported improved and good glucose control, relief of abdominal pain after discontinuation of extended release cornstarch and normalization of appetite, after which glucose was stable on oral diet only. Reports of insufficient ($n = 3$) or no ($n = 2$) improvement in glucose control, or hyperglycemia ($n = 1$) was associated with early discontinuation. The ePEP therapy was reportedly easy to use in seven and difficult to use in three. One reported skin irritation.

Conclusion

ePEP therapy with carbohydrates is a promising supplement to selected patients with CHI or pKH, although not continued by all due to insufficient effect, hyperglycemia or difficulties. This should encourage to formal trials with long-term follow-up on dose, effect, quality of life and adverse effects, e. g. on the intestinal microbiome.

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P361

JOINT2059

Association of the triglyceride/HDL cholesterol ratio with cholesterol efflux in adolescents with type 2 diabetes mellitus

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Background

Cardiovascular disease is a frequent cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2D). In adult patients with T2D, it has been observed that the elevation of the triglyceride (Tg)/HDL-C ratio is positively correlated with cardiovascular disease, and that the capacity to promote cholesterol efflux from peripheral cells to HDL is decreased, which is inversely associated with the incidence of cardiovascular disease (CVD). Currently, there are no studies that relate the Tg/HDL-C ratio with the functionality of HDL particles (cholesterol efflux) in adolescent patients with T2D.

Objective

To evaluate the association of the Tg/HDL-C ratio with cholesterol efflux in adolescents with DM2.

Material and Method

This Cross-sectional study included a total of 70 adolescents, 47 of which had T2D treated at the Diabetes Clinic of the Federico Gómez Children's Hospital of Mexico and 23 healthy adolescents of the same age and sex were included. The protocol was approved by the local Ethics and Research Committees. Anthropometric and biochemical variables (HbA1c, lipid profile, aminotransferases) were determined. Cholesterol efflux capacity (CEC) was determined by measuring the efflux of fluorescently labeled cholesterol from J774 mouse macrophages cells.

Results

In Our study, differences were observed between both groups in the concentrations of glucose ($P < 0.001$), total cholesterol ($P = 0.043$), triglycerides ($P < 0.001$), c-HDL ($P < 0.001$), Tg/c-HDL ratio ($P < 0.001$), Apo A ($P = 0.029$) and GGT ($P = 0.010$). When evaluating cholesterol efflux in both groups, no significant difference was observed ($P = 0.600$).

Conclusions

In the present study, we found no association between the Tg/HDL-C ratio and cholesterol efflux in adolescents with T2D. Further studies are required to assess whether some cardiovascular risk indices that have already been evaluated in adults would be applicable to the pediatric population with T2D.

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P362

JOINT1954

Effects of transition from basal insulin glargine 100 u/ml to 300 u/ml on glycemic control in children and adolescents with type 1 diabetes - real-world data

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Introduction

Insulin glargine 300 U/mL (Gla-300), a second-generation basal insulin, has shown in phase 3 trials to provide better glycemic control than insulin glargine

Table 1: Glycemic Parameters Before and After Transition in the Patients

	Glargine U100	Glargine U300	p
Weight SDS	0. 35 ± 0. 99	0. 51 ± 1. 10	0. 113
Total Insulin Dose (IU/kg/day)	0. 75 ± 0. 24	0. 81 ± 0. 22	0. 082
Basal Insulin Ratio (%)	42 ± 15	48. 39 ± 7. 86	0. 036
HbA1c (%)	7. 79 ± 1. 18	7. 60 ± 0. 75	0. 376
Stage 2 (>250 mg/dL)	11. 61 ± 10. 91	13. 63 ± 12. 82	0. 486
TAR (Time above range) (180-250 mg/dL)	24. 22 ± 8. 48	24. 47 ± 6. 97	0. 540
TIR (Time in range) (70-180 mg/dL)	60. 11 ± 12. 72	58. 79 ± 16. 64	0. 505
TBR (Time below range) (54-70 mg/dL)	3. 5 ± 3. 13	2. 68 ± 2. 00	0. 316
Stage 2 (<54 mg/dL)	0. 67 ± 1. 28	0. 47 ± 1. 12	0. 616
GMI (glucose management index) (%)	7. 25 ± 0. 68	7. 23 ± 0. 49	0. 966
CV (Coefficient of variation) (%)	37. 41 ± 4. 03	52. 64 ± 62. 7	0. 309
Active Sensor Time (%)	83. 11 ± 16. 88	89. 11 ± 15. 26	0. 091
Average Blood Glucose (mg/dL)	164. 39 ± 29. 08	168. 33 ± 31. 45	0. 480
Hypoglycemic Events	7. 38 ± 6. 22	6. 69 ± 4. 09	0. 622

100 U/mL (Gla-100), while reducing hypoglycemia risk and glycemic variability. However, real-world data in the pediatric age group is limited. This study aims to evaluate the impact of switching from Gla-100 to Gla-300 on glycemic control in children and adolescents with type 1 diabetes (T1D).

Methods

The study included 20 patients aged 8-20 years with T1D who were using continuous glucose monitoring (CGM) systems and transitioned from Gla-100 to Gla-300. Glycemic parameters assessed before and three months after the transition.

Results

Mean age and mean duration of diabetes was 13. 14 ± 2. 89, 4. 71±3. 26 years, respectively. The mean age at transition to Gla-300 was 12. 58 ± 2. 85 years. Glycemic data from the patients' CGM is shown in Table 1. Basal insulin ratio increased significantly ($P = 0.036$), and an increase in total insulin dose was also observed, although it was not statistically significant. No significant changes were found in glycemic parameters, nor was there a reduction in the number of hypoglycemic events or the time below range before and after the transition.

Conclusion

Gla-300 provides glycemic control similar to Gla-100, but with a higher basal insulin ratio, without significant differences in overall glycemic outcomes.

Key words

Pediatric, Glarjin U100, Glarjin U300

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P363

JOINT2391

Early detection of peripheral and autonomic neuropathy in children and adolescents with type 1 diabetes mellitus

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Introduction

Clinical neuropathy manifestations emerge during the initial stages of diabetes in children with type 1 diabetes mellitus (T1DM). Early detection and intervention of these changes leading to neuropathy are crucial for the follow-up of patients diagnosed with T1DM. Our objective was to identify a more sensitive method that can be implemented in clinical settings for the early detection of neuropathy in children. The present data constitute initial findings from our pilot study.

Methods

Thirty-one children with T1DM aged 6-18 years were evaluated using nerve conduction studies (NCS) (motor and sensory), autonomic tests (sympathetic skin responses and R-R interval variability studies), Sudoscan®, and neuropathy screening questionnaires (Composite Autonomic Symptom Score-31 (COMPASS-31) and Michigan Neuropathy Screening Instrument (MNSI)).

Results

This study recruited 31 children (F/M: 15/16), two of whom were prepubertal. The mean age of the T1DM patients was 13. 8±2. 9 years and mean duration of diabetes was 6. 1±1. 8 years. Mean insulin requirement of the study population was 1. 1±0. 4 U/kg/day, while their mean HbA1c level in the preceding year was 9. 2%±1. 8. All nerve conduction studies were within normal ranges, except for one patient. The COMPASS-31 scores were within the normal range for all the patients. The Sudoscan® results were within the normal range for all patients, except for one patient who exhibited moderate risk. Although within normal ranges, the median, peroneus, and tibial nerve motor latencies and amplitudes of the medial plantar and sural sensory nerves were affected by the duration of diabetes ($P < 0.05$). Our research has demonstrated that prolonged diabetes duration correlates with diminished amplitudes and extended latencies in the aforementioned nerves. Multivariate regression analysis showed that T1DM duration was significantly associated with peroneus motor latency (β=5. 164, $P = 0.011$), tibial motor conduction velocity (β=-1. 748, $P = 0.006$), total COMPASS-31 score (β=0. 254, $P = 0.010$), Sudoscan® foot mean value (β=-0. 229, $P = 0.013$), and HbA1c level (β=-2. 069, $P = 0.004$) (R^2=0. 73). The results of this study suggest that duration of diabetes affects autonomic dysfunction and electrophysiological parameters in the pediatric population.

Conclusion

In children with T1DM, screening for diabetic neuropathy is recommended during the early stages. It may be possible to detect early changes in the pediatric population using nerve conduction studies, autonomic tests, Sudoscan®, and diabetic neuropathy screening. To detect early changes, it also seems important to determine normative data for NCS in the pediatric population.

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P364

JOINT3355

Does celiac disease have an impact on hypoglycemia awareness in children with type 1 diabetes?

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Background

Hypoglycemia awareness is the ability to recognize when blood sugar is low, through the activation of counter-regulatory hormones and the perception of symptoms. It is a known fact that frequent hypoglycemic events can impair this awareness. Celiac disease increases the risk of hypoglycemia in type 1 diabetes (T1D). However, there is a lack of data in the literature regarding whether celiac disease leads to hypoglycemia unawareness in children with T1D. We aimed to investigate the possible effects of celiac disease on hypoglycemia awareness in pediatric patients with T1D.

Materials and Methods

This prospective cross-sectional study included children aged 5-18 years with T1D, who visited our clinic between November 2024 and January 2025. The participants were divided into two groups: one with both T1D and celiac disease, and another with T1D alone. The sample size was determined through a power analysis with a 3:1 case-to-control ratio. Hypoglycemia awareness was evaluated by the Clarke's questionnaire, and participants' knowledge about hypoglycemia management was noted. The results are presented as means (±standard deviation) or medians (25-75th percentile) depending on the distribution of the data.

Results

The study was conducted with 87 T1D patients (54% male, age 12. 5 ± 3. 5 years). The mean diabetes duration was 5. 1 (±3. 5) years, and the average HbA1c level was 8. 5% (±1. 8). The most common symptoms reported during hypoglycemic events were hand trembling (46. 5%), weakness (23. 3%), and dizziness (10. 5%). Celiac disease was present in 24. 4% ($n = 21$) of the participants, with a median disease duration of 3. 1 (1. 4 – 5. 3) years. No significant differences were found between the two groups in age, diabetes duration, HbA1c, or hypoglycemia knowledge ($p > 0.05$). Among the individuals with celiac disease, 19% ($n = 4$) had impaired hypoglycemia awareness, while 12% ($n = 8$) of those with only T1D had this issue. There was no significant difference between the two groups regarding hypoglycemia unawareness ($P = 0.476$). Additionally, there were no significant differences in age, HbA1c levels, diabetes duration, or knowledge about hypoglycemia between patients with and without impaired hypoglycemia awareness ($p > 0.05$).

Conclusion

To our knowledge, this is the first study to show that celiac disease did not affect hypoglycemia awareness in children with T1D. We also found no correlation between HbA1c levels and hypoglycemia awareness. These findings suggested

that while children with T1D and celiac disease, or those with poor metabolic control, may experience more frequent hypoglycemic events, the duration of hypoglycemia may be more critical in the development of hypoglycemia unawareness.

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P365

JOINT2840

Prognostic value of the neutrophil-to-lymphocyte ratio for acute appendicitis in children with acute abdominal pain and T1DM

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Background
Abdominal pain is often associated with T1DM and DKA in children. Underlying causes include not only functional disorders and impaired motility of GIT but also common surgical emergencies, namely acute appendicitis (AA) and peritonitis. The neutrophil-to-lymphocyte ratio (NLR) has recently become a valuable tool for diagnosing DKA and endothelial dysfunction in T1DM. Moreover, several studies have shown that NLR serves as an indicator of systemic inflammation and reflects a balance between the latter and immunity. However, its prognostic discriminative role between surgical emergencies and abdominal pain in DKA in children with T1DM remains unclear.
Aim
We aimed to analyze the utility of NLR in the differential diagnosis of surgical (acute appendicitis and peritonitis) and non-surgical causes of acute abdominal pain in children with T1DM and/or DKA.
Material and Methods
102 pediatric patients were enrolled in this study and further divided into three groups: group I – patients with DKA and acute abdominal pain ($n = 21$); group II ($n = 70$) - patients with acute appendicitis; group III ($n = 11$) – patients with acute appendicitis and T1DM/DKA. Diagnosis of acute appendicitis was confirmed by pathology. All patients underwent routine workup. Additionally, blood gases were evaluated in groups I and III. NLR was calculated as a ratio between the neutrophil and lymphocyte counts measured in peripheral blood. Written informed consent was obtained from the parents.
Results
The mean level of NLR was significantly different between group I (5. 06 ± 3. 13) and two other groups with AA (group II – 9. 40 ± 8. 03; group III – 9. 95 ± 8. 6), $P = 0$, 01786; $P = 0$. 0254, respectively). However, there was no difference between groups II and III($P = 0$. 8348). It may be due to the leading role of intraabdominal infection in the development of inflammation in both groups. Further ROC analysis has shown that NLR may be used as a prognostic marker of intraabdominal surgical diseases (AUC = 0. 827; 95% CI = 0. 671-0. 983; $p < 0$. 01) at a cut-off value of 7. 81 with sensitivity = 72. 7% (CI = 43. 4-90. 2 %) and specificity = 85. 7% (65. 3-95. 0 %), Youden's index – 0. 58. We also found that NLR strongly inversely correlates with the LYM fraction of CBC ($r_s = -0.98$; $p < 0$. 0001). It shows the crucial role of immunity in the natural course of AA in children with T1DM.
Conclusion
NLR is significantly higher in children with T1DM and AA than in children with non-surgical acute abdominal pain. A cut-off value of 7. 81 may be used to predict the surgical cause of acute abdominal pain (AA) in children with T1DM and/or DKA.

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P366

JOINT4019

Beyond glycemic control: managing rare complications in type 1 diabetes

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Effective metabolic control is crucial for preventing microvascular and macrovascular complications in patients with type 1 diabetes mellitus (T1DM). Here, we present a case of a young woman with T1DM who developed two rare complications: acute insulin neuritis and diabetic myonecrosis. A 45-year-old woman with T1DM since 2009, followed by the Endocrinology Department, experienced, since her diagnosis, irregular medical follow-up, poor adherence to treatment, and inadequate glycemic control. She developed severe microvascular complications, including proliferative diabetic retinopathy (treated with photocoagulation), diabetic nephropathy, and autonomic dysfunction with gastroparesis. Additionally, she suffered from significant macrovascular complications, such as an acute myocardial infarction in 2015 (managed with angioplasty) and peripheral arterial disease of the lower limbs. In 2022 and 2023, her adherence to treatment improved, leading to intensified insulin therapy and a rapid reduction in HbA1c from 14. 2% to 6. 6%. During this period, she reported paresthetic pain in the lower limbs along with mild-to-moderate paraparesis. Electromyography confirmed moderate sensorimotor axonal neuropathy, which later progressed to Charcot neuroarthropathy. The most likely cause was treatment-induced neuropathy, also known as acute insulin neuritis. She was started on tapentadol and pregabalin, resulting in significant pain relief. She was referred to a Diabetic Foot specialist and, in October 2024, underwent surgery to stabilize her left foot. In 2023, she had a prolonged hospitalization due to diabetic myonecrosis with abscess formation in the gastrocnemius muscles. She presented with pain, swelling, and redness in the right calf, along with functional impairment that lasted for two weeks, without fever or trauma history. MRI revealed multiple abscessed collections within the muscular planes of the right leg, with an extensive inflammatory process suggestive of abscessed hematomas. A muscle biopsy confirmed acute inflammatory infiltration and necrosis of skeletal muscle, consistent with spontaneous diabetic myonecrosis. She underwent surgical drainage of the abscesses and received broad-spectrum antibiotic therapy for 20 days. Currently, she remains under regular follow-up, with HbA1c levels ranging between 7. 6% and 8. 4%. This case underscores the complexity of managing T1DM and highlights the importance of recognizing rare complications early to minimize their impact on patients' quality of life.

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P367

JOINT190

The interplay of cortisol, trygliceride glucose index and microalbuminuria in type 2 diabetes: a prospective observational case-control study

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Background
Studies have suggested possible link between diabetic kidney disease (DKD) and cortisol levels. Relationship between DKD and triglyceride-glucose (TyG) index is currently investigating. However sole relationship between cortisol, TyG index and microalbuminuria in diabetic population is unknown. This study aims to investigate the potential association and interplay between microalbuminuria, cortisol, and TyG index in DMT2 patients.
Material and Methods
One hundred and seventy participants were enrolled in this study, comprising one hundred patients with DMT2 and seventy healthy volunteers. Anthropometric and biochemical characteristics were evaluated in all participants. Parameters measured included fasting blood glucose, HbA1c, 8h cortisol, cortisol after low-dose overnight dexamethasone suppression test (DEX cortisol), ACTH, urinary albumin-to-creatinine ratio (UACR), Trygliceride Glucose Index (TyG) (calculated as TYG = ln (fasting triglycerides × fasting glucose/2)). Microalbuminuria is defined as UACR > 30-≤ 300mg/g. Statistical analyses included correlation analysis, multiple regression, and subgroup analysis. The study protocol was approved by the Ethical Committee of the University Clinical Centre Tuzla, under the number 02-09/2-50/14.
Results
ROC analysis showed that cortisol (AUC: 0. 733, $p < 0$. 001) and TyG index (AUC: 0. 968, $p < 0$. 001) effectively discriminate between T2DM patients and controls, with optimal cut-off values of >342 for cortisol and >8. 49 for TyG. Strong correlations were found between TyG index and microalbuminuria ($r = 0$. 7463, $p < 0$. 0001) and cortisol and microalbuminuria ($r = 0$. 5151, $p < 0$. 0001), suggesting that higher levels of TyG index and cortisol are associated with more pronounced microalbuminuria. Median cortisol levels increased from 324. 0 (IQR: 233. 0–400. 0) in the normoalbuminuria group to 518. 7 (IQR: 424. 0–593. 2) in the microalbuminuria group, while the Tyg values increased from 8. 5 (IQR: 8. 2–8. 9) in normoalbuminuria to 10. 2 (IQR: 9. 8–10. 5) in microalbuminuria.

Additionally, the TYG index showed a correlation with cortisol ($r = 0.4071$, $p < 0.0001$), suggesting that higher cortisol levels are associated with higher TYG index values. We did not find a significant association of DEX cortisol and ACTH with the TyG index and microalbumin.

Conclusion

Elevated cortisol levels and the TyG index are strong predictors of microalbuminuria in patients with type 2 diabetes mellitus. Additionally, a higher TyG index is associated with higher cortisol levels. This connection is particularly important as it establishes a foundation for further research on how reducing the Tyg index may influence cortisol levels and decrease the risk of microalbuminuria.

Key-words

cortisol, TYG Index, Microalbuminuria

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P368

JOINT2224

Unveiling the spectrum of mitochondrial diabetes – a single center, multidisciplinary case series analysis

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Introduction

Mitochondrial diabetes is a rare form of adult-onset diabetes mellitus (DM) caused by mutations in mitochondrial DNA, most commonly in the MT-TL1 (m.3243ANG) genotype. It manifests clinically as Maternally Inherited Diabetes and Deafness (MIDD) or Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like episodes (MELAS). The primary abnormality causing DM is inefficient and suboptimal glucose-stimulated insulin secretion. Treatment strategies for mitochondrial diabetes remain unclear due to sparse published evidence. Metformin therapy is generally avoided due to the high risk of lactic acidosis in this population.

Aim

To better define and understand the natural history of mitochondrial diabetes.

Results

A case series analysis was conducted on 14 patients treated at a multidisciplinary MELAS clinic over the past two years. Among them, 7 patients exhibited glucose homeostasis abnormalities: 6 were diagnosed with DM and 1 with Impaired Fasting Glucose. The mean age at DM diagnosis was 36.1 years, while MELAS was diagnosed at 44.3 years. Two patients were primarily diagnosed as type 1 DM despite negative anti GAD antibodies, and four patients were classified as type 2 DM on presentation. Treatment regimens included Insulin therapy (via Insulin pump or injections), GLP-1 agonists, SGLT2 inhibitors, Sulfonylurea and lifestyle modifications. Two patients had a history of lactic acidosis secondary to Metformin use, and one patient reported a history of Diabetic Ketoacidosis. The mean HBA1C level is 7.04%. Microvascular complication were observed in three patients and included nephropathy and neuropathy, while none developed macrovascular complications. Additional comorbidities included overweight, dyslipidemia and hypertension in 3/7 patients. Other MELAS manifestations were hearing loss, stroke like events and cardiac complications in 6/7, 1/7 and 3/7 patients respectively. When compared to the 7 MELAS patients with normal glucose homeostasis, the patients with DM tended to be older (47 vs 35 years), had higher BMI (23.8 vs 17.9) and more comorbidities.

Conclusion

Mitochondrial diabetes is underrecognized, often diagnosed before MELAS, leading to potential mismanagement and complications. A multidisciplinary approach is essential to improve diagnosis, treatment, and patient outcome. Our specialized MELAS clinic provides valuable insights into the natural history and therapeutic strategies for this rare condition.

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P369

JOINT3834

Diabetic foot recurrence: a study of predictive factors

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Introduction

Diabetic foot recurrence involves lesions reappearing after completely healing, leading to serious complications like amputations and decreased quality of life. This study identifies characteristics and predictive factors for recurrence.

Patients and Methods

This is an analytical retrospective cohort study conducted among patients hospitalized in our department for diabetic foot, including those who presented a recurrence from January 2018 to December 2024. Data were analyzed using IBM SPSS Statistics 27.0.1, with chi-square and Student's t-tests used to identify significant associations with recurrence.

Results

Our study included 405 patients, 89 of whom had a recurrence (22%). The average age was 56.7 years, with 78.65% being over 50 years old. The male gender predominated with a sex ratio of 2.8.85.6% of the patients had type 2 diabetes. The average duration of diabetes was 14.35 years. The average Hba1c was 10.24%. 79% of patients were on insulin. 21.35% of cases had a history of amputation. Peripheral artery disease (PAD) was present in 46% of cases, diabetic retinopathy in 69.6%, peripheral neuropathy in 55%, and autonomic neuropathy in 28%. The average duration of progression was 72 days. 51.7% had a deformity. 40.5% of the cases had bone involvement. Statistical analysis of our sample revealed several factors significantly associated with the recurrence of diabetic foot lesions: Age over 50 ($P = 0.03$) has a notable impact on recurrence. Additionally, a longer duration of diabetes ($P = 0.019$), insulin treatment ($P = 0.02$), and glycemic imbalance ($p < 0.01$) are key factors. Complications such as peripheral artery disease (PAD) ($p < 0.01$), retinopathy ($p < 0.01$), and peripheral neuropathy ($p < 0.01$) play a crucial role. Bone involvement ($P = 0.03$), a history of amputation and deformities ($p < 0.01$) are also associated with recurrence.

Conclusion

Diabetic foot lesion recurrence is influenced by several factors, including age, duration of diabetes, treatment type, glycemic imbalance, presence of retinopathy, neuropathy, and peripheral artery disease (PAD), bone involvement, history of amputation, and foot deformity. Our study suggests that developing treatment strategies based on these factors could help prevent recurrences and improve patients' quality of life.

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P370

JOINT2297

Simulation-based education enhances healthcare professionals' confidence in managing acute diabetes scenarios

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Background

The JOINT consensus by the American Diabetes Association and the European Association for the Study of Diabetes emphasises the importance of practical and up-to-date training in acute diabetes care. Simulation via Instant Messaging for Bedside Application (SIMBA) is a Simulation-Based Learning (SBL) model that provides healthcare professionals hands-on learning for various medical conditions, including acute diabetes.

Objectives

- Measure the change in participants' confidence in managing acute diabetes post-SBL.
- Evaluate participants' satisfaction and the relevance of the intervention to clinical practice.

Methods

This mixed-methods study took place in the UK between July and October 2024. Clinical experts were interviewed to assess general needs in acute diabetes care, while students and resident doctors were interviewed to assess specific needs for focused simulation sessions. The team employed the SIMBA model to deliver SBL on nine acute diabetes-related conditions. Healthcare professionals interested in acute diabetes care were invited to participate in the session. After the session, participants were invited to post-simulation interviews to discuss their satisfaction with and perceptions of the case's relevance to clinical practice. Those who completed both pre- and post-SIMBA surveys were included in the analysis. Two independent authors performed inductive thematic analysis on the interviews.

Results
17 participants completed both pre- and post-session surveys and were included in the analysis. Confidence in managing acute diabetes scenarios improved significantly (pre- vs post-session: 33. 3% vs. 78. 4%, $P < 0.001$). All participants rated the SIMBA session as excellent or good. 94. 1% strongly agreed that the cases were relevant to their practice, and 82. 3% preferred this teaching method over traditional approaches. Post-session interviews and surveys revealed that experts and residents appreciated the benefits of simulation in promoting safer learning environments and enhancing guideline implementation. Future sessions desired by participants included antenatal and perinatal diabetic care, diabetes remission, hypoglycaemia, and perioperative diabetes care.
Conclusion
SIMBA significantly improved participants' confidence in managing acute diabetes conditions. Participants highly rated the model, which they found relevant to their clinical practice. This model shows great promise in enhancing training and education for healthcare professionals involved in acute diabetes management. Future sessions should include a broader range of acute diabetes scenarios, incorporating the wider multi-disciplinary team, to enhance holistic care for people with diabetes in the acute setting and better prepare healthcare professionals.

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P371

JOINT676

Development and validation of hba1c prediction models using CGM metrics in korean pediatric patients with type 1 diabetes: insights on average glucose and recent glycemic trends of CGM

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Introduction
HbA1c has long been used as the gold standard marker for reflecting average blood glucose levels over the previous three months. As continuous glucose monitoring (CGM) systems are becoming a part of the standard care for type 1 diabetes (T1D), there is greater recognition of the limitations of HbA1c in revealing hyperglycemia, hypoglycemia, and glycemic variability. Meanwhile, CGM metrics such as Time in Range (TIR) have emerged as important parameters for glycemic control. In this study, we aimed to explore the relationship between CGM metrics and HbA1c in Korean pediatric patients with T1D and to develop and validate the HbA1c prediction models based on different CGM metrics and time intervals.
Methods
A total of 85 children and adolescents with T1D, using CGM (G6 or G7, Dexcom, USA), were included. Twelve weeks of CGM records were analyzed to evaluate the relationship between HbA1c and CGM metrics, including TIR, Time Above Range (TAR), Time Below Range (TBR), Coefficient of Variation (CV), and Average Glucose, across time intervals of 0–2 weeks, 0–4 weeks, 4–8 weeks, 8–12 weeks, and 0–12 weeks prior to HbA1c measurement. HbA1c prediction models were developed using Ridge regression modeling and cross validation with CGM metrics as the training data set. Additionally, to assess the performance of the HbA1c prediction models, a separate test data set comprising 12-week CGM records from 80 patients was used.
Results
Average Glucose had the greatest impact on A1c across all time periods, and was identified as the most suitable metric for HbA1c prediction with higher R^2 and lower AIC values than TIR and TAR. Validation using test data confirmed that regression models based on Average Glucose demonstrated the best performance, with the lowest MSE (MSE = 0.1425) and highest R^2 ($R^2 = 0.8444$). Among time periods, the 0–4 week interval consistently had the largest coefficients, suggesting it is the most predictive of HbA1c compared to other intervals.
Conclusion
Average Glucose, TIR, and TAR are highly related with HbA1c, with Average Glucose being the most predictive metric. The 0–4 week period showed the strongest association with HbA1c changes, highlighting the importance of closely reviewing recent glycemic data, especially in the 4 weeks preceding an HbA1c test, to better understand glycemic trends and inform clinical decisions.

Keywords: Continuous glucose monitoring; CGM metrics; HbA1c; prediction modeling

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P372

JOINT2077

Challenges in transitioning from pediatric to adult diabetes care in armenia: patient experiences and systemic gaps

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Background
The transition from pediatric to adult care for patients with type 1 diabetes mellitus (T1DM) is a vulnerable period marked by gaps in care continuity and self-management. Limited data exist on patient-reported experiences in low-resource settings.
Objective
To evaluate healthcare accessibility, quality of care, self-management support, and satisfaction during transition in Armenia.
Methods
A questionnaire-based study was conducted with 60 T1DM patients (30% male, 70% female; age 18–≥22 years), stratified by disease duration (≤5, 6–10, ≥11 years) and residence (60% urban, 40% rural). A 25-item survey compared care across four domains: accessibility, quality, self-management support, and outcomes. Qualitative feedback was thematically analyzed.
Results
Accessibility: Visit frequency declined post-transition:33. 3% visited pediatric endocrinologists biannually vs. 21. 7% in adult care, while 23. 3% attended adult clinics less than annually (vs. 3. 3% pediatric). Scheduling adult appointments was harder (28. 4% vs. 10% pediatric, $P < 0.05$), and provider accessibility dropped sharply (66. 7% pediatric vs. 28. 3% adult, $P < 0.01$). **Quality of Care**: Staff knowledge was rated "excellent" by 83. 3% in pediatric vs. 23. 3% in adult care ($P < 0.01$). Discussions on mental health, nutrition, and insulin management were less frequent in adult care (85% vs. 32% for mental health, $P < 0.01$). Specialist referrals declined from 75% (pediatric) to 35% (adult, $P < 0.01$). **Self-Management Support**: Education on critical skills (insulin devices, carbohydrate counting) declined from near-universal pediatric coverage to 30–50% in adult care. Support for patient independence dropped from 86. 7% ("very supportive" pediatric) to 30% (adult, $P < 0.01$). **Outcomes**: Post-transition, only 20% had HbA1c ≤7. 4%, 11. 7% - 7. 5–8. 4%, and 25%-≥8. 5%; 43. 3% did not even check HbA1c in the past year. Hyperglycemia worsened in 52% (vs. 18% improved). **Satisfaction**: Satisfaction dropped post-transition: 88% were "very satisfied" in pediatric care vs. 25% in adult care, and 97% vs. 63% would recommend their diabetes provider. Only 20% in adult care felt their needs were "always" met.
QualitativeThemes
- **Pediatric strengths**: Family-centered care, structured and continuous education, tight monitoring and contact with diabetes providers.
- **Adult gaps**: Fragmented communication, abrupt transitions, inadequate psychosocial support.
- **Patient priorities**: Financial subsidies for glucometer strips/CGMS and empathetic providers. One participant emphasized, *"Doctors must listen and discuss, not just prescribe. "*

Conclusion
T1DM patients in Armenia face significant declines in care quality, self-management education, and provider empathy post-transition, exacerbated by financial barriers and rural disparities. Systemic reforms—gradual transition protocols, subsidized diabetes technologies, and training to foster patient-centered communication—are urgently needed to address these gaps.

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P373

JOINT1073

New criteria of 1-hour post-load plasma glucose for the diagnosis of intermediate hyperglycaemia and type 2 diabetes in adolescents

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Introduction
According to the International Diabetes Federation (IDF) Position Statement, people with a 1-h G ≥ 155 mg/dL (8. 6 mmol/l) during an oGTT are considered to

have intermediate hyperglycemia (IH) and people with a 1-h G ≥ 209 mg/dL (11. 6 mmol/l) are considered to have type 2 diabetes (T2D). There are few papers that analyze those findings in children/adolescents. The aim of this study is to analyze the oGTT response in adolescents with overweight/obesity and compare the frequency of IH according to fasting glucose, 1-h and 2-h post-load.
Methods
This study comprised 195 pubertal adolescents with overweight/obesity who underwent oGTT. They were classified into 3 groups: Group 1: Fasting glucose > 100 mg/dL, Group 2: 1-h post-load (1hG) ≥ 155 mg/dL and group 3: 2-h post-load PG (2hG) >140 mg/dL. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), and Oral Disposition Index (oDI) were calculated.
Results
A total of 195 curves were evaluated, 63 male and 132 female with a mean chronological age (SD) of 12. 5 years (2. 1). The mean zBMI and Waist-to-Height Ratio (WHtR) relation were 2. 7 kg/m^2 (0. 7) and 0. 61 (0. 06), respectively. No patient had diagnosis of T2D based on 2hG, but one patient was diagnosed as T2D after 1hG. 16 (8. 2%) patients had IFG, 10 (5. 1%) had 1hG ≥ 155 mg/dL and 8 (4. 1%) had IGT after 2hG. Compared to patients with normal oGTT, those in all 3 groups were older (P = 0. 002, 0. 022 and <0. 001, respectively), had higher HOMA-IR (P = 0. 031), but there were no differences in zBMI or waist/height ratio. Patients in groups 2 and 3, with higher 1hG and 2hG, had lower oDI value (p < 0. 05), suggesting worse β-cell function.
Conclusion
There is limited literature in adolescents indicating that an 1h post-load PG ≥ 155 mg/dL with NGT during an oGTT is highly predictive for detecting progression to T2D. However, our findings suggest worse β-cell function and that the same cut-offs could potentially be used in children/adolescents. Surprisingly, in this group of patients, the severity of obesity did not correlate with the presence of β-cell dysfunction, a fact that could be associated with duration of disease progression instead of the anthropometric parameter. Further studies are needed to confirm these findings.

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P374

JOINT2247

Causal association between diabetes and herpesvirus infections: a bidirectional two-sample mendelian randomization study

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Objective
Diabetes, marked by elevated blood sugar, raises the risk of serious health issues, including heart and nerve problems, and is linked to a variety of diseases caused by herpesviruses. This study investigates the causal associations between genetically predicted diabetes, its complications, and herpesvirus infections.
Patients
Using summary data from genome-wide association studies (GWAS) on diabetes and herpesvirus infections, the population was primarily of European descent.
Measurements
We employed a bidirectional two-sample Mendelian Randomization (MR) design. Analyses were conducted using the Inverse Variance Weighted (IVW) method, weighted median, weighted mode, and MR-Egger regression. Sensitivity analyses included MR-Egger, MR-PRESSO, Cochran's Q test, and leave-one-out analysis.
Results
Our Mendelian Randomization study revealed no significant causal association between diabetes and herpesvirus infections. The forward analysis showed odds ratios for Type 2 diabetes and herpes zoster (OR: 0. 99, 95% CI: 0. 92-1. 08, P = 0. 855) and Type 1 diabetes and infectious mononucleosis (OR: 0. 98, 95% CI: 0. 92-1. 04, P = 0. 478) that were not statistically significant. Notably, the IVW analysis showed no significant association between diabetic polyneuropathy and herpesvirus infections, the Weighted Median method suggested a marginal association with herpes zoster (OR: 1. 08, 95% CI: 1. 00-1. 17, P = 0. 05), warranting further research. The reverse analysis also demonstrated non-significant. Sensitivity analyses, including MR-Egger, weighted median, and MR-PRESSO, confirmed these findings, indicating no pleiotropy or outliers affecting the Results
Conclusions
This rigorous MR study provides evidence against a direct causal association between diabetes or its complications and herpesvirus infections, highlighting the need for further exploration into this complex association.

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P375

JOINT3570

Epidemiology of monogenic diabetes in the czech republic

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Background
Monogenic diabetes results from a single-gene defect affecting pancreatic beta cells. Accurate diagnosis enables personalized treatment. While precise European prevalence data are lacking, the U. K., a global leader in monogenic diabetes research, reports an estimated prevalence of 24. 8/100, 000 and an observed prevalence of 5. 8/100, 000. This study assessed diagnostic trends and determined the minimum prevalence of monogenic diabetes in the Czech Republic. The clinical indication criteria for genetic investigation were: positive family history of diabetes, diagnosis of diabetes up to 25 years of age, positive C-peptide and negative pancreatic autoantibodies. Since 2011, milder criteria have been used without the necessity of a positive family history of diabetes and the age of diagnosis of diabetes up to 30 years of age.
Material and Methods
Clinical and genetic data were collected from individuals suspected of having monogenic diabetes referred for genetic testing and registered in the National Registry for Monogenic Diabetes between 1999 and 2023. Covariates were analysed using the t-test, and categorical variables with $\chi 2$.
Results
By 2023, we registered 1, 879 families (i. e., probands) with suspected monogenic diabetes, and 728 (39 %) received a confirmed diagnoses (1, 473 individuals from the Registry in total). The causative variant was identified in 13 different genes, most commonly in *GCK* (69 %), *HNF1A* (15 %), and *HNF4A* (8 %). The minimum prevalence of monogenic diabetes was 13. 6/100, 000. The number of referred probands increased from 42 per year between 1999-2001 to 142 in 2023. Between 1999 and 2011, stricter clinical criteria resulted in a detection rate of 67% while milder clinical criteria for genetic testing have led to a currently stable detection rate of 30- 40%. The average age of diabetes diagnosis was 15. 5 (± 9. 4) years, with 76 % of probands having a family history of diabetes.
Conclusion
We reported an increasing referral rate and stable detection rate of monogenic diabetes in the Czech Republic. However, considering the U. K. prevalence estimates, about half of the Czech patients with monogenic diabetes remain un- or misdiagnosed. Supported by Czech Ministry of Health (NW24-01-00160)

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P376

JOINT719

Closed-loop CamAPS system shows time-specific glucose variability and hypoglycemic patterns in very young children with type 1 diabetes

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Introduction
Type 1 diabetes (T1D) incidence is increasing in very young children (i. e. under 6 years of age). Achievement of glycaemic targets in this subgroup is challenging due to their variable insulin needs, unpredictable eating habits, and activity levels. This leads to poor metabolic control and increased diabetes-related complications. Hybrid closed-loop (HCL) systems offer promising solutions to improve glycaemic outcomes. However, studies in very young children are scarce and show inconsistent results in reducing hypoglycemia and glycaemic variability. The aim of this study was to evaluate the impact of HCL on glycaemic control and more specifically the patterns of glycemic parameters throughout the day.
Materials and Methods
Data were collected from fifty children with T1D for ≥6 months who switched to HCL (CAM APS FX) before 6 years of age in two pediatric diabetes centre.

Clinical and continuous glucose monitoring (CGM) data were collected before (Pre-HCL) and at 1, 3, and 6 months post-HCL initiation. From the raw CGM data, metrics of hyperglycemia, hypoglycemia, euglycemia and glucose variability (global, intra-day and inter-day) were calculated. Comparisons between Pre-HCL and every post-HCL periods were performed using student t-tests.

Results

Time in range (TIR, 70-180mg/dL) significantly increased of 11. 9% ± 11% from 1 month after HCL ($P < 0.001$) with a concomitant decrease of target above range (TAR, >180 mg/dL) of -13% ± 13. 4% ($P < 0.01$). The improvement in glycemic control was sustained at 6 months with greatest differences observed during the night ($P < 0.001$). Hypoglycaemic episodes (< 70mg/dL and <54mg/dL) remained similar before and after HCL (all $p > 0.05$). However, hourly glycaemic patterns sustain that the morning period (7AM-1PM) was at significantly higher risk for hypoglycemia after HCL initiation with time below range (<70mg/dL) and LBGI peaking at respectively 6. 6% ± 7. 5% and 1. 5±1. 5 at 1 month compared to 1PM-7AM period ($P < 0.0001$). This risk of hypoglycaemia persisted for up to 6 months ($P < 0.01$). Finally, while the coefficient of variation remained stable at all time points ($p > 0.05$), a significant decrease in intra-day (MAGE) and inter-day glucose variability (CONGA, MODD) was observed from 1 month post-HCL (all $P < 0.05$).

Conclusion

In real life, HCL significantly improved the TIR and TAR in very young children with T1D from the first month after activation of the system. Morning time demonstrated to be a period at risk of hypoglycaemia in this age group, highlighting the importance of optimizing HCL therapy and informing parents of these specific times at risk of glycaemic instability.

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P377

JOINT3836

Comprehensive genetic testing reveals a deep intronic variant in HNF1A in a family with early-onset diabetes mellitus

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Maturity Onset Diabetes of the Young (MODY) is a form of diabetes characterized by autosomal dominant inheritance and early age at diagnosis. Pathogenic variants in HNF1A are associated with MODY3 and most of them are in the coding region. We describe the case of a patient with early-onset diabetes mellitus (DM). Comprehensive genetic testing, including whole-exome-analysis via next generation sequencing (NGS) performed due to multiple affected family members, revealed a heterozygous deep intronic variant in HNF1A, 14 years after DM diagnosis. The index patient (female, 10 years old) was admitted for further evaluation due to random hyperglycemia after a minor trauma. The girl mentioned no symptoms of polyuria, polydipsia or weight loss. At admission she had a HbA1c of 8. 1%, C-peptide was 0. 9 μg/dl and type 1 diabetes associated autoantibodies were negative. An oral glucose tolerance confirmed DM. Regarding her family history, her mother was suffering from DM since the age of 15 years and was treated at first with sulfonylureas and later on with insulin. Her maternal grandmother had kidney cysts and was suffering from DM since the age of 30 years and was treated with oral antidiabetic drugs. Three other family members from the mother's side were diagnosed with DM at a young age and were treated with sulfonylureas or insulin. None of them had a definite diagnosis regarding DM type. Sequencing of genes associated with MODY types 1-5 (incl. exon/intron boarders ± 20 bp) was performed of the index patient at diagnosis, but revealed no pathologic Results Treatment with sulfonylureas was started due to her strong family history, which was suggestive of monogenic diabetes. A good glycemic control with sulfonylureas was achieved until the age of 16 years, when HbA1c levels increased and treatment with prandial insulin injections was initiated. At the age of 18 years, targeted NGS panel including MODY types 6-14 was, also, negative. At the age of 24 years, whole-exome-sequencing via NGS and re-evaluation of the 14 MODY associated genes including deep intronic regions, revealed the heterozygous intronic variant c. 327-28A > G;p. ? in the HNF1A gene in the index patient, as well as in 4 other affected family members. The variant is absent from gnomAD and clinical databases. Expanding genetic testing, including re-evaluation for deep intronic variants, for young individuals with a strong family history of DM, non-autoimmune DM and negative routine genetic testing, is recommended as it can determine prognosis, treatment and family counseling.

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P378

JOINT2066

Cross sectional and longitudinal study of arterial stiffness in pediatric patients with type 1 diabetes mellitus (T1DM), with glycemic metrics derived from continuous glucose monitoring (CGM) devices

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Aim

To investigate early indicators of cardiovascular disease (CVD) in youths with type 1 diabetes mellitus (T1DM), focusing on pulse wave velocity (cfPWV) and augmentation index (AIx@75) and their associations with various glycemic parameters and new metrics derived from continuous glucose monitoring (CGM) systems.

Patients and Methods

The study had two parts: for the cross-sectional part, 124 youths with T1DM (58 boys, mean age: 10. 75 ± 3. 57 years and mean disease duration: 3. 09 ± 2. 91years) were assessed, whereas for the longitudinal part, 87 patients (44 boys, mean age 10. 72 ± 3. 35 years and mean disease duration: 3. 27 ± 2. 84 years at the first assessment), completed 3 visits with a six month interval. In each visit, cfPWV and AIx@75 were quantified using a validated non – invasive method, while glycemic parameters such as HbA1c, time in range (TIR), time above range (TAR) and time below range (TBR) were assessed during the last 3 months from the assessment. For the longitudinal part patients were divided in 2 groups: *TIR improvers*: patients with constantly TIR≥ 70% or constantly TIR ≥ 60% and improved by + ≥ 10% from the beginning of the study vs *TIR non-improvers* and *HbA1c improvers*: patients with constantly HbA1c ≤ 7% or constantly HbA1c ≤ 8% and improved by -≥0. 8% from the beginning vs *HbA1c non-improvers*. Univariate and multivariate linear regression were used to explore the association of cfPWV and AIx@75 with glycemic variables.

Results

In the cross-sectional study all arterial stiffness parameters were significantly correlated with systolic and diastolic blood pressure (SBP, DBP), whereas AIx@75 was negatively correlated with TIR ($r = -0.190$, $P = 0.034$) and positively correlated with TAR ($r = 0.212$, $P = 0.018$). In the longitudinal study, TIR improvers had lower PWV values ($P = 0.013$) at the 3rd assessment compared to TIR non-improvers and showed significant improvement in ΔPWV Z score according to age ($P = 0.022$) and ΔSBPindex ($P = 0.036$). Finally, no significant difference regarding arterial stiffness parameters was shown between HbA1c improvers and HbA1c non-improvers.

Conclusion

Higher AIx@75 values were significantly correlated to lower TIR and higher TAR values. Children and adolescents who had TIR in the suggested target or improved their TIR, showed significantly lower PWV values in their final assessment and significantly improved both PWV and SBP. Such a finding was not shown when HbA1c was used as a metric of glycemia, indicating TIR as a more sensitive index for CVD.

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P379

JOINT2225

Development and validation of diabetes interpreter, a mobile application-based tool for point-of-care evaluation of children with diabetes

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Background

Inappropriate classification of pediatric diabetes has significant short and long-term implications.

Aim
To develop and validate Diabetes Interpreter Application (DIA), a mobile tool for point-of-care guidance for classifying pediatric diabetes.
Methods
DIA provides suggestions for diagnosis and work-up based on clinical parameters (age at diagnosis, disease duration, presentation, and insulin requirement). The guidance of the DIA, an adult endocrinologist (AE), a senior Pediatric endocrinologist (SPE), a young pediatric endocrinologist (YPE), a pediatrician (PED), and a pediatric trainee (PT) were compared to the gold standard management and diagnosis of 302 children with diabetes (250 Type 1, 35 Type 2, six monogenic, and 11 neonatal).
Results
DIA had the highest concordance rate (score 596 out of 604, 98. 6%). The concordance score for SPE (546; 90. 4%) and YPE (491; 81. 3%) was higher than the AE (405; 67. 1%), PED (287; 47. 5%) and PT (258; 42. 7%). The proportion of correctly classified subjects with Type 1 diabetes was higher for the SPE (249, 99. 6%), DIA (247, 98. 8%), and AE (234, 93. 6%) compared to the YPE (214, 85. 6%), PED (229, 91. 6%) and PT (206, 82. 4%). Type 2 Diabetes was correctly classified by Diabetes Interpreter, YPE, AE, SPE, PED, and PT in 34 (97. 1%), 33 (94. 3%), 30 (85. 7%), 18 (51. 4%), 20 (57. 1%) and 14 (40%) subjects, respectively. The SPE classified 15 subjects (43%) with Type 2 Diabetes as Type 1 without autoimmune work-up in 5 (33. 3%). Work-up was suggested in a greater proportion of subjects not needing evaluation by PT (250, 100%), PED (245, 98%), and AE (124, 49. 6%) compared to SPE (8, 3. 2%), YPE (25, 10. 0%), and DI (3, 1. 2%). Autoimmunity work-up was not recommended in 28 (66. 7%) by the AE, 36 (85. 7%) by YPE, 11 (26. 2%) by SPE, and 1 (2. 4%) by Diabetes Interpreter where indicated.
Conclusion
The high concordance score of the Diabetes Interpreter suggests its role in point-of-care guidance for assessing children and adolescents with diabetes. Using the Diabetes Interpreter would have prevented diagnostic errors and unwarranted work-up. To the best of our knowledge, this is the first mobile application-based tool for pediatric and adolescent diabetes classification.

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P380

JOINT225

Fibrosis and severe steatosis contribute to liver dysfunction in patients with insulin resistance after hematopoietic stem cell transplantation

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Background
Hematopoietic stem cell transplantation (HSCT) survivors can develop a unique form of diabetes mellitus (DM) characterized by severe insulin resistance (IR) and dyslipidemia, despite having a non-obese body habitus. These clinical features resemble those of partial lipodystrophy (PL), and have recently been conceptualized as HSCT-associated PL. In classic PL, liver fibrosis, notably metabolic dysfunction-associated steatohepatitis (MASH), is recognized as a crucial factor determining long-term outcomes. However, few studies have investigated the hepatic status of non-obese post-HSCT patients with DM, emphasizing the need for greater understanding of their underlying pathophysiology.
Methods
We examined 20 non-obese (BMI $<$ 25) HSCT recipients at two Japanese institutions (Institute of Science Tokyo and Hiroshima University). To reduce confounding influences, we excluded patients receiving ongoing corticosteroids or immunosuppressants, as well as those with drug-induced liver injury or hepatic graft-vs-host disease (GVHD). Participants were divided into two groups: those who developed DM with IR (DM group) and those who had not yet manifested DM (DM(-) group). We compared serum markers of liver fibrosis (type IV collagen, hyaluronic acid) alongside hepatic steatosis and fibrosis scores measured by ultrasound elastography, FibroScan® (controlled attenuation parameter [CAP] and liver stiffness measurement [LSM], respectively).
Results
Between the two groups, we found no significant differences regarding age at evaluation, BMI, intensity of conditioning regimens, or serum liver fibrosis markers (type IV collagen and hyaluronic acid). However, time since HSCT was significantly longer in the DM group. Although there was no statistically significant difference in serum fibrosis markers, FibroScan® measurements revealed that both hepatic steatosis and fibrosis scores were significantly higher in the DM group. (CAP: DM group 307 [261–343. 5] dB/m vs. DM(-) group 237 [216. 5–271] dB/m, $P = 0.041$, and LSM: DM group 6. 7 [5. 9–9. 9] kPa vs. 4. 1 [3. 5–4. 7] kPa, $P = 0.007$)
Discussion
These findings suggest that non-obese HSCT survivors with DM show a pattern of hepatic steatosis and fibrosis consistent with PL. Based on our results, FibroScan® surveillance may be more sensitive than conventional serum markers for detecting early hepatic abnormalities in this population. In a certain case, liver biopsy highlighted a form of fibrosis differing from typical MASH, underscoring the need for further investigation into disease mechanisms.
Conslusion
HSCT survivors can develop not only abnormal glucose and lipid metabolism, but also hepatic dysfunction probably due to PL. FibroScan® is an effective non-invasive tool for assessing liver dysfunction in post-HSCT patients.

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P381

JOINT500

Three-year OCT/OCTA follow-up of retinal neurovasculature in pediatric type 1 diabetes

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Purpose
To investigate three-year changes in retinal neurovascular structure in children and adolescents with type 1 diabetes (T1D) without clinical diabetic retinopathy using optical coherence tomography (OCT) and OCT angiography (OCTA).
Methods
This prospective, cross-sectional, observational study included T1D patients without DR, assessed between May and September 2022 (T1D-C group). Retinal neurovascular structures in the macular and peripapillary regions were quantitatively analyzed using OCT and OCTA and compared with data collected three years prior (T1D-P group). Associations with Tanner's pubertal stage, diabetes duration, and HbA1c were assessed. Statistical significance was set at $P < 0.05$.
Results
Ninety-two eyes from 46 T1D patients were included. The T1D-C group exhibited significantly lower vessel densities(VDs) in the foveal and parafoveal superficial capillary plexuses(SCP) and deep CP(DCP) compared to the T1D-P group. Conversely, central foveal thickness, central inner retinal thickness, peripapillary retinal nerve fiber layer thickness (pRNFLT), and nasal inferior disc VD were significantly higher in the T1D-C group ($p < 0.05$ for all). Tanner's pubertal stage was significantly and negatively correlated with SCP VDs ($r = -0.345$ to -0.166, $p < 0.001$) and inferior nasal and temporal disc VDs. HbA1c and diabetes duration negatively correlated with foveal avascular zone diameter($r = -0.346$ and -0.267; respectively, $p < 0.01$) and SCP/DCP VDs ($p < 0.05$).
Conclusion
In young T1D patients, while initial peripapillary microvascular changes may be more pronounced, macular microvasculature shows significant decline over three years. Concurrently, foveal retinal thickness and pRNFLT increase. These findings highlight the importance of longitudinal monitoring of retinal neurovascular structure in young T1D patients, even in the absence of clinical DR.

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P382

JOINT2440

Factors affecting caregiver burden in families of children with type 1 diabetes

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Introduction
Managing type 1 diabetes (T1D) in childhood imposes significant burdens on families, influenced by factors such as the child's age, diabetes duration, glycemic control, and use of technologies like insulin pumps and continuous glucose monitors (CGMs). Caregiver burden in families of children with T1D has not been sufficiently explored. This study evaluates caregiver burden and its relationship with these factors.
Methods
This cross-sectional study included 100 children with T1D from a single pediatric endocrinology clinic. Demographic, clinical, and laboratory data were collected. The Zarit Burden Interview (ZBI) assessed caregiver burden across four subcategories: demands of care and social impact, control over the situation, psychological impact, and worry about caregiving performance. Participants were divided into three groups: non-users of diabetes technologies, CGM users, and insulin pump users. Statistical analyses were conducted using non-parametric tests.
Results
Among the children, 48% were girls ($n = 48$) and 52% were boys ($n = 52$), with a mean age of 12. 2 ± 4. 1 years (range: 2. 5–18. 3 years). The mean age at diagnosis was 7. 4 ± 3. 9 years, and the mean duration of diabetes was 4. 9 ± 3. 8 years. Of the participants, 32% were prepubertal, and 68% were pubertal. Regarding technology use, 44% did not use technology, 43% used CGMs, and 13% used insulin pumps. Mothers constituted the majority of primary caregivers (90%). The mean ZBI total score was 24. 8 ± 14. 2, indicating mild to moderate burden. No statistically significant differences were found in total caregiver burden or its subcategories based on gender or pubertal status ($p > 0.05$). Correlation analyses revealed no significant relationship between diabetes duration and caregiver burden ($r = -0.03$, $P = 0.774$). However, a significant negative correlation was observed between the child's age and total caregiver burden ($r = -0.2$, $P = 0.018$), as well as between age and caregiving demands and social life impact ($r = -0.3$, $P = 0.007$). No significant correlation was found between HbA1c levels and caregiver burden ($r = 0.1$, $P = 0.259$). Caregivers of children using diabetes technologies reported significantly lower total burdens compared to non-users ($P = 0.001$), with no notable differences between CGM and insulin pump users ($P = 0.954$).
Conclusion
Diabetes technologies were associated with reduced caregiver burden. Families of older children experienced less burden, while diabetes duration had no significant effect. Improving access to diabetes technologies and developing support strategies, especially for families with younger children, is essential.

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P383

JOINT260

Omnipod5 real-world data from the first paediatric users universal coverage under the united kingdom national health service

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Background
Hybrid closed-loop (HCL) systems combine continuous glucose monitoring (CGM) with insulin pumps to automate insulin delivery through specific algorithms and user input. The recent updated UK NICE Technology Appraisal (TA943) on HCLs for T1D was published in December 2023. It advocates for widespread National Health Service (NHS) adoption and access to these systems for all children with T1D. This represents a significant and positive move towards universal health accessibility to advanced diabetes technologies. The Omnipod 5 system (OP5) by Insulet Corp. is a tubeless automated insulin delivery system, and as of June 2023, was the latest HCL system to be introduced in the United Kingdom (UK). This real-world study aimed to evaluate the effectiveness of the Omnipod5 HCL system on HbA1c, time-in-range (TIR), hypoglycaemia frequency, and sensor glucose variability over 3 and 6 months in children and young people with type 1 diabetes at two NHS-funded paediatric diabetes centres in the North West of England.
Methods
Children under 18 years of age in two teaching hospital-based diabetes centres were started on Omnipod5 between August 2023 and January 2024. Sensor glucose metrics and HbA1c were collected within 3 months prior to Omnipod5 initiation and compared at 3 and 6 months post-initiation. Metrics included %TIR (sensor glucose 3. 9–10. 0 mmol/l), time above range (TAR) (sensor glucose $>$ 10. 0 mmol/l and $>$13. 9 mmol/l), and time below range (TBR) (sensor glucose $<$3. 9 mmol/l and $<$3. 0 mmol/l), with variability assessed by coefficient of variation (CV) and standard deviation (SD).
Results
A total of 144 children were included, with 46% males and a mean age of 7. 1 years (SD 4. 3). The cohort was predominantly white (80%), with diabetes duration averaging 4. 4 years (SD 3. 9). Prior to Omnipod5, 54% used multiple daily injections, 41% a non-integrated pump, and 5% another HCL system. At 3 and 6 months post-initiation, there were significant improvements in HbA1c (from 60. 2 mmol/mol to 54. 4 mmol/mol at 3 months, and 55. 2 mmol/mol at 6 months), TIR (from 53. 3% at baseline to 67. 4% at 3 months and 68. 8% at 6 months), and reductions in TAR and CV.
Conclusions
These findings highlight the Omnipod5 system's safety and effectiveness in improving glycaemic control for CYP with T1D in a real-world NHS setting. Further research is needed to explore the long-term benefits and cost-effectiveness of this tubeless HCL system in routine clinical care.

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P384

JOINT2249

Navigating complexity and challenges in managing type 1 diabetes in children with neurodiverse diagnoses – a qualitative study

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Background
Managing type 1 diabetes (T1D) in children with neurodiversity presents unique challenges. This population often faces difficulties with communication, sensory sensitivities, and adherence to complex medical regimens meaning that management of chronic disease can be difficult. These challenges are further compounded by variations in cognitive abilities and social understanding, requiring tailored strategies for effective diabetes care. However, they have also had to overcome significant barriers in day-to-day life and education and this resilience may help in self-management of complex management of T1D. We explore the impact of neurodiversity on diabetes self-management and caregiving dynamics, aiming to highlight evidence-based interventions, the importance of interdisciplinary collaboration, and the role of assistive technologies. Co-morbidity of autism spectrum disorder and T1D has been shown to have poorer outcomes of diabetic control, but there is little evidence available on how these patients show resilience in managing their diabetes and what challenges they face.
Methods
This qualitative study explores the lived experiences of children with co-occurring neurodiverse diagnosis and T1D, alongside their primary caregivers. We completed semi-structured interviews with 10 adolescents and parents to understand the unique barriers and how these families have shown resilience in managing these dual conditions. The interviews focussed on diabetes education, the interplay between neurodiversity and diabetes, diabetes technologies, personal management and transition, and the impact on daily life.
Results
Thematic analysis revealed five key themes: management and fear of hypoglycaemia, worries regarding future planning and transition, use of diabetes technology, sleep, and support structures and relationships. Both patients and their caregivers noted that diabetes technology, including continuous glucose monitoring (CGM), reduced anxiety and improved sleep quality. Patients also highlighted that they did not feel that their neurodiverse diagnoses impacted on their management of T1D. Families also recognised that there was a lack of general resources covering neurodiversity and T1D.
Conclusion
We have highlighted the resilience that families demonstrate in managing T1D alongside neurodiversity. This study underscores the need for personalised, neurodiversity-affirming care models that integrate behavioural strategies and caregiver training to optimise health outcomes. The findings highlight the importance of fostering collaborative care frameworks to address the dual

demands of neurodiversity and T1D, promoting improved quality of life for both children and their families.

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P385

JOINT2128

A longitudinal analysis of the impact of alarmed sensors on anxiety, depression, sleep quality, quality of life and treatment satisfaction in patients with type 1 diabetes

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Introduction
Type 1 diabetes mellitus (T1DM) plays an important role on living standards in affected patients. The use of technologies has been shown to have important benefits on glycemic compensation, but studies regarding the impact on psychosocial indicators are currently limited in the literature.
Aim
To dynamically observe in a population of T1DM patients how living standards change in relation to new technology upgrades and clinical parameters
Subjects and Methods
In this longitudinal analytical study, the following questionnaires were administered to 143 patients with T1DM: Hospital Anxiety and Depression Scale (HADS), Pittsburgh Sleep Quality Index (PSQI), Diabetes Treatment Satisfaction Questionnaire (DTSQ), Diabetes Distress Scale (DDS), and Diabetes Quality of Life (DQOL). In the HADS scale, specifically, 3 categories were assigned: normal, borderline or pathological. The number of patients changing their category was considered as the primary endpoint. Questionnaires were collected at the Endocrinology Unit of IRCCS S. Orsola in April 2021 and then 3 years later in September 2024.
Results
The cohort enrolled in 2021 consisted of 77 men and 66 women: mean age 45 ± 14 years, HbA1c 56 ± 11 mmol/mol. During the period from 2021 to 2024, 83 patients switched from capillary glycemic monitoring to the use of a sensor equipped with low and high glucose alarms, 37 remained on capillary, and 23 maintained a sensor associated with or without a pump. A statistically significant improvement in HbA1c (57. 6 ± 10. 4 vs 56 ± 13 mmol/mol, $p < 0.001$) and TBR (3. 2 ± 4. 2 vs 1. 62 ± 1. 59%, $P = 0.009$) was confirmed in the cohort who had an alarmed sensor at 3 years. In the subgroup that upgraded to an alarmed sensor, there was no significant change in the degree of anxiety ($P = 0.780$), or depression ($P = 0.158$) on the HADS scale, nor a significant worsening of the PSQI sleep quality score ($P = 0.667$) and disease-related distress ($P = 0.831$), in contrast to treatment satisfaction, which instead appeared to be significantly reduced compared to baseline (26. 9 ± 5. 5 vs 28. 7 ± 4. 8, $P = 0.008$). Similar situation occurred for quality of life, which was found to be worse (30. 5 vs 30. 1, $P = 0.012$)
Conclusions
In individuals with type 1 diabetes, the introduction of sensors equipped with alarms seems likely to improve glucometabolic compensation and prevent hypoglycemia without leading to a deterioration in anxiety, depression, and sleep quality status, whereas it may worsen satisfaction with care and quality of life.

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P386

JOINT1800

The trend in hospitalizations for diabetes mellitus in brazilian children under 10 years of age: an analysis from 2013 to 2023

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Introduction
Brazil occupies the third position both in the ranking of countries with the highest healthcare expenses related to Diabetes Mellitus (DM) and in an estimated number of prevalent cases of DM1, totaling 92, 300 diabetics aged 0 to 19 years. This scenario results in numerous annual hospitalizations due to complications such as diabetic ketoacidosis. This study aimed to determine the temporal trend of hospitalizations due to DM in Brazilians aged less than 10 years from 2013 to 2023.
Methods
This is an epidemiological, descriptive, and retrospective study with a quantitative approach to reported cases of hospitalizations for Diabetes Mellitus in children aged 0 to 9 years in Brazil. Data was obtained from the SUS Hospital Admissions System (SIH/SUS) and accessed electronically on the portal of the Department of Information of the Unified Health System (DATASUS) of the Ministry of Health. Hospitalization rates were calculated as expressed per 100, 000 inhabitants. For the temporal trend, raw hospitalization and population data per year were imported into the Joinpoint regression program version 5. 1. 0. 0., calculating the annual percentage change (APC) and the confidence interval (95% CI).
Results
In the analyzed period, 32, 184 hospitalizations due to DM were reported in children aged 0 to 9 years, with an annual average of 2, 925. 82. The trend of hospitalizations proved to be increasing, with an APC of 3. 38 (95%CI: 2. 30;4. 39; $P < 0.001$). From 2013 to 2019, there was a stationary trend, with APC = 1. 3% (95%CI: -2, 89;2. 78; $P = 0.41$), and from 2019 to 2023, an increasing trend was observed, with APC = 6. 58% (95%CI: 4. 08;12. 18; $P < 0.001$). The highest number of hospitalizations occurred in mixed-race female children aged 5 to 9 years in the Southeast region. The highest hospitalization rates were seen in the Central-West, South, and Southeast regions, respectively.
Conclusion
We observed high rates of hospitalization in the period analyzed for DM in children under 10 years of age, with an increasing temporal trend after 2019. This epidemiological profile agrees with the international literature that shows a significant increase in DM diagnoses after the COVID-19 pandemic. 19. Hospitalizations of northern, indigenous, and elective children were the minority. There is limited data regarding children with Diabetes in Brazil, highlighting the importance of more epidemiological studies to direct care and resources to groups at higher risk of hospitalization.

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P387

JOINT2245

A novel GCK gene variant causing juvenile-onset adult-type diabetes in a family is reported for the first time

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Adult-onset diabetes mellitus (MODY) in adolescents represents a distinct category of autosomal dominant inherited monogenic diabetes disorders. It typically exhibits a subclinical onset and is characterized by clinical manifestations such as family-based, mild, and non-progressive fasting glucose hyperglycemia. Unfortunately, due to its relatively subtle and atypical features, it is often prone to misdiagnosis and excessive treatment. This report meticulously delineates a freshly diagnosed case of MODY that was triggered by a variant in the glucokinase (GCK) gene, specifically identified as p. A379L. The proband manifested the disease during adolescence, presenting with mild impairment in fasting glucose levels, negative insulin antibodies, and a moderately compromised pancreatic function. Intriguingly, both the proband and his father were found to carry a heterozygous variant in the ninth exon of the GCK gene at the genomic location of Chr7:44145614. Both of them maintained normal blood sugar levels through diet and health management. The GCK gene variant p. A379L was identified as the main pathogenic gene in this MODY2 family, which is the first report of its kind both at home and abroad.

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P388

JOINT409

Depressive symptoms in youths with diabetes mellitus and their associating factors: an observational study in a single centre in hong kong

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Objectives
Paediatric diabetes mellitus is of increasing prevalence over the past decade worldwide. It is a life-long endocrine illness that poses both physical and psychogical burdens to our affected youths. Up to 14% of youths with diabetes reported at least mildly depressed mood. Mental health screening in these

individuals, is therefore a standard of medical care in diabetes according to latest recommendations. Regular screening allows early identification of patients who are at risk of depression, and timely psychological intervention can lead to better diabetic control and overall well-being in these patients. The aim of our study is to evaluate the prevalence and severity of depressive symptoms in paediatric patients with diabetes mellitus, and identify factors associated with the development of depressive symptoms.
Research Design and Method
The Patient Health Questionnaire-9 (PHQ-9), a validated and efficacious self-reported tool recommended by the American Diabetes Association (ADA) and the U. S. Preventive Services Task Force (USPSTF) for screening depression, was completed by 90 paediatric patients with diabetes mellitus from year 2020- 2022 who received regular follow up in our hospital. Data including demographics and characteristics of patients were collected and analysed.
Results
Sixteen out of 90 patients (17. 8%, 95% CI: 9. 9%- 25. 7%) reported moderate or above severity of depressive symptoms as defined by a PHQ-9 score $\geq$10. 13. 7% and 12. 2% of patients had a PHQ-9 score $\geq$10 in year 2021 and 2022 respectively, compared to none in year 2020. Higher body mass index (BMI) (P=0. 048), presence of diabetic-related complications (P = 0. 049), greater number of hospital admissions related to poor diabetic control (P = 0. 003), poor family dynamics with parental marital conflicts (P = 0. 002) and parent-child relationship problems (P < 0. 001), known psychological or behavioural problems (P < 0. 001) were identified as factors associated with increased risk for developing depressive symptoms. Patients who used continuous glucose monitoring system (CGMS) (P = 0. 014) and had more frequent blood sugar monitoring (P = 0. 002) were associated with less risk for developing depressive symptoms. A higher haemoglobin A1c (HbA1c) value (P = 0. 023) was found to be positively related to depressive symptoms in the subgroup analysis for patients with type 1 diabetes mellitus but not type 2.
Conclusion
Depressive symptoms are common in youths with diabetes mellitus. Regular mental health screening by using a validated self-reported questionnaire is a cost-effective and reliable method that should be advocated in all eligible patients.

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P389

JOINT1814

Twenty-four hours glycemic profile of women with early gestational diabetes mellitus

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Introduction
Traditionally GDM has been diagnosed as hyperglycemia in 24-28 weeks of gestation. Glucose abnormalities seen before this period were attributed to pre-existing or undetected diabetes. However, the HAPO study has changed this understanding, recognizing that any degree of hyperglycemia at any gestational age can increase the risk of adverse outcomes for the mother, fetus, and newborn. Early GDM (eGDM) occurring before 20 weeks of gestation, likely represents an intermediate state between normal glucose metabolism and prediabetes/diabetes outside of pregnancy. The clinical impacts of eGDM are still debatable.
Materials & Methods
All eligible patients diagnosed with early GDM according to the World Health Organization (WHO 2013) criteria were prospectively followed after the placement of the Freestyle Libre Pro CGMS on the day of diagnosis between September 2021 and May 2023. The 24-hour glycemic profile of women with eGDM was compared with that of age- and gestational-age-matched normoglycemic pregnant women.
Results
Thirty-nine early GDM patients whose mean age was 29. 4 $\pm$ 2. 4 years with a gestational age of 12. 9$\pm$4. 2 weeks and 113 pregnant women with normoglycemia whose mean age was 27. 6 $\pm$ 3. 8 years and gestational age of 13. 4$\pm$4. 5 weeks were enrolled in the study. Glycemic variability indices like standard deviation of blood glucose, J index, and mean amplitude of glycemic excursions were also significantly higher in eGDM patients. Women with eGDM showed a similar "time in range"(93. 4% vs. 89. 1%, p=. 73) and a considerably higher "time above range"(2% vs. vs1. 7%, p=<0. 05) compared to those with normoglycemia. While in most cases glycemic targets could be achieved with lifestyle interventions, 2 out of 39 patients (5%) required insulin therapy. Forty-three percent of women with eGDM had a normal vaginal delivery, 23% experienced neonatal complications, and 10% had macrosomia. Maternal and fetal outcomes differed significantly between the early GDM and normoglycemia groups.

Comparison of CGMS parameters

Parameters	Early GDM (39)	Normoglycemia (113)	P value
Fasting Glucose (mg/dl)	79. 9$\pm$9. 9	73. 8$\pm$8. 9	0. 004
Premeal Glucose(mg/dl)	81. 5$\pm$9. 2	74. 8$\pm$8. 1	0. 001
1hr Post meal Glucose(mg/dl)	101. 8$\pm$17. 4	94. 8$\pm$12. 7	0. 031
2hr Post meal Glucose(mg/dl)	91. 2$\pm$13. 4	84. 1$\pm$10. 2	0. 006
24hr Glucose(mg/dl)	91. 9$\pm$10. 8	84. 1$\pm$8. 7	0. 002
Day time Glucose(mg/dl)	95. 2$\pm$11. 3	86. 1$\pm$10. 1	0. 001
Nocturnal Glucose(mg/dl)	83. 7$\pm$12. 2	78. 2$\pm$10. 1	0. 041

Conclusion
Women with early GDM, despite mild hyperglycemia, exhibit abnormal glycemic patterns on CGMS and higher rates of macrosomia and neonatal complications in a South Asian population, though the small sample size in the eGDM group remains a limitation.

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P390

JOINT2633

Association between serum lipid profile and glycemic control in adolescents with newly diagnosed type 2 diabetes: a single center study

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Background
Worldwide prevalence of young onset type 2 diabetes (DM) is showing an increasing trend with the increase in prevalence of pediatric obesity. The prevalence of type 2 diabetes in young Korean population have reached more than 4. 4-fold when compared with the early 2000s. The aim of this study is to investigate factors associated with glycemic control in adolescents with type 2 diabetes to reduce the risk of complications.
Method
Data from adolescents aged 10–19 years who were newly diagnosed with type 2 diabetes mellitus from 2014 to 2023 and had at least one year of follow-up at Korea University Hospital were analyzed. The study compared trends in glycemic control and associated factors, including the patients' metabolic profile. Patients were classified into good and poor glycemic control groups based on HbA1c in which good glycemic control is HbA1c$\leq$7. 0% and poor glycemic control is HbA1c greater than 7. 0% in addition to those with subcutaneous(SC) insulin injection. Each group were further analyzed for differences in clinical characteristics and laboratory findings
Results
Total of 134 adolescents were newly diagnosed as type 2 DM over 10 years at Korea University Hospital, with mean age of 14. 4$\pm$1. 9 years and mean Body Mass Index of 27. 8$\pm$5. 5 kg/m2. Mean HbA1c at diagnosis was 10. 6$\pm$2. 6% and 81(60. 5%) patients required SC insulin combined with PO medication as initial treatment. Among 93 patients with follow-up duration of 2 years, 47(50. 5%) patients manifested good glycemic control with mean HbA1c of 5. 9$\pm$0. 5 and 46(49. 5%) patients had poor glycemic control with mean HbA1c of 8. 6$\pm$2. 5%. Patients with poor glycemic control at 2 years had higher AST/ALT, LDL cholesterol, and triglyceride compared with patients with good glycemic control(P < 0. 05). Total of 40 patients required SC insulin injection up to 2 years from diagnosis, and their SPISE index at 2 year was significantly lower than patients treated with PO medication alone or without any medication (4. 8($\pm$1. 3) vs 6. 1($\pm$2. 1), P < 0. 05).
Conclusion
Newly diagnosed type 2 diabetic adolescents showed poor glycemic control at 2 years from diagnosis and presented with metabolic problems confirmed by laboratory Results Close monitoring and proper management of lipid profile as well as glucose level is required to achieve good glycemic control in pediatric type 2 DM patients.

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P391

JOINT632

Fasting blood glucose as predictor in achieving glycemic control among patients with gestational diabetes mellitus on non-pharmacologic therapy: a retrospective cohort study

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Background
Gestational diabetes mellitus (GDM) is associated with adverse maternal and neonatal outcomes. There is currently no uniform guidelines for the management of GDM and the observation period when to progress from non-pharmacologic to pharmacologic treatment varies. This will lead to a delay in initiation of a definitive therapy which will probably increase risk of complication from GDM. This study aims to investigate the association between fasting blood glucose at diagnosis of GDM and glycemic control based on self-monitoring blood glucose (SMBG) after 2 weeks of non-pharmacologic therapy.
Methodology
We conducted a single-center observational retrospective cohort study of patients with GDM at Ospital ng Makati (OsMak) from 2013-2023. Included were patients with fasting blood sugar (FBS) values of 92-125 mg/dL who had their prenatal visits and delivery at OsMak. Medical records were reviewed and the following data were collected: current age, weight, height, BMI on initial prenatal visit, comorbidities such as hypertension, diabetes mellitus, autoimmune diseases (SLE, APAS) and obstetric history. FBS at initial visit or at 24-28 weeks AOG and SMBG values were recorded. Subsequent mode of therapy, either non-pharmacologic or pharmacologic, was assessed.
Results
We included a total of 112 patients with GDM in the study. 50% (95% CI: 40. 4-59. 6%) achieved glycemic control through non-pharmacologic therapy. There was no significant difference between the two groups (glycemic control achieved vs not achieved) in any of the variables except for FBS at the time of GDM diagnosis. Median FBS was significantly higher in patients who did not achieve glycemic control than those who did. Patients with FBS at GDM diagnosis of $>$ 99 mg/dl had about 23 times higher odds of non-achievement of glycemic control than those with FBS of $\leq$99 mg/dl.
Conclusion
The result of this study demonstrates that FBS at GDM diagnosis was significantly associated with glycemic control and showed excellent discriminative ability with a sensitivity of 87. 50% and specificity of 76. 79 %. Patients with FBS at GDM diagnosis of $>$99 mg/dl had about 23 times higher odds of non-achievement of glycemic control than those with FBS of $\leq$99 mg/dl.
Keywords: "gestational diabetes mellitus", "fasting blood sugar", "glycemic control"

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P392

JOINT3683

Association between genetic variants of SLC30A8, CDKAL1 and HHEX and increased risk of gestational diabetes mellitus: implications for early detection and personalized management

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Gestational Diabetes Mellitus (GDM) is a common pregnancy-related condition, affecting 14. 2% of women worldwide and 12. 2% in Europe. It increases the risk of long-term complications for both mother and child, including cardiovascular disease, obesity, and type 2 diabetes (T2D). Early diagnosis and appropriate management are crucial in minimizing these risks. Although the exact causes of GDM remain unclear, it is linked to insufficient insulin production and an inability to counteract pregnancy-induced insulin resistance. Genetic factors are increasingly recognized as contributors to GDM development. Variants in *SLC30A8* (rs13266634, rs11558471) and *CDKAL1* (rs10946398) have been associated with alterations in insulin secretion, beta-cell function, and glucose regulation. Additionally, SNPs near genes responsible for pancreatic development, such as rs1111875, rs5015480, and rs7923837 in *HHEX*, have been linked to an increased risk of GDM in several studies. This study investigates the association between the SNPs mentioned above and the risk of GDM in the Polish population and evaluates their impact on phenotypic traits using mathematical indices of insulin resistance (HOMA-IR), insulin sensitivity (Matsuda index), and beta-cell function (IGI, DI30, DI120, and AUC-based indices), calculated from a four-point glucose tolerance test. A total of 104 women diagnosed with GDM and 372 normoglycemic controls (NGT) were included in the study. Women with GDM exhibited higher glucose levels, greater insulin resistance (HOMA-IR), and reduced indices of beta-cell function ($P < 0.0001$). GDM was significantly associated with *SLC30A8* polymorphisms in both the dominant model (rs13266634: OR 1. 63 [1. 04-2. 53], rs11558471: OR 2. 02 [1. 28-3. 16]) and the allelic model (OR 1. 47 [1. 03-2. 09] and OR 1. 68 [1. 17-2. 41]). Additionally, rs10946398 in *CDKAL1* showed an association with GDM in both the genotypic (OR 1. 77 [1. 1-2. 83]) and allelic models (OR 1. 4 [1. 02-1. 91]) ($P < 0.05$). Carriers of the risk genotypes exhibited higher glucose levels and impaired insulin secretion in response to glucose, as reflected by the disposition index (DI), ΔAUCins/glc, and reduced beta-cell function (IGI index) across the study population ($P < 0.05$). This study confirms the association between *SLC30A8* and *CDKAL1* polymorphisms and an increased risk of GDM. Carriers of risk genotypes exhibited higher glucose levels and impaired beta-cell function, indicating a genetic influence on glucose metabolism during pregnancy. Identifying these SNPs could aid in early detection of GDM, enabling personalized management strategies to improve maternal and fetal outcomes and reduce the long-term risk of type 2 diabetes. These findings support the potential clinical use of genetic testing to identify high-risk individuals and implement targeted interventions.

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P393

JOINT2416

Performance of an algorithms predicting mortality in medical vs surgical patient with diabetes

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Introduction
Patients with diabetes have an increased risk of hospital complications including complications related to surgical treatment. Computer-based early warning systems (EWS) implemented in the hospital wards can identify patients at risk of deterioration, and trigger lifesaving interventions. In general, these systems often perform differently in subpopulations of patients. There is also concern with risk factors associated with chronic conditions that are usually not part of the variables used by these algorithms. We present preliminary data of the performance of an EWS in the general hospital wards in patients with diabetes assigned to medical vs surgical treatment.
Methods
Adult ($\geq$18 y-o) patients with diagnosis of diabetes, hospitalized in general wards were grouped based on medical vs. surgical treatment. We collected EWS scores generated every 15 min during the entire hospitalization. The scores estimated the probability of total mortality on scale 0 to 100. We compared the distributions of the Highest Score (at any time during the hospitalization) and calculated diagnostic accuracy using a cutoff of $\geq$60.
Results
There were 15, 727 patients with diabetes, 10, 234 in the medical group (age mean(SD) 68. 8(13. 9) years; female 44%; length of stay 5. 0(5. 7) days) and 5, 493 in the surgical group (age mean(SD) 67(12. 7) years; female 40%; length of stay 6. 3(8. 9) days). Hospital mortality in the medical vs. surgical group was 88 (0. 86%) vs. 6 (0. 1%). Using a score of $\geq$60 to predict mortality, the model had an accuracy in the medical group of 85% (95%CI: 84. 44 to 85. 83) and Sens 89. 78%, Spec 85. 11%, PPV 4. 97% and NPV 99. 9%. In the surgical group the accuracy was 81. 83% (95%CI: 80. 79 to 82. 84) and Sens 66. 67%, Spec 81. 85%, PPV 0. 40% and NPV 99. 96%.
Conclusion
The performance of the EWS model predicting mortality was different among patients with diabetes admitted for medical vs. surgical treatment. The overall accuracy of the model is statistically better in the medical group with Sens and Spec above 85%; while in the surgical group the Sens is quite low at 66%. The NPV in both groups is clinically relevant at more than 99%, but the PPV is extremely low. The difference among these subpopulations should be validated with other EWS and should be considered when using the predictions of these models in medical decision making. Our results should be interpreted cautiously, given they are from a single institution with a fairly low prevalence of adverse events including hospital mortality.

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P394

JOINT764

Weight stigma in pediatric type 1 diabetes: evaluating patient level factors and diabetes related outcomes

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Background
Weight stigma is defined as discrimination based on weight and body size and is well-documented among adults and children. Individuals who experience weight stigma are at risk of adverse physical and mental health outcomes. To our knowledge, there are no studies evaluating weight stigma in the pediatric Type 1 diabetes (T1D) population despite weight often being reviewed and discussed in diabetes clinic follow-ups.
Objective
Our study aimed to evaluate the prevalence of weight stigma in our pediatric □OBJT1D population and to identify any patient level factors associated with higher prevalence of weight stigma. We also aimed to determine if weight stigma is associated with poorer diabetes related health outcomes and increased diabetes distress.
Methods
A cross-sectional study was conducted among pediatric patients at BC Children's Hospital. Participants completed questionnaires that included experienced weight stigma (EWS), weight bias internalization scale (WBIS), weight self-stigma questionnaire (WSSQ), modified brief illness perception questionnaire (BIPQ) and diabetes distress scale (DDS). Data was extracted from the BC pediatric diabetes registry and chart review to gather patient level data and outcomes. Descriptive statistics and logistic regression analysis were used to analyze the data.
Results
There were a total of □OBJ□95 participants with a response rate of 30. 6%. The prevalence of experienced weight stigma was found to be 19. 4%, of which 20% identified family members to be the leading source of stigma. Of the participants endorsing weight stigma, 28. 5% scored high for weight self stigma, and 57. 1% scored high for internalized weight stigma. Female sex was found to be associated with weight stigma(P-value <0.05). Participants experiencing weight stigma had higher diabetes distress ($p<0.001$), and presented a non-significant trend towards increased residential instability (OR 1. 46, 95%CI 0. 98-2. 17), and higher A1c (OR 1. 34, 95%CI 0. 98-1. 84).
Discussion
In our institution, we identified 1 in 5 youth living with T1D experience weight stigma. Factors associated with weight stigma are female sex with a trend towards residential instability and higher A1c. As families and peers are key contributors to stigma, these findings underscore the importance of adopting a sensitive approach to discussions about weight in pediatric diabetes clinic. Given the complex interplay of obesity, weight stigma and diabetes management, this remains an important area research for developing interventions in clinical care.

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P395

JOINT3696

Levels of antioxidants and oxidizing agents in patients with different types of diabetes mellitus – a serum biomarker assessment

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Introduction
Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia and oxidative stress.
Objective
This study aimed to evaluate oxidative stress by assessing lipid peroxidation through the thiobarbituric acid reaction with malondialdehyde (MDA) and the plasma antioxidant capacity (FRAP) in patients with type 1 and type 2 DM. Correlations with other biomarkers were examined.
Methods
Serum samples were collected from 67 individuals, categorized into three groups: type 1 DM ($n=21$), type 2 DM ($n=32$), and non-DM controls ($n=14$) matched for age, sex, and body mass index (BMI), defined according to the 2022 American Diabetes Association guidelines. The MDA index was determined photometrically by measuring lipid peroxidation at 530 nm. Plasma FRAP levels were assessed based on the reduction of the Fe^{3+}-TPTZ complex to Fe^{2+}-TPTZ, measured at 593 nm. Statistical analysis was conducted using SPSS statistical software, version 26.
Results
The study included 67 participants: non-DM ($n=14$, 20. 9%), type 1 DM ($n=21$, 31. 3%), and type 2 DM ($n=32$, 47. 8%). The median age (min-max) in years was 41 (21–44) for non-DM, 47 (19–64) for type 1 DM patients and 43. 50 (21–66) for type 2 DM patients. Median BMI (min-max) in kg/m^2 was significantly higher in type 2 DM: 26 (21. 50–31. 60) compared to non-DM: 23. 50 (21. 30–26. 00), $p<0.001$ and type 1 DM: 25. 1 (17. 70–32. 70), $P=0.001$. The glycated hemoglobin (HbA1c) levels were significantly higher in patients with DM (Type 1: 7. 20%, 6. 30–11. 40; Type 2: 9. 70%, 5. 40–14. 00) compared to non-diabetics (5. 20%, 4. 90–5. 50, $p<0.001$). Triglycerides levels were significantly elevated in type 2 DM (89. 00 mg/dL, 72. 00–106. 00) compared to non-DM (61. 00 mg/dL, 56. 00–231. 00, $p<0.001$). No significant differences were observed in total cholesterol, HDL, LDL, uric acid, C-reactive protein (CRP), ferric reducing ability of plasma (FRAP), or thiobarbituric acid (TBA)/malondialdehyde (MDA) levels. Correlation analysis revealed significant associations between FRAP and triglycerides in type 1 DM ($r=0.600$, $P=0.011$) and between CRP and FRAP in type 2 DM ($r=0.380$, $P=0.042$).
Conclusion
Significant correlations between FRAP and triglycerides in type 1 DM and between CRP and FRAP in type 2 DM highlight the role of oxidative stress, lipid metabolism, and inflammation in diabetes progression. Monitoring oxidative stress markers alongside metabolic parameters may enhance our understanding of diabetes-related complications, aiding in targeted interventions.

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P396

JOINT101

Efficacy of frequency rhythmic electrical modulated system (FREMS) in the treatment of diabetic neuropathy: a systematic review and meta-analysis of randomized controlled trials

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Background
Painful diabetic peripheral neuropathy (DPN) is a debilitating complication of diabetes with limited therapeutic options. Frequency Rhythmic Electrical Modulation System (FREMS), a non-invasive electrotherapy, has shown potential in managing the symptoms. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) on FREMS for symptomatic DPN.
Methods
Databases, including PubMed, Scopus, and Embase, were searched until October 2024. Studies involving adults with DPN comparing FREMS with placebo were included. Data on Visual Analog Scale (VAS) scores and nerve conduction were extracted. Standardized mean differences (SMDs) with 95% confidence intervals (CIs) were pooled using random-effects models. Risk of bias was assessed using RoB 2. Heterogeneity was quantified via I^2 statistics, with sensitivity analyses and publication bias evaluation.
Results
Five RCTs (302 participants) were included. FREMS significantly reduced daytime VAS pain scores post-treatment (SMD -0. 56, 95% CI -0. 82 to -0. 29, $I^2=4\%$) and at follow-up (SMD -0. 47, 95% CI -0. 73 to -0. 21, $I^2=0\%$). Nighttime VAS pain scores also improved post-treatment (SMD -0. 54, 95% CI -0. 80 to -0. 27, $I^2=44\%$) and at follow-up (SMD -0. 38, 95% CI -0. 65 to -0. 12, $I^2=1\%$). FREMS improved motor nerve conduction but showed no effect on sensory conduction or microvascular blood flow.

Conclusion
FREMS is effective in reducing DPN pain with sustained benefits and a favorable safety profile. Future research should focus on standardizing treatment protocols and exploring long-term outcomes to integrate FREMS into clinical practice effectively.

Keywords: Diabetic peripheral neuropathy; Frequency Rhythmic Electrical Modulation System (FREMS); pain management; nerve conduction; microvascular function; non-invasive treatment.

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P397

JOINT2343

Anti-parietal cell antibodies prevalence and clinical implications in youths with type 1 diabetes

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Introduction
Children and adolescents with type 1 diabetes (T1D) have an increased risk to develop other autoimmune diseases. Autoimmune gastritis (AIG) is the third most frequent autoimmune comorbidity in T1D adults, while few data are available for children.
Objectives
Single-center, cross-sectional, observational study aimed to evaluate the prevalence of serum anti-parietal cell antibodies (APCA) and its related clinical alterations in children and adolescents with T1D.
Methods
Data on APCA assay [positive (+) or negative (-)], autoantibodies against β-cells at T1D onset (IAA, GAD, ICA) and other organ-specific autoantibodies, AIG-related symptoms (dyspepsia, abdominal pain and early postprandial satiety), anaemia, and mean corpuscular volume (MCV) alterations were recorded (last annual routine outpatients visit). In confirmed APCA(+) subjects, additional laboratory tests [iron, vitamin B12, chromogranin A, gastrin-17, and intrinsic factor autoantibodies (IFAs)] and gastrointestinal endoscopy (GE) were performed.
Results
146 patients with T1D were recruited [54. 1% males, 70% Caucasian, mean age 14. 5±3. 55 yrs, T1D duration 8. 36±4. 01 yrs, A1c 60±15 mmol/l]. Eight out of 146 subjects were APCA(+) (prevalence 5. 5%). APCA(+) subjects, compared to APCA(-) ones, had a higher prevalence of AIG symptoms ($P < 0.001$), thyroid autoimmunity ($P = 0.002$), and combination of IAA+GAD autoantibodies at T1D onset ($P < 0.001$) (Table). They also had a trend towards a higher prevalence of anaemia ($P = 0.054$). In APCA(+) subjects we found anaemia (25%), microcytosis (25%), iron deficiency (37. 5%), vitamin B12 deficiency (57. 1%), high levels of gastrin-17 (28. 6%) and chromogranin A (42. 9%). None was positive for IFAs. Lastly, 6 out of 8 APCA(+) patients underwent GE: 2 subjects showed endoscopic features of AIG (thinned and oedematous areas of the gastric antrum and corpus mucosa). Histological examination identified signs of chronic gastric mucosal inflammation in all patients (4 mild and non-specific alterations, indicating early stages of AIG; 1 marked alterations in glandular structure; 1 advanced AIG and discrete mucosal atrophy).
Conclusions
The prevalence of APCA(+) we found in our youths with T1D was 5. 5%, consistent with findings from few available previous studies. In contrast, we didn't found a higher prevalence in females. Our data suggest the usefulness of a regular screening for AIG, mainly in patients with thyroid autoimmunity, IAA+GAD at T1D onset, and AIG symptoms. The early is the diagnosis, the early is the treatment of its related symptoms and deficiencies.

		AIG symptoms (%)		Thyroid autoantibodies (%)		IAA + GAD (%)	
		POS	NEG	POS	NEG	POS	NEG
APCA	POS	**25. 0**	75. 0	**62. 5**	37. 5	**28. 6**	71. 4
	NEG	1. 4	98. 6	17. 5	82. 5	2. 3	97. 7

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P398

JOINT2175

Seasonal trends, clinical characteristics, and glycemic control in type 1 diabetes mellitus: a descriptive study from two private tertiary hospitals in nairobi, Kenya

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Introduction
Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder leading to insulin deficiency. Lifelong use of insulin and optimal glycemic control (HbA1c < 7. 5%) is essential for preventing long-term complications and ensuring a good quality of life. Globally, variations in T1DM incidence, seasonal trends, clinical features, and glycemic control have been reported, largely influenced by ethnic, socioeconomic, and healthcare disparities. However, there is a paucity of comprehensive studies investigating these parameters among newly diagnosed T1DM patients in sub-Saharan Africa. Understanding these factors is crucial for identifying potential environmental triggers, optimizing treatment protocols, and improving patient care tailored to regional contexts.
Objective
To describe the seasonal trends, clinical characteristics, and glycemic control of T1DM patients at two private tertiary level hospitals in Nairobi, Kenya, from 2013 to 2023.
Methods
A retrospective descriptive study was conducted at Aga Khan University Hospital, and Gertrude's Children Hospital Nairobi, involving 109 paediatric T1DM patients. Sample size was determined using Daniel's formula. Clinical data, including age at diagnosis, diabetes duration, Diabetic ketoacidosis (DKA) at presentation, month of diagnosis, HbA1c levels, and insulin regimen, were analyzed using SPSS-25. Descriptive statistics summarized categorical and continuous variables.
Results
Among 109 patients analysed, 52. 3% were male, the mean age at diagnosis was 8. 67 years (SD = 4. 28), the peak age group being 5-12 years A seasonal trend was observed, with peak diagnosis during the cool dry season (June–September, 34. 3%) and short rainy season (October–December, 26%). DKA was observed in 55% of cases at the time of diagnosis. Basal-bolus therapy was the predominant insulin regimen (84. 4%). The mean HbA1c was 9. 49% (SD = 2. 3), with values ranging from 6. 4% to 15. 37% with mean diabetes duration of 6. 49 years (SD= 3. 6). Private insurance (54. 3%) and self-pay (33. 3%) were the main payment methods.
Conclusion
This study identified a distinct seasonal pattern in paediatric T1DM diagnosis with peaks in the cool dry season (June–September) and short rainy season (October–December), suggesting potential environmental or infectious triggers. Notably, 52% of patients presented with DKA at diagnosis - significantly lower than the estimated 80% DKA prevalence in Africa. This indicates better awareness and healthcare access in our urban setting. However, despite earlier diagnosis and with relatively short disease duration (6. 4 years) - glycemic control remains poor (mean HbA1c 9. 49%) underscoring the need for enhanced diabetes management strategies, including use of diabetes technology such as continuous glucose monitoring and insulin pumps.

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P399

JOINT2622

Exploring the early symptoms of depression in children, adolescent and young adults: a review with public patient involvement

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Background
Type 1 diabetes (T1D) is a chronic condition that significantly impacts both physical and mental health. Depression is prevalent among children, adolescents, and young adults with T1D but often remains underdiagnosed. Identifying early symptoms of depression in this population is crucial for timely intervention and improved disease management.
Objective
This study explores early markers of depression in children, adolescents, and young adults with T1D through a comprehensive literature review and public patient involvement (PPI).
Methods
A two-phase approach was employed. The first phase involved a systematic literature review (2000–2024) focusing on depression prevalence, symptoms, and screening tools in T1D. The second phase incorporated PPI through focus group discussions (FGDs) with patients, guardians, and clinicians to identify and rank early depressive symptoms. The findings were then compared with established depression and diabetes distress screening tools.
Results
Depression prevalence in children and adolescents with T1D varied from 6. 3% to 46. 3%. Commonly used screening tools, such as the Children's Depression Inventory (CDI), Center for Epidemiological Studies Depression Scale (CES-D), and Patient Health Questionnaire-9 (PHQ-9), effectively captured general depressive symptoms but lacked diabetes-specific emotional burdens. Diabetes distress tools, such as the Problem Areas in Diabetes (PAID) scale and Diabetes Distress Scale (DDS), identified unique stressors but did not comprehensively screen for depression. FGDs highlighted early depression markers, including sadness, social withdrawal, academic decline, diabetes-related distress, and feelings of unfairness about having diabetes.
Conclusion
Early depressive symptoms in children and young adults with T1D encompass both general and diabetes-specific features. Current depression screening tools may not fully capture these nuances. Developing an integrated screening approach that incorporates diabetes-specific distress along with depression screening tools could improve early identification and intervention.
Keywords: Type 1 diabetes, depression, diabetes distress, early symptoms, children, adolescents, screening tools

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P400

JOINT3188

A rare metabolic puzzle: the case of an infant with hadh mutation

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Background
Recurrent hypoglycemia in infants can result from a variety of causes, complicating the diagnostic process. The episodic nature of symptoms and the need for timely metabolic and genetic testing make the workup particularly challenging. Early and accurate identification of the underlying cause is essential to prevent neurological damage and guide appropriate management.
Clinical presentation
A 2 month old female presented with a history of seizures from 17 days of life. At the age of 2 months it was noticed that her seizures were secondary to hypoglycaemia. She was born at term with a birth weight of 2. 73kg. She has no positive family history. Of note, she has 3 siblings, 1 of which demised at the age of 9 months due to unknown causes but was noted to be malnourished.
Results and discussion
Biochemistry revealed a hypoglycaemia (glucose 2. 2 mmol/l) with an inappropriately normal insulin of 5. 9m IU/l and normal c-peptide of 3. 2μg/l. Her serum growth hormone however at the time was 2. 8μg/l (reference: 0. 12-7. 79 μg/l) and she had a serum cortisol of only 118nmol/l, indicating the presence of hypocortisolism and possibly even growth hormone deficiency. Her CT Brain was normal and the Ga-68 Dotatate whole body PET/CT showed no avid disease. Genetic testing revealed a mutation in the hydroxyacyl-CoA dehydrogenase (HADH) gene, a key enzyme in fatty acid oxidation and insulin regulation. Thus, a genetic diagnosis of autosomal recessive congenital hyperinsulinism, subtype HADH was made. There is no know association in the literature with a HADH mutation presenting with a combination of hyperinsulinism and hypercortisolism or hypopituitarism. She responded however to treatment with diazoxide and oral hydrocortisone and is currently growing well without any hypoglycaemic events.
Conclusion
This case highlights the critical role of HADH in energy metabolism and the challenges of diagnosing and managing rare metabolic conditions in infancy.
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P401

JOINT3586

Morphofunctional assessment in type 1 diabetes mellitus: usefulness of muscle ultrasound in the evaluation of body composition and its relationship with metabolic variables

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Introduction
Sarcopenia has been proposed as a complication of diabetes. However, there are few body composition studies in type 1 diabetes mellitus (T1DM). Thus, the use of ultrasound as a portable and emerging clinical tool could be useful for the early diagnosis of sarcopenia. Our objectives were to describe ultrasound parameters of body composition in people with T1DM and to determine if there are associations with metabolic variables.
Material and Methods
Cross-sectional study in people with T1DM. Demographic (age, sex), analytical (glycosylated hemoglobin: HbA1c) and clinical variables (total insulin dose (DTI), muscle strength measured with Jamar dynamometer in kilograms (kg) - cut-off point: <p10 of Spanish population-, quadriceps rectus femoris muscle mass and abdominal subcutaneous fat adipose mass (superficial adipose tissue - TASu- and total adipose tissue-TAT-) with ultrasound -Sonosite S-Nerve®) were collected. Statistical analysis was performed with IBM SPSS v. 25.
Results
Fifteen patients with T1DM were evaluated (53% female, mean age 35 $\pm$ 12 years, BMI 22. 8 $\pm$ 3. 3kg/m2 and mean HbA1c 9. 2$\pm$2. 3). Low muscle strength was detected in 28%. The mean rectus femoris quadriceps muscle thickness or Y-axis was 1. 5$\pm$0. 3 and its mean area, 5. 6$\pm$2. 1. Mean adipose tissue (TAT) was 1. 2$\pm$0. 8, mainly dependent on superficial adipose tissue (TASu), with mean 0. 6$\pm$0. 4. The Y-axis correlated positively with muscle strength ($r = 0.5$, $P = 0.04$) and negatively with metabolic control in T1DM ($r = 0.6$, $P = 0.03$). Worse metabolic control (higher HbA1c) correlated positively with DTI ($r = 0.4$, $P < 0.001$), TASu($r = 0.7$, $P < 0.001$) and TAT($r = 0.7$, $P < 0.001$).
Conclusions
In this preliminary study, metabolic control correlated with ultrasound measurements of muscle mass and abdominal adipose tissue. Therefore, the assessment of morphofunctional status seems to be useful and could propose new therapeutic strategies in T1DM.
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P402

JOINT1501

Pancreatic steatosis in newly diagnosed type 2 diabetes: relationships with glycemic control and exocrine function

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Background
Pancreatic steatosis (PS) is characterized by abnormal fat accumulation in pancreatic tissue and is often associated with obesity, metabolic syndrome, and type 2 diabetes mellitus (T2DM). While its pathophysiology and impact on pancreatic functions have been explored, the interplay between PS, glycemic control, and exocrine dysfunction in T2DM remains inadequately defined.
Objective
To evaluate the presence of pancreatic steatosis, the factors affecting it, and its relationship with endocrine and exocrine pancreatic functions in newly diagnosed T2DM patients.

Methods
A total of 126 individuals were included in the study, comprising 63 newly diagnosed T2DM patients and 63 healthy controls matched for age, sex, body mass index and body fat distribution. Body composition, biochemical parameters (glucose, insülin, C-peptide, HbA1c), fecal elastase levels, and pancreatic/hepatic steatosis grades (evaluated using ultrasonography) were assessed.
Results
Newly diagnosed T2DM patients exhibited significantly higher hepatic steatosis grades ($P = 0.018$) and lower fecal elastase levels ($P < 0.001$) compared to controls. Pancreatic exocrine insufficiency was more prevalent in the T2DM group ($P < 0, 001$). A positive correlation was observed between pancreatic steatosis grade, hepatic steatosis grade, and hepatic fat fraction. HbA1c levels demonstrated a nonlinear (inverse U-shaped) relationship with pancreatic steatosis, peaking at 9. 8% and declining thereafter, while showing a continuous negative relationship with fecal elastase levels. HbA1c predicted low fecal elastase (<200 μg/g) with a cutoff value of 7. 4%. Patients with HbA1c levels $>$ 9. 8% exhibited reduced pancreatic steatosis alongside persistent exocrine insufficiency.
Conclusions
Pancreatic steatosis is closely associated with hepatic steatosis, glycemic control, and pancreatic exocrine dysfunction in newly diagnosed T2DM patients. Fecal elastase, with an HbA1c cutoff value of 7. 4%, serves as a practical marker for detecting pancreatic exocrine insufficiency. The interplay between pancreatic steatosis, glycemic control, and exocrine dysfunction highlights the need for comprehensive metabolic assessments in this population.
Key words
Exocrine pancreatic insufficiency, fecal elastase, HbA1c, hepatic fat fraction, hepatic steatosis, pancreatic steatosis
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P403

JOINT3444
Neonatal diabetes: clinical characteristics, genetic analysis and long-term follow-up from a single-center experience
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Introduction
Neonatal diabetes mellitus (NDM) is a rare monogenic form of diabetes that presets within the first six months of life, and is classified as either transient (TNDM) or permanent (PNDM). This study aims to describe the clinical characteristics, genetic findings, treatment strategies, and long-term follow-up of 11 NDM patients based on a single-center experience.
Methods
This study involved 11 patients with NDM diagnosed, treated, and followed between 2013 and 2025 years. Clinical, biochemical, and genetic data were evaluated retrospectively. Genetic analysis was performed in all patients.
Results
Among 11 patients (7 male) from 9 unrelated families, TNDM and PNDM were diagnosed in 1 and 10 patients. Sixty-four percent were born to consanguineous parents. Genetic mutations were identified in 64%, the most common mutation was in the PTF1A distal enhancer ($n = 6$)), one patient had KCNJ11 mutation. Fifty-four percent were born prematurely, and 90. 9% were small for gestational age. The median age at diagnosis was 1 day, All patients received insulin replacement therapy. *Glibenclamide was initiated in the patient with the KCNJ11 mutation*. In PNDM patients, the median insulin dose was 0. 55 U/kg/day initially and 0. 58 U/kg/day at last follow-up, with no significant difference. Six patients received insulin via insulin pumps. Median HbA1c at last control was 7. 5% and there was no difference in HbA1c levels compared to conventional insulin treatment. Patients with PTF1A mutations diabetes was associated with pancreas agenesis, thus they required pancreatic enzyme replacement. Pancreas agenesis was not associated with other abnormalites. One patient whose genetic analysis is pending has also exocrine pancreas insufficiency whose pancreas could not be visualized. All males exhibited catch-up growth, surpassing -2 SDS; whereas two females under two years remained below -2 SDS. These females with height below -2 SDS also had low weight. Except for the deceased KCNJ11-positive patient, all males achieved weight above -2 SDS at last follow-up.
Conclusion
NDM is a rare disorder with variable genotypes and clinical phenotypes. PTF1A mutation was the most common genetic cause in our cohort, particularly relevant in populations with high consanguinity rates. Genetic testing is crucial for identifying conditions such as pancreatic agenesis and initiating timely treatment, as well as guiding appropriate treatments such as sulfonylurea therapy in KCNJ11 mutations.
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P404

JOINT1492
Comparative analysis of ventricular repolarization in patients with type 1 diabetes vs. control and patients using insulin pump vs. multiple daily injections
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Objective
The frequency of cardiovascular mortality is increased in type-1 diabetes mellitus(T1DM). Both hyperglycemia and hypoglycemia increase the risk of cardiac complications. This study aimed to use the ECG parameters of ventricular repolarisation times to assess the risk of arrhythmogenesis in patients with T1DM.
Methods
Age, sex, age at diagnosis of T1DM, duration of T1DM, insulin-pump use status, duration of insulin-pump use, biological and diabetic age at insulin pump insertion, continuous glucose monitoring(CGM) status, carbohydrate counting status, diet compliance status, history of technical problems with insulin-pump, total insulin doses, presence of hypertension, history of diabetic foot, hyperlipidemia, stroke, coronary heart disease, symptomatic hypoglycemia at least once a week, diabetic foot, peripheral vascular disease, hospitalization for hypoglycemia, presence of diabetic neuropathy, presence and type of diabetic retinopathy, diabetic nephropathy status, hemoglobin A1c(HbA1c) value, creatinine, microalbuminuria status, and spot urine microalbumin/creatinine ratio levels were recorded. Electrocardiographic(standard 12-lead ECG) parameters, parameters corresponding to ventricular repolarisation times, and used as indicators of arrhythmogenesis were collected. These were P-wave, QRS-wave, T-wave, PR-interval, QT, QTmax, QTmin, QTc, QTcmax, QTcmin, QT-dispersion, QTc-dispersion, Tp-e, JTc, Tp-e/QT, Tp-e/QTc, index of cardio-electrophysiological-balance(iCEB). Obtained parameters were evaluated between patients with T1DM and the control group. In addition, the patient group was divided according to the method of insulin therapy used(basal-bolus insulin therapy vs insulin-pump) and compared within themselves.
Results
125 patients with T1DM and 50 controls were included in the study. 62 patients were on basal-bolus insulin therapy, and 63 were on insulin pump therapy. Patients who used insulin pumps had lower HbA1c than those who did not(8.45 ± 1.60 vs 9.62 ± 2.01, $P = 0.001$). The incidence of symptomatic hypoglycaemia was lower in the insulin pump group, but the history of hospitalisation due to hypoglycaemia was similar in both treatment groups. P-wave, QT, QTmax, QTmin, QTc, QTcmax, QTcmin, Tp-e, and JTc were longer in T1DM patients(p values $=0.024$, 0. 012, 0. 007, 0. 001, <0.001, <0.001, 0. 001, 0. 001, and 0. 004, respectively). QRS duration was significantly shorter, and JTc, iCEB, and iCEBc were significantly longer in insulin pump patients(p values $=0.045$, 0. 031, 0. 019, and 0. 005, respectively).
Conclusion
In conclusion, patients with T1DM have prolonged ventricular repolarisation time and may be predisposed to arrhythmias. This study also suggests that insulin pump therapy may provide better glycemic control and less hypoglycemia. However, when assessing the effect of this condition on the risk of arrhythmia, it is essential to consider the patient's medical history and to remember that the risk of arrhythmia may persist despite improvements in the course of the disease.
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P405

JOINT2186
Investigation of the relationship between alexisomia and treatment adherence in diabetic obese individuals: a pilot study
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Objective
Alexisomia is defined as the difficulty in recognizing and expressing bodily sensations and emotions. The Alexisomia Scale evaluates individuals through three sub-dimensions: DIB, difficulty in describing bodily emotions; LHM, lack of health management based on bodily emotions; OA, over adaptation. In chronic diseases like diabetes mellitus(DM), the inability to recognize and respond to bodily sensations may negatively impact treatment adherence. Our study aimed to investigate the relationship between alexisomia and treatment adherence in diabetic obese individuals and evaluate the effects of GLP-1 receptor agonist therapy on alexisomia, depression, anxiety, and stress.
Methods
This cross-sectional study included diabetic obese individuals. Adult patients diagnosed with type 2 DM and a body mass index (BMI) of $\geq$30 kg/m^2 were included, while those with active psychiatric disorders and undergoing related treatment were excluded. Anthropometric, demographic, and clinical characteristics, as well as laboratory data and ongoing treatments for at least three months, were recorded. Internal awareness of the participants was assessed using the Alexisomia Scale, while depression, anxiety, and stress levels were evaluated with the Depression, Anxiety, and Stress Scale (DASS). Treatment adherence was assessed using the 8-item Morisky Medication Adherence Scale (MMAS-8).
Results
The study included 38 patients (mean age 60. 2 $\pm$ 11. 06 years, 60. 5% female), with a median BMI of 32. 1 kg/m^2 (range: 30. 0–52. 8). Fifty percent of the patients used insulin, and 39. 5% were receiving GLP-1 receptor agonist therapy. When diabetic obese patients were examined in terms of alexisomia, alexisomia subgroups, depression, anxiety, stress, and treatment adherence, a statistically significant relationship was found between alexisomia and treatment adherence (P = 0. 043, r = 0. 330). Specifically, a significant relationship was observed between DIB and treatment adherence (P = 0. 017, r = 0. 385). Patients were also compared in terms of alexisomia, depression, anxiety, stress, and treatment adherence based on GLP-1 RA usage, but no statistically significant differences were found between the groups (P = 0. 740, P = 0. 464, P = 0. 532, P = 0. 717, P = 0. 532, respectively).
Discussion and Conclusion
Our study found that patients experiencing difficulty in identifying and perceiving their bodily sensations had lower treatment adherence. Screening for these characteristics in patients may contribute to strategies aimed at improving treatment adherence. While GLP-1 receptor agonists are effective therapies for type 2 diabetes, our findings suggest that GLP-1 RA therapy does not significantly impact alexisomia, depression, anxiety, or stress levels. Due to the limited sample size, these findings should be confirmed in larger-scale studies.

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P406

JOINT3721

Clinical characteristics, risk factors, and outcomes of DKA in type 1 diabetes: a comparative study of continuous subcutaneous insulin infusion (CSII) vs multiple daily injections (MDI)

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Background
Diabetic ketoacidosis (DKA) is a severe complication of type 1 diabetes (T1D) that requires prompt intervention to avoid life-threatening outcomes. Continuous subcutaneous insulin infusion (CSII) has been shown to improve glycaemic control and reduce hypoglycaemic episodes compared to multiple daily injections (MDI). However, the impact of insulin delivery method on DKA risk remains unclear, particularly with concerns over CSII device malfunction.
Objective
This study compared the frequency of DKA admissions, precipitating factors, clinical features, and outcomes in adults with T1D using CSII vs MDI to identify any differential impact of insulin delivery methods on DKA risk and outcomes.
Methods
A retrospective analysis of DKA admissions from January 2020 to July 2023 within the Digital Evaluation of Ketosis and Other Diabetes-related Emergencies (DEKODE) cohort was conducted. Participants were grouped into two cohorts: CSII users (cases) and MDI users (controls). Propensity score matching was applied with a 1:5 matching ratio. Key outcomes assessed included precipitating factors, biochemical markers, hypoglycaemic events, DKA duration, length of hospital stay, and mortality.
Results
Among the 1, 594 DKA episodes reviewed, 6. 3% (n = 100) occurred in CSII users. CSII users were younger (mean age 35. 7 years vs. 39. 6 years for MDI, P=0. 028) and had a higher proportion of females (59% vs. 45. 4% for MDI, P=0. 011). Suboptimal compliance was the most common precipitant in both groups, followed by intercurrent illness, with CSII malfunction being a notable cause in the CSII cohort. After matching, there were no significant differences in age, gender, ethnicity, or BMI across the groups. CSII users presented with higher admission ketone levels (6. 1 vs. 5. 6 mmol/l, P = 0. 043) and potassium levels (5. 2 vs. 5. 0 mmol/l, P = 0. 036) compared to MDI users. In addition, CSII users had fewer hypoglycaemic events during DKA management (7% vs. 17. 2%, P = 0. 015). DKA duration (13. 9 hours vs. 17. 9 hours in MDI, P = 0. 005) and length of hospital stay (2. 9 vs. 5. 5 days, P = 0. 0003) were significantly shorter in the CSII group. No deaths occurred in the CSII group.
Conclusions
Although CSII offers benefits in glycaemic control and reduced hypoglycaemia, DKA remains a significant risk, with 1 in 16 episodes occurring in CSII users. Despite shorter DKA duration and hospital stay, CSII users require careful monitoring to prevent and manage DKA effectively. Importantly, 18% of DKA cases in CSII users were linked to device malfunction, emphasising the need for improved education on device maintenance and troubleshooting to minimise this risk.

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P407

JOINT1717

Association of arterial stiffness with mineral metabolism in type 2 diabetes patients with chronic kidney disease

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Background and Aims
Type 2 diabetes mellitus (T2DM) is a major cause of chronic kidney disease (CKD), affecting 30–40% of diabetic patients. CKD progression increases the risk of cardiovascular disease (CVD), with arterial stiffness playing a crucial role in CVD pathogenesis. Pulse wave velocity (PWV) is a reliable marker of arterial stiffness. This study aims to assess the relationship between arterial stiffness (measured by PWV) and mineral metabolism parameters in T2DM patients with CKD.
Materials and Methods
This cross-sectional study included 105 adult patients with T2DM and CKD, classified into five -stages per KDIGO 2012 guidelines: CKD 1 n = 24, CKD 2 n = 21, CKD 3 n = 25, CKD 4 n = 15, CKD 5 n = 20. Arterial stiffness was assessed using PWV measured at the carotid-femoral level with the SphygmoCor XCEL system. Serum calcium, phosphorus, alkaline phosphatase, vitamin D, parathyroid hormone (PTH), calcitriol, and fibroblast growth factor 23 (FGF-23) levels were analyzed. Statistical analysis was conducted using the Spearman correlation coefficient, with P-values $<$0. 05 considered significant.
Results
The mean age of participants was 60. 3$\pm$8. 1 years, with 58. 1% female. The duration of illness with T2DM was 12. 87$\pm$7. 34 years. PWV increased with CKD progression, from 9. 06$\pm$2. 20 m/s in CKD stage 1 to 10. 75$\pm$2. 34 m/s in stage 5 (P = 0. 004). FGF-23 levels showed a strong positive correlation with PWV (r = 0. 618, P $<$ 0. 001). No significant correlation was found between PWV and serum calcium (r = -0. 098, P = 0. 409), phosphorus (r = 0. 162, P = 0. 169), vitamin D (r = 0. 005, P = 0. 962), or PTH (r = 0. 062, P = 0. 696).
Conclusion
Arterial stiffness, as indicated by PWV, increases with CKD severity in T2DM patients and is strongly correlated with FGF-23 levels. These findings highlight the potential role of FGF-23 as a biomarker for vascular complications in CKD. Further research is needed to elucidate the mechanisms linking FGF-23 and arterial stiffness.

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P408

JOINT1906

Functional analysis of RFX2 gene as a candidate gene for monogenic diabetes

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Introduction

Monogenic diabetes (MD) makes up up to 5% of diabetes cases, with over 40 genes confirmed to cause it, though many remain unidentified. A Lithuanian-Swiss study identified a novel variant in the *RFX2* gene, suggesting its potential role in diabetes. The study aimed to explore how *RFX2* gene knockdown impacts insulin production and its clinical implications in a patient with this variant.

Methods

A novel c. 1894G > A (p. Ala632Thr) variant in the *RFX2* gene was confirmed by PCR and Sanger sequencing. Functional analysis was performed by knocking down the gene in INS-1 832/13 cells, and insulin production was assessed using ELISA after glucose stimulation at 0 mM, 2. 5 mM, and 15 mM concentrations. Statistical analysis was conducted using IBM SPSS software 23. 0, and data are presented as median (min. -max. values).

Results

A 9-year-old boy diagnosed with diabetes and treated for type 1 diabetes was later found to have a novel c. 1894G > A (p. Ala632Thr) variant in the *RFX2* gene at age 16. Autoantibodies for glutamic acid decarboxylase and tyrosine phosphatase-like protein were negative, though insulin autoantibodies were at the cut-off range for positivity, considering the ongoing insulin treatment, patient was suspected to have genetic diabetes. Co-segregation analysis showed no family members with diabetes signs or the same variant, prompting functional analysis of *RFX2* in cell culture. Insulin production of *siRFX2* cells vs. wild-type cells after stimulation with glucose (2. 5 mM) was lower, 1. 5 $\times$ 10^{-5} (1. 4 $\times$ 10^{-5} – 1. 7 $\times$ 10^{-5}) vs. 1. 6 $\times$ 10^{-5} (1. 3 $\times$ 10^{-5} – 1. 8 $\times$ 10^{-5}), respectively, $P = 0.049$. Stimulation with 15 mM glucose concentration triggered the same insulin production from both, wild-type and knocked-down cells. Insulin secretion in *siRFX2* cell after using different glucose solutions, showed higher response with higher glucose concentration, 0 nM glucose - 0. 5 $\times$ 10^{-5} (0. 4 $\times$ 10^{-5} – 0. 8 $\times$ 10^{-5}); 2. 5 mM glucose –1. 5 $\times$ 10^{-5} (1. 4 $\times$ 10^{-5} – 1. 7 $\times$ 10^{-5}), 15 mM glucose - 6. 6 $\times$ 10^{-5} (6. 1 $\times$ 10^{-5} – 7. 6 $\times$ 10^{-5}), respectively, $P < 0.001$.

Conclusion

This experiment investigated the effect of *RFX2* gene knockdown on insulin production *In vitro*. While the findings did not confirm *RFX2* as a causative gene for monogenic diabetes, they suggested an altered glucose threshold in mutant cells, with impaired insulin production at low glucose and normal secretion at high glucose concentrations. This highlights the complexity of diabetes classification and underscores the need for further research into its etiology and pathogenesis.

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P409

JOINT1012

Three case studies of congenital hyperinsulinism - variants and clinical outcomes

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Introduction

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in neonates and encompasses a heterogeneous group of genetic, syndromic, and reversible causes. Timely and targeted diagnostics and therapy are crucial to prevent developmental damage and fatal outcomes. Genetic diagnostics are of particular importance, especially in Diazoxide-resistant cases, as they provide insight into further treatment steps and prognosis.

Methods

We present the cases of two neonates and one infant with different genetic causes of CHI (1-HFN4A, 2-, 3-ABCC8). The clinical course during the neonatal period, diagnosis, acute therapy, further diagnostic and therapeutic steps, and follow-up are described. Differences between medication-sensitive, diffuse, and focal forms are discussed.

Results

1. A female full-term infant who was large for gestational age (39 weeks gestation, 4670g) with postnatal hypoglycemia. Despite a carbohydrate-enriched diet, euglycemia could not be achieved. Diagnosis of CHI was confirmed through blood sampling during hypoglycemia, successful therapy with Diazoxide. HFN4A variant was identified. 2. A female pre-term infant who was large for gestational age (35 weeks gestation, 3330g) with postnatal and persistent hypoglycemia under carbohydrate diet. CHI was confirmed. Diazoxide therapy was ineffective, Octreotide provided insufficient response. A heterozygous compound ABCC8 mutation was found. Surgical intervention revealed a diffuse form histologically and 50% pancreas resection. Post-surgery, hyperinsulinism persisted. A therapy trial with lanreotide is planned. 3. A male full-term infant who was large for gestational age (40 weeks gestation, 4280g) with postnatal euglycemia, developing generalized seizures at 7 months due to hypoglycemia. Fewer hypoglycemic events under Diazoxide and carbohydrate diet. Paternal ABCC8 mutation was detected. PET-CT showed no focal abnormality, and a Diazoxide withdrawal trial has not yet resulted in severe hypoglycemia.

Conclusion

Persistent hypoglycemia in the neonatal period and infancy requires prompt and sequential diagnostics and therapy. Rapid genetic testing can help narrow down differential diagnoses. Until genetic results are available, a Diazoxide trial is recommended. In focal forms of CHI, PET-CT and surgery are often beneficial, whereas in diffuse forms, partial pancreatectomy rarely achieves euglycemia. Effective collaboration between neonatology, pediatric endocrinology, and human genetics is crucial for timely diagnosis and treatment.

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P410

JOINT2120

Multi-center investigation of pediatric diabetes in China

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Objective

To investigate the characteristics and trends of diabetes mellitus in Chinese children and compare type 1 and type 2 diabetes mellitus.

Methods

The first pages of medical records of 13322 newly diagnosed children with diabetes aged 1 to 18 from children's medical centers in 30 provinces were collected from 2016 to 2022. The study analyzed the epidemiology, complications, and disease burden of childhood diabetes.

Results

A total of 13, 322 hospitalized children were analyzed, including 6, 477 males (48. 62%) and 6, 845 females (51. 38%). Of these, 11, 965 were diagnosed with T1DM and 1, 357 with T2DM. The mean age for T1DM patients was 8. 23 $\pm$ 3. 97 years, with a male-to-female ratio of 0. 91:1. For T2DM patients, the mean age was 12. 64 $\pm$ 2. 06 years, and the ratio was 1. 35:1. T1DM most commonly occurred in children aged 5 to 14, while T2DM was prevalent in those aged 10 to 14. The peak incidence seasons for T1DM were July, August, and January, with August being the peak for T2DM. From 2016 to 2022, the proportion of hospitalized children with diabetes rose from 1. 40‰ to 2. 42‰, with T2DM hospitalizations growing significantly faster than T1DM (19. 14% vs 8. 68%). The rate of diabetic ketoacidosis (DKA) was higher in T1DM than T2DM (39. 92% vs. 11. 94%, $P < 0.01$). Conversely, conditions such as hyperlipidemia, fatty liver, hyperuricemia, hypertension, metabolic syndrome, and obesity were significantly more prevalent among T2DM patients. However, cerebral edema rate did not significantly differ between T1DM and T2DM. The analysis indicated that T2DM, ketoacidosis, hyperuricemia, and length of hospital stay significantly increase costs.

Conclusion

The incidence of both T1DM and T2DM in Chinese children is rising, with a more pronounced increase in T2DM. Significant differences exist between the two types regarding age, gender distribution, complication rates, and hospitalization costs.

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P411

JOINT1803

Therapeutic education in children and adolescents with type 1 diabetes mellitus; systematic review

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Introduction
The therapeutic education of Type 1 Diabetes Mellitus (T1DM) in children and adolescents is an ongoing process and an integral part of its successful management. Therapeutic education programs, taking into account the unique characteristics and developmental needs of each child/adolescent, aim to empower and promote autonomy, enabling them to effectively take over self – management of their disease which contributes to improving their quality of life and preventing complications.
Purpose
The purpose of this systematic review was to evaluate the impact of therapeutic education in children and adolescents with T1DM on self- management of their disease.
Method
International bibliography was reviewed using electronic database such as PubMed, Cochrane Library and Scopus. Keywords such as "Therapeutic education", "Type 1 diabetes mellitus", "children", "adolescents, "self-management", "glycemic control", "educational programs" in combination with Boolean operators (AND, OR) were used in English language to search for studies conducted during 2014 - 2024.
Results
A total of 23 studies were reviewed and evaluated based on predefined quality and relevance criteria. 19 of these studies demonstrated an improvement in the glycemic control of children and adolescents with T1DM, although 9 of them did not show a statistically significant reduction in glycated hemoglobin (HbA1c). Additionally, 6 studies showed better adherence to treatment after attending a therapeutic educational program, with 2 of them emphasizing an increase in diabetes-related knowledge. Specifically, combined educational approaches incorporating psychoeducational interventions appeared to improve T1DM self-management. Moreover, 10 studies reported that using digital tools such as Continuous Glucose Monitoring (CGM) can also strengthen the adherence to treatment. Benefits on quality of life were recorded in 8 studies, but in 4 of them, these benefits were not maintained on the long term. Furthermore, according to 4 studies, parental participation in therapeutic programs improved family relationships and children's confidence in managing the disease. Finally, 5 studies highlighted the contribution of specialized diabetes interdisciplinary team, integral members of which are nurses, in the overall improvement of T1DM management.
Conclusion
Therapeutic education is a key factor in the effective management of T1DM in children and adolescents. Its impact is further enhanced through personalized support, family involvement, and the integration of new technologies. Specialized diabetes nurses play a crucial role as primary health providers of education and support for children and their families. Further studies are needed to delve into therapeutic education in children and adolescents as a cornerstone of monitoring their glycemic control.

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P412

JOINT2929

Hamman's syndrome as a rare complication of diabetic ketoacidosis in a newly diagnosed pediatric patient with type 1 diabetes mellitus

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Hamman's syndrome, an uncommon complication of diabetic ketoacidosis (DKA), is characterized by spontaneous subcutaneous emphysema and pneumomediastinum. The pathophysiology of Hamman's syndrome in the context of DKA is multifactorial, with increased intra-alveolar pressure due to Kussmaul respiration and recurrent vomiting being key contributors to alveolar rupture. This case report describes an 11-year-old female of Indian origin, newly diagnosed with type 1 diabetes mellitus (T1DM), presenting with severe DKA. Upon admission, the patient had a blood pH of 7. 11, bicarbonate levels of 5. 4 mmol/l, a partial pressure of carbon dioxide (pCO2) of 16. 5 mmHg and Glu: 405mg/dl. Her vital signs were the following: Blood pressure: 133/89mmHg, heart rate: 144bmp, respiratory rate: 50/min, temperature: 36, 7°C. Clinical symptoms included a 7-day history of polydipsia, polyuria, and weight loss (3 kg), along with acute onset of chest pain and shortness of breath for 1 hour prior to presentation. On examination, the patient demonstrated Kussmaul breathing and tachycardia. Initial management with intravenous fluids and *insulin infusion* was initiated at a local general hospital. Following stabilization, she was transferred to a tertiary pediatric center for further evaluation and care. Routine physical examination at the tertiary center revealed *bilateral neck crepitus* and a mediastinal crunch on auscultation, suggestive of Hamman's syndrome. The diagnosis was confirmed with imaging, including chest X-ray and computed tomography (CT). During her hospital stay, the patient underwent continuous pediatric, cardiological, pulmonological, and endocrinological evaluations to ensure comprehensive management of both her acute condition and underlying comorbidities. Successful treatment of DKA led to complete resolution of her symptoms, and she was discharged with a structured follow-up plan. This case underscores the importance of recognizing Hamman's syndrome as a potential complication of DKA in pediatric patients. Early identification and differentiation from more severe conditions, such as Boerhaave's syndrome, are critical for ensuring optimal outcomes. Increased awareness and understanding of this rare syndrome can aid in prompt diagnosis and effective management, thereby improving patient care.

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P413

JOINT3710

Multidisciplinary team transition model of care for type 1 diabetes: health outcomes after 2 years of implementation

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Introduction
The transition of young adults with type 1 diabetes mellitus (T1DM) is challenging for the young person, their families and health care providers. They must assume higher levels of autonomy and often neglect their healthcare. For a more successful change of care, structured transition programs are necessary. Our aims are to characterize T1DM patients who went from pediatric to adult care in the last 2 years, evaluate their glycemic control over time, and the occurrence of acute complications.
Methods
The transition model adopted in our center consists of a multidisciplinary team that includes nurses, the pediatric endocrinologist, and the adult endocrinology team. Data regarding demographic characteristics, time since diagnosis, glycemic control, and complications was collected from electronic clinical files. Glycemic control was evaluated using HbA1c, glucose management indicator (GMI), coefficient of variation (CV), time in range (TIR) and time below range (TBR), at 6 months intervals.
Results
25 patients with T1DM had transition appointments in the last 2 years, 40% female, median age at diagnosis 11 years and at transition 19 years. Median time since diagnosis at transition of 8 years. All had continuous subcutaneous insulin infusion (CSII), 80% had continuous glucose monitoring. 76% are currently enrolled in higher education. No patient was lost to follow-up, and all are still with CSII, 24% changed to automated insulin delivery (AID) systems. There was 1 hospitalization for ketoacidosis (around 12 months after transition), with no previous serious acute complications. There was a statistically significant worsening of HbA1c ($P < 0.001$), GMI ($P = 0.001$) and TIR ($P < 0.001$) 6 months after transition. GMI values improved 18 months after transition ($P = 0.027$).
Discussion
Our center's transition model for T1DM patients has been successful, with no losses to follow-up. Only one showed a serious acute complication. Glycemic control worsened initially after transition, with a subsequent improvement after

	6 months before transition	At transition	6 months after transition	12 months after transition	18 months after transition	24 months after transition
N	25	25	24	15	12	5
HbA1c	7. 3%	7. 5%	8. 1%	9. 2%	7. 4%	7. 2%
GMI	7. 2%	7. 5%	8. 1%	8%	7. 6%	7%
CV	40. 9%	40. 9%	39. 6%	39. 4%	37. 3%	34. 2%
TAR	38. 7%	46. 1%	47. 8%	48. 5%	39. 1%	28. 4%
TIR	55%	48. 8%	47. 2%	45. 4%	54. 8%	68. 6%
TBR	6. 2%	5. 5%	4. 9%	3. 9%	3. 3%	3%

18 months, that seems to extend into the 24-month mark, which might reflect their increasing autonomy in self-care, reinforcing the need for therapeutic re-education aimed at young adults.

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P414

JOINT312

Correlation between inflammation, metabolic syndrom and visceral fat in young type 1 diabetes patients

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Introduction
Insulin resistance (IR), feature of type 2 diabetes, is an inflammatory state that promotes atherosclerosis and increases cardiovascular mortality. IR is often underrecognized in young adults with type 1 diabetes (T1D). The aims of this study were to determine the prevalence of IR in young T1D and evalue the inflammatory status of T1D with IR.
Methods
We conducted a cross-sectional study including 68 T1D. The study subjects were young adults, aged between 18 and 45 years. Each patient underwent a physical examination (anthropometric parameters and blood pressure), a fasting biological sample collection for the measurement of HbA1c, lipid parameters and C reactive protein (CRP), an evaluation of body composition by DXA Scan which measured the the visceral fat mass (VFM). Proportion of visceral fat (PVF) was calculated using the formula: PVF = (VFM/weight)*100 High visceral fat levels (HVF) was defined by a PVF >1, 1 in men and >0, 7 in women. MS was diagnosed according to the International Federation of Diabetes (IDF) criteria.
Results
The study population consisted of 29 men (42. 6%) and 39 women (57. 4%). The mean age was 29. 4±7. 23 years. The median duration of diabetes was 11 years (4. 2–17. 0), with a range from 1 to 29 years. MS was observed in 14 patients (20. 6%). HVF was present in 15 patients (23, 4%). CRP levels were higher in T1D patients with MS (2. 6 mg/l [1. 85–5. 5]) compared to those without MS (1. 6 mg/l [1–3. 8]), with a *P*-value of 0. 068. CRP levels were Significantly higher in T1D patients with MS (3, 85 mg/l [1, 92-6, 77]) compared to those without MS (1, 45 [1, 00-3, 02]) with a *P*-value of 0, 006.
Conclusion
Although inflammation due to IR was well established in the general population and type 2 diabetes patients, it is less studied in T1D patients. In our study, the inflammation measured by CRP, was more strongly correlated in T1D with HVF than MS. Indeed the visceral fat, promotes the development of chronic low-grade inflammation by secreting cytokines like IL-1, IL-6, TNF-alpha, and leptin.

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P415

JOINT2937

Can c-peptide/glucose ratio at the diagnosis be a marker for predicting short or long term metabolic control in type 1 diabetes?

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Background
New biomarkers are needed to assess prognosis and metabolic control at the time of diagnosis in pediatric patients with type 1 diabetes (T1D). Studies in adults with type 2 diabetes showed that patients with a low postprandial c-ceptide/glucose ratio had worse metabolic control. However, there is a lack of knowledge on this biomarker ratio in children with T1D. We aimed to investigate the relationship between the c-peptide/glucose ratio (CGR) at the diagnosis time and short- or long-term metabolic control in T1D.
Materials and Methods
We included children diagnosed with T1D between 2013 and 2019, who had measured pre-treatment c-peptide and glucose levels, and were followed up for 3-5 years. Relevant data were obtained from medical records retrospectively. Results are presented as mean ± standard deviation or median (25-75th percentile) based on the normality of distribution.
Results
The study was conducted with 97 patients (54. 6% female, age 8. 9 ± 3. 8 years). Of these, 46. 4% ($n = 45$) were diagnosed with diabetic ketoacidosis (DKA) and 44. 3% ($n = 43$) with diabetic ketosis. At the diagnosis, serum glucose was 446 (303-537) mg/dL, c-peptide was 0. 36 (0. 2-0. 6) ng/mL, insulin was 2. 9 IU/mL (1. 7-4. 0 IU/mL; $n = 88$), and HbA1c was 11. 6±1. 8%. During the follow-up, 31 patients (32%) observed the honeymoon period for a median of 15 (7-21) months. The CGR (x1000) at the diagnosis was 0. 80 (0. 48-1. 54), and the insulin/glucose ratio (x1000) was 62. 5 (35. 9-115. 9). The insulin/glucose ratio correlated positively with age, initial pH, HCO3, and c-peptide levels ($P < 0. 05$) and negatively with HbA1c in the first year of T1D ($P = 0. 028$). The CGR was positively correlated with age, pH, HCO3, and insulin levels at the first admission ($P < 0. 001$). Also, it was negatively correlated with the mean HbA1c in the first year after the diagnosis ($P = 0. 031$), but not with HbA1c in 2 to 5 years ($p > 0. 05$). The ratio was higher in patients who had honeymoon period (1. 29 vs 0. 74; $P = 0. 020$). A CGR of >0. 46 predicted severe DKA (sensitivity: 83. 3%, specificity: 81. 4%, AUC=0. 795, $P = 0. 002$).
Conclusions
In this study, we found that the CGR in children with T1D can predict the presence and severity of DKA at the diagnosis, as well as metabolic control during and the first year. Also, it can be a useful marker to predict the honeymoon period. These results highlighted the importance of close monitoring and adjusting treatment plans of children with T1D who had lower c-peptide responses to hyperglycemia and reduced beta cell reserve at the diagnosis time.

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P416

JOINT2307

Alpelisib associated hyperglycemia in patients with advanced breast cancer

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Introduction
Alpelisib is an emerging treatment for advanced breast cancer. It promotes α-selective phosphatidylinositol 3-kinase (PI3K) inhibition, which impairs insulin action and promotes hepatic glycogenolysis, leading to hyperglycemia and compensatory insulin release. Hyperglycemia has an early onset (median 2 weeks) and has been reported in 60% of the patients, with 28% facing moderate (fasting plasma glucose >250-500 mg/dL) and severe (>500 mg/dL) hyperglycemia. Alpelisib's short half-life (8–9 hours) facilitates glucose normalization within 24–72 hours after interruption. We present two cases of severe hyperglycemia associated with alpelisib in metastatic breast cancer patients.
Clinical Cases
Patient 1, a 71-year-old woman with ER-positive, HER2-negative breast cancer submitted to bilateral mastectomy and hormone therapy. Bone metastasis appeared 28 years after the diagnosis and did not respond to multiple therapeutic regimens. Patient 2, a 44-year-old woman with the same breast cancer subtype, underwent neoadjuvant chemotherapy, left mastectomy and hormone therapy. Widespread metastasis developed 4 years later, unresponsive to 6 lines of chemotherapy. Both patients had PIK3CA mutations and started alpelisib (300 mg/day). Neither had previous diabetes (HbA1c 5, 4% and 5, 1%) and the BMIs were 35. 2 kg/m^2 and 23. 1 kg/m^2, respectively. Asymptomatic severe hyperglycemia (glucose 525 mg/dL and 552 mg/dL) occurred within 2 weeks (Patient 1) and 1 month (Patient 2) after initiating treatment. In both cases, metformin (850 mg twice daily) was initiated and alpelisib was stopped. Fasting glucose normalized within 72 hours, allowing alpelisib (200 mg/day) resumption 1 week after. Both patients experienced recurrent hyperglycemia, requiring basal insulin (10 IU/day). Patient 1 needed no further treatment, while Patient 2 had to

increase basal insulin up to 18 IU/day and start prandial insulin for glycemic control. Despite initial control, alpelisib was discontinued within 4 months in patient 1 and 1 month in patient 2 due to disease progression. After stopping alpelisib blood glucose levels normalized in the next 24 hours and both patients could halt anti-diabetic drugs.
Conclusions
The anticipated expansion of alpelisib use will probably result in a significant rise of secondary hyperglycemia cases. Delayed diagnosis can affect metabolic control, potentially leading to alpelisib dose reduction or discontinuation and compromising efficacy and patient survival. The rapid onset of severe asymptomatic hyperglycemia may warrant regular glucose monitoring in patients initiating this treatment.

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P417

JOINT1239

Understanding severe hypoglycaemia in diabetes mellitus: a retrospective analysis into risk factors, management and outcomes

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Background
Severe hypoglycemia poses major complications for patients with diabetes mellitus (DM), varying from significant mortality risk to increased healthcare dependence.
Aims
This study aims to characterise the demographics, precipitating factors, and clinical outcomes of severe hypoglycemia episodes in DM patients, focusing on differences between inpatient and outpatients. This research seeks to inform targeted interventions to improve patient outcomes and reduce hospitalisations.
Methods
A retrospective analysis was conducted between October 2023 and July 2024 and involved 9 UK hospitals as part of the DEKODE hypoglycemia study. The exclusion criteria included cases of pre-diabetes (3), uncertain diagnosis (7) or non-DM cases (293). This study defined hypoglycaemia as per the International Hypoglycaemia Study Group (IHSG); excluding IHSG level 1 episodes, 1, 451 episodes were analyzed from 946 DM patients. Data included key patient demographics, DM type, treatments received, main precipitating factors, Charlson Comorbidity Index (CCI) and overall clinical outcomes. Results were analysed using Fisher's test, with a significance level of $P < 0.05$ being used.
Results
Among 1, 451 cases analyzed, 53. 1% occurred in females, with 72. 2% of patients of White ethnicity. The median age was 73 years, and the median CCI score was 6. Type 2 diabetes accounted for 68% of episodes, with insulin use reported in 79% of cases. Intercurrent illness was the most common precipitating factor (42. 1%), followed by fasting (39. 8%) and incorrect medication (18. 6%). Treatment methods also varied; oral glucose was used in 72. 6% of cases, dextrose in 43. 9%, and glucagon in 13. 8%. Severe cases requiring hospital or Intensive Treatment Unit admission occurred in 4. 4%, with a mortality rate of 5. 2%. Median glucose was 2. 3 mmol/l (IQR: 1. 9 - 2. 7), and the median hospital stay was 7 days (IQR: 2-17). Comparing inpatient and outpatient episodes (77. 1% vs 22. 9%), outpatient episodes showed higher rates of preceding cognitive impairment (72. 6% vs 50. 2%). Fasting was also the most common precipitating factor among outpatients (42. 9% vs. 29. 5%, $P < 0.0001$) and with glucagon administered as a treatment more often to outpatients (45. 7% vs. 4. 6%, $P < 0.0001$).
Conclusion
This study highlights the clinical diversity of hypoglycemia episodes, including precipitating factors, management, and outcomes, with notable differences between inpatients and outpatients. Future research should prioritise tailored interventions, such as patient education and medication review, to reduce hospitalisations and improve outcomes.

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P418

JOINT2865

Real-world evidence of the effect of adjunctive semaglutide on weight change, liver steatosis and metabolic control in people with type 1 diabetes

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Introduction
Obesity is increasingly prevalent in type 1 diabetes (T1D), contributing to insulin resistance, metabolic syndrome, and MASLD. While semaglutide has proven effective for weight loss, glycemic control, and cardiovascular benefits in type 2 diabetes, its use in T1D remains unapproved.
Aims & Methods
This real-world study evaluates the effects of once-weekly subcutaneous 1. 0 mg semaglutide in adults with T1D. Inclusion criteria were stable glycemic control (Δ HbA1c $< 0.3\%$), stable body weight (Δ weight $< 3\%$), and a consistent insulin regimen (Δ insulin dose $< 5\%$) over the preceding year. Changes in body weight, total daily insulin dose (TDI), HbA1c and metabolic markers - including estimated glucose disposal rate (eGDR), controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) - were assessed at baseline, 6 months and 12 months.
Results
Among 42 subjects (53% male, mean age 46 $\pm$ 12 years, diabetes duration 28 $\pm$ 12 years, HbA1c 7. 4 $\pm$ 0. 8%), mean BMI was 32. 0 $\pm$ 4. 6 kg/m^2 at baseline, with 76% classified as obese. Eight subjects discontinued treatment, primarily due to gastrointestinal intolerance. At 12 months, mean weight change was -10. 3 $\pm$ 7. 9 kg ($p < 0.001$), ranging between +2. 3 to -30. 9 kg, with 76. 4% attaining $\geq$ 5% weight loss. Obesity rate at cohort level decreased from 76. 5 to 29. 4% ($p < 0.001$). Mean HbA1c evolution was -0. 4 $\pm$ 0. 6% ($p < 0.001$), with 42% reaching an HbA1c reduction of $\geq$ 0. 5%. Relative TDI reduction was 13. 6 $\pm$ 16. 0% ($p < 0.001$) after 12 months, TDI/kg of bodyweight did not change significantly. Among those with serial hepatic imaging ($n = 23$), MASLD prevalence reduced from 82. 6 to 30. 4% ($p < 0.001$). CAP decreased with 45 $\pm$ 33 dB/m, while the prevalence of significant fibrosis based on LSM fell from 20. 6 to 4. 5% ($p < 0.001$). Insulin sensitivity based on eGDR increased significantly (5. 60 $\pm$ 2. 62 to 7. 42 $\pm$ 2. 35, $p < 0.001$).
Conclusion
Adjunctive semaglutide in T1D was safe, well-tolerated, and significantly improved weight, insulin needs, glycemic control, and MASLD markers.

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P419

JOINT3767

Prevalence and characteristics of patients with cystic fibrosis-related diabetes in croatia

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Introduction
Cystic-fibrosis related diabetes (CFRD) is an important emerging complication of patients with cystic fibrosis (CF). This study investigated the prevalence of CFRD in the Croatian CF population, the age at CFRD diagnosis, insulin regimens used, and the relationship between age at CFRD diagnosis, insulin requirements, glycated hemoglobin (HbA1c), and body mass index (BMI).
Participants and Methods
Medical records from 157 patients with genetically and laboratory-confirmed CF were reviewed up to January 2025. All patients were followed at the *Cystic fibrosis center for children and adults*, University Hospital Centre Zagreb, the

country's primary treatment facility for CF. The American diabetes association (ADA) criteria were used to classify patients as CFRD. Anthropometric and clinical data were collected from the most recent medical records. Descriptive statistics were employed to summarize the prevalence and clinical characteristics of CFRD patients. Spearman's rank correlation coefficient was used to assess the relationships between age at CFRD diagnosis, age of insulin initiation, insulin doses, HbA1c, and BMI.
Results
Seventeen out of 157 patients (10. 8%) were identified with CFRD. The prevalence of CFRD was 4. 5% (4/89) in the pediatric CF population and 19. 1% (13/68) in the adult CF population. The median age of CFRD diagnosis was 14 years (range 9 – 22 years, SD = 3. 95), with the majority diagnosed between 9 and 15 years. The median BMI of patients with CFRD was 23. 0 kg/m^2 (range 13. 5 – 30. 5 kg/m^2, SD = 3. 73) and the median age was 24 years (SD = 6. 64). Fifteen patients (88%) were receiving combination therapy with ivacaftor, tezacaftor and elexsacaftor, and one patient was using ivacaftor only. At the last visit, 76. 5% (13/17) were using insulin. One patient was treated with bolus insulin only, 53. 4% (7/13 patients) were using basal-bolus multiple daily injections, and 38. 5% (5/13) were using insulin pumps. The average total daily insulin/kg to treat diabetes was 0. 854 U/kg (SD = 0. 398). The age at CFRD diagnosis and age at insulin introduction were positively correlated with BMI (P = 0. 02853, P = 0. 0254, respectively), and total daily insulin/kg was postively correlated with HbA1c (P = 0. 03308).
Conclusion
The prevalence of CFRD in Croatia and the age at CFRD diagnosis is consistent with previous studies. Patients diagnosed at a younger age and requiring insulin earlier had lower BMIs, likely to due to a faster decline in beta cell function and an earlier onset of insulinopenia.

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P420

JOINT1307

Partitioning the genetic risk of obesity and type 2 diabetes using single-cell multi-omics of the gastrointestinal tract

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The worldwide increase in the prevalence of Type 2 Diabetes (T2D) and obesity constitutes a major threat to global health; however, the complex nature of these diseases is severely hampering the development of prognostic tools and clinical interventions. Both T2D and obesity have a strong genetic component; yet, the functional impact of the identified genetic variants in terms of causal genes, cell types, and organs remains largely unknown. The gastrointestinal (GI) tract is located at the junction between the gut microbiome and the gut-brain axis, which links intestinal function to the central nervous system, resulting in changes in appetite and behavior. Due to the complex regionality and cellular composition of the GI tract, it is largely unknown to what extent genetics play a role in metabolic diseases mediated by the GI tract, in particular, T2D and obesity. We are performing single-cell sequencing on human biopsies from multiple locations in the colon using the 10x Multiome assay for gene expression and chromatin accessibility. This allows us to map the location, activity, and interaction of promoters and enhancers in individual cell types and integrate these with genome-wide association studies (GWASs) of T2D and obesity. Using the resulting multi-omic and cell type-specific map of gene regulation, we can i) partition the genetic risk of T2D and obesity across cell types of the GI tract, ii) prioritize causal genetic variants and genes, and iii) perform data-driven stratification of T2D and obesity patients based on their cell type-specific polygenic risks. Ultimately, this will lead to novel molecular clinical targets and non-invasive prognostic tools for T2D and obesity.

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P421

JOINT30

A proof-of-concept study of type 2 diabetes remission with pharmacotherapy

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Background
This study evaluates the effectiveness of semaglutide and dapagliflozin alongside metformin, comparing it to vildagliptin and glimepiride alongside metformin in achieving diabetes remission.
Methods
An open-label, parallel, randomized controlled trial involving 85 participants diagnosed with T2DM within the past two years was conducted. The trial arm received semaglutide, dapagliflozin, and metformin, while the control arm received vildagliptin, glimepiride, and metformin. After 24 weeks, all medications were withdrawn to assess remission and relapse rates. The primary outcome was the proportion of patients achieving remission (HbA1c < 6. 5% without medication) and the time to relapse after stopping therapy.
Results
At the end of the 12 weeks after the completion of therapy, 26 (93%) and 11 (39%) patients were in remission in the trial and control arm, respectively. When compared at the end of 24 weeks, 36 weeks, and 52 weeks of completion of therapy, the remission rate was 71. 42% (n-20), 67. 85% (n-19), and 43. 42 % (n-13) in the trial arm as compared to 25% (n-7), 21. 42% (n-6), 3. 57% (n-1) in the control arm. The mean time to relapse was 39 weeks in the trial arm, compared to 19. 75 weeks in the control arm ($p < 0.001$). Additionally, the trial arm, as compared to the control arm, exhibited a difference in median weight reduction of 5. 96 kgs. Factors associated with a delayed relapse included a greater decrease in HbA1c from baseline, improved beta-cell function as assessed by HOMA-β and the disposition index, and a reduction in insulin resistance measured by HOMA-IR and a decrease in BMI.
Conclusion
The combination of semaglutide and dapagliflozin, used alongside metformin, effectively induces remission and promotes weight loss in patients with type 2 diabetes mellitus (T2DM). This treatment demonstrates significant potential as a transformative approach to diabetes management. Additionally, discontinuing medications for three months supports sustainable remission outcomes, with positive results maintained even one year after the therapy has ended.

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P422

JOINT3330

Type 1 diabetes children with less sleeping time have higher HbA1c level and shorter stature

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Background
Type 1 diabetes mellitus (T1DM) is a complex metabolic condition marked by persistent hyperglycemia resulting from the autoimmune destruction of pancreatic β cells. Sleep is essential for sustaining the equilibrium of bodily functioning. A recent study indicates that sleep modification influences several physiological systems, including metabolic and endocrine control. A sufficient sleep is needed for optimum growth and development in children. Poor sleep in children with T1DM can lead to decreased insulin sensitivity and impair glycaemic control. High blood glucose level in uncontrolled diabetes can disrupt the normal production of growth hormones, leading to growth failure. The Asia-Pacific agreement advises 9–11 hours of sleep for children aged 9 to 13 years and 8–10 hours for those aged 14 to 18 years. The aim of this study is to analyse the correlation between sleep duration, HbA1c, and growth in children with T1DM
Methods
37 T1DM Children who had been diagnosed with diabetes for > 6 months and had regular visits at the paediatric endocrinology outpatient clinic at Dr. Soetomo Hospital were included. Sleep duration was obtained from the average of self-reported sleep duration in the last weeks. Weight measurements were performed using a GEA Medical® digital scale, offering precision to within 100 grams. Height measurements were obtained using a Onemed® microtoise or stadiometer, assuring accuracy to the closest 1. 0 millimetre. Height and weight was transformed into z-scores standard deviations (SDS) according to the WHO growth chart. HbA1c data was taken from the most recent examination of the medical record. Spearman correlation test and St. Nicholas House Analysis (SNHA) in RStudio were used to process the data with $p < 0.05$ considered significant.
Results
The mean age of the children is 158. 6 ± 45. 7 months old. The average HbA1c is 10 ± 2, and height SDS is -1. 389 ± 1. 28. The correlation test showed a

significant correlation between sleep duration and HbA1c (rho= -0. 54; $P < 0.01$), also a correlation between HbA1c and height SDS (rho= -0. 44, $P < 0.01$), while there is a weak correlation between height SDS and sleep duration (rho=0. 25; $P = 0.1$).

Conclusions

There is an association between sleep duration, growth, and HbA1c in children with T1DM. Children with less sleep duration have higher levels of HbA1c and lower height. Children with T1DM should have sufficient sleep to attain optimal glycaemic control, along with other established diabetic management like insulin administration, physical exercise, and dietary regulation.

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P423

JOINT1966

Predictive factors of type 2 diabetes and prediabetes diagnosis in women with gestational diabetes

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Introduction

Women with gestational diabetes (GD) are at increased risk of developing type 2 diabetes (T2D), and 20-33% of them are diagnosed with either prediabetes or T2D immediately postpartum. Therefore, a postpartum 75g oral glucose tolerance test (75g-OGTT) is recommended for all women with GD.

Aims

To identify predictive factors for postpartum diagnosis of T2D or prediabetes in women with GD.

Methods

This retrospective study included all women diagnosed with GD that delivered at a tertiary center from 2019 to 2023. Logistic regression models were used to evaluate associations between abnormal postpartum 75g-OGTT and demographic and clinical characteristics.

Results

Of 700 women with GD, only 318 (45. 4%) attended their scheduled postpartum 75g-OGTT, while 54. 6% missed their appointments. Higher age [OR (odds ratio) 1. 07, 95%CI (95% confidence interval) 1. 05-1. 1, $P < 0.001$] and higher education levels (OR 1. 56, 95%CI 1. 35-1. 8, $P < 0.001$) were identified as predictors of postpartum OGTT attendance. Among the 318 women who completed testing, 259 (81. 4%) had normal results, and 59 (18. 6%) had abnormal results, with 13 diagnosed with T2D and 46 with prediabetes. The identified predictors of abnormal postpartum 75g-OGTT were:

- Higher HbA1c levels during pregnancy (3rd trimester HbA1c: OR 3. 72, 95%CI 1. 89-7. 33, $P < 0.001$; average HbA1c: OR 3. 98, 95%CI 2. 02-7. 86, $P < 0.001$);
- Requirement of pharmacological treatment for GD control (OR 2. 86, 95%CI 1. 55-5. 29, $P < 0.001$). A subanalysis of only the pharmacologically treated GD cases showed that treatment with both insulin and metformin further increased postpartum prediabetes/T2D risk, vs treatment with insulin or metformin alone (OR 2. 33, 95%CI 1. 11-4. 91, $P = 0.03$);
- Higher plasma glucose levels at GD diagnosis (fasting plasma glucose levels: OR 1. 04, 95%CI 1. 02-1. 05, $P < 0.001$; 1-hour plasma glucose levels of diagnostic OGTT: OR 1. 014, 95%CI 1. 003-1. 03, $P = 0.014$; 2-hour plasma glucose levels of diagnostic OGTT: OR 1. 011, 95%CI 1. 001-1. 021, $P = 0.035$).

Other evaluated factors were not predictive of abnormal postpartum 75g-OGTT Results age, parity, positive family history of T2D, positive personal history of GD, pre-pregnancy BMI, weight gain during pregnancy or trimester of GD diagnosis.

Conclusion

This study showed that HbA1c levels during pregnancy, GD pharmacological treatment requirement and plasma glucose levels at GD diagnosis were predictors of abnormal postpartum 75g-OGTT in women with GD. These factors should be considered in order to optimize GD management strategies. Additionally, similarly to what is described in the literature, over half of women with GD did not attend their postpartum OGTT appointments, highlighting the need for interventions to improve adherence.

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P424

JOINT1482

Using the telegram bot for differential diagnosis of diabetes mellitus and risk assessment of its complications

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Relevance

Diabetes Mellitus (DM) ranks among the most prevalent endocrine disorders, requiring accurate differential diagnosis to determine the optimal treatment strategy. Variability in clinical manifestations, the presence of atypical forms (LADA, MODY, pancreatogenic diabetes), and limited resources complicate this process. A critical aspect also involves the timely detection of complications, notably diabetic retinopathy (DR), a leading cause of blindness among DM patients. The adoption of digital technologies, including Telegram Bots, can significantly enhance the efficiency of diagnosis and patient monitoring.

Materials and Methods

The Telegram Bot "DiaPredict" was developed to implement an algorithm for differential diagnosis of DM types and complication risk assessment. This algorithm is based on an analysis of international guidelines (ADA, WHO, IDF) and clinical data. The Bot automates the collection of anamnestic information, evaluates laboratory indicators, analyzes DR risk factors, and generates personalized recommendations for further examinations.

Results

The functionalities of the "DiaPredict" Telegram Bot include:

- Interactive collection of anamnesis, symptoms, and laboratory indicators.
- Patient stratification based on phenotypic characteristics.
- Risk assessment for the development of DR based on a multifactorial analysis (glycemic control, duration of DM, comorbidities).
- Formation of personalized recommendations for additional examinations and ophthalmological monitoring. "DiaPredict" approbation demonstrated high accuracy in the differential diagnosis of DM types and stratification of DR risks. Using the Bot allowed:
- Minimization of cognitive biases in doctors when diagnosing;
- Automation of clinical data processing, reducing decision-making time;
- Increased awareness among primary care physicians regarding atypical forms of DM and DR;
- Optimization of referrals for ophthalmological examination.

Conclusions

The "DiaPredict" Telegram Bot is an effective tool for optimizing the diagnostic process in DM, and the timely detection of DR. Its implementation can enhance the quality of medical care, reduce the burden on doctors, and improve patient management outcomes. Further research is directed towards integrating the Bot with electronic medical systems and evaluating its long-term effectiveness.

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P425

JOINT70

An unusual case of MODY

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Our patient was diagnosed with gestational diabetes at age 21. At 28 years of age, she was diagnosed with type 2 diabetes. She was diagnosed in Poland moving to England shortly. The patient unfortunately knew very little about her biological family. She reported her mother had diabetes diagnosed as type 2 diabetes, but diet controlled which was diagnosed during pregnancy. She believed her mother possibly had a rarer form of diabetes. Her current medications were Gliclazide, Basal insulin, Linagliptin Dapagliflozin and Metformin. Her BMI at diagnosis was 22. 7. Whilst in UK, she was found to require insulin and tested negative for anti-GAD, anti-Islet cell antibodies, and had measurable blood C-peptide levels 7 years from diagnosis of diabetes. Her age and low BMI prompted a genetic screening revealing a NEUROD 1 mutation. It is believed that the patient is part of a large family in Poland with the same gene mutation. She has a son and daughter who do not have diabetes, so genetic testing is available for her children should she wish to proceed. There is no exact penetrance figure for the NEUROD1, but it is believed to be lower than the HNF1A mutation. There is no certainty as to whether the children will go on to develop diabetes and testing will not provide predictive onset for the children's diagnoses of diabetes. It was advised to only test if the children became symptomatic and the mother was happy with this with prior counselling if genetic testing was required.

NEUROD1 gene is expressed in pancreatic and neuronal cells, being associated with MODY type 6. NEUROD1 gene mutations have been reported in 20 families worldwide to date. Two mutations in NEUROD1, are associated with the development of type 2 diabetes in the heterozygous state. The first is a missense mutation while the second is a truncated polypeptide lacking the carboxy-terminal trans-activation domain, a region that associates with the co-activators CBP and p300. The clinical profile of patients with the truncated NEUROD1 polypeptide is more severe than that of patients with the Arg 111 mutation. A deficient binding of NEUROD1 or binding of a transcriptionally inactive NEUROD1 polypeptide to target promoters in pancreatic islets could lead to the development of type 2 diabetes. We surmise that patients with a family history of diabetes, normal BMI, early onset of diabetes, and no autoimmunity should be at least initially screened for a known MODY mutation.

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P427

JOINT216

Exploring a synergistic approach: dual GLP-1 agonist combined with degludec basal insulin for early type 1 diabetes treatment and its impact on albumin-insulin producing cells expression

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Purpose
This manuscript explores the potential of dual glucagon-like peptide 1 (GLP-1) agonists combined with degludec basal insulin to treat early type 1 diabetes. The study aims to evaluate the efficacy and mechanistic impact of semaglutide, a GLP-1 agonist, on newly diagnosed type 1 diabetes patients.
Methods
A retrospective analysis was conducted to assess the effects of semaglutide on individuals with early type 1 diabetes. The analysis focused on the elimination of prandial and basal insulin, changes in C-peptide levels, and overall glycemic control. The study also examined the potential for GLP-1 agonists to protect residual beta cells, stimulate cell proliferation, and reprogram liver cells into insulin-producing cells. Additionally, the modification of GLP-1 agonists with albumin ligands to extend their half-life and enhance their anti-diabetic effects was investigated.
Results
The findings demonstrate the elimination of both prandial and basal insulin requirements, an increase in C-peptide levels, and improved glycemic control among the patients. Despite the positive outcomes, the study's retrospective nature and absence of a control group highlight the necessity for larger, prospective trials.
Conclusion
GLP-1 agonists show considerable potential in the management of type 1 diabetes by protecting residual beta cells, promoting cell proliferation, and reprogramming hepatic cells. The integration of modified GLP-1 agonists with albumin ligands could further enhance these effects. The manuscript underscores the need for continued research to fully explore this therapeutic approach. The proposed treatment strategy, which combines the autoimmune hypothesis, the proliferative effects of GLP-1, and albumin ligand modifications, aims to restore beta cell mass and function, thereby improving the quality of life for individuals with type 1 diabetes. Clinical trials are planned for 2024 under the registration 'Amr Ahmed, Maher M. Akl, Semaglutide GLP1 Agonists with Degludec Basal-bolus Insulin in Early Type 1 Diabetes to Basalbolus' (ClinicalTrials. gov Identifier NCT06057077).

Keywords: Adult human hepatic tissue; Anti-diabetic effects; Cell proliferation; Degludec basal insulin; Dual GLP-1 agonist; Early type 1 diabetes; GLP-1 agonists; Insulin-producing cells; Modified GLP-1 derivat; Type 2 diabetes.

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P428

JOINT1317

Comparative study on clinical indicators of type 1 diabetes mellitus in children in southwest china before and after the COVID-19 pandemic

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Objective
Viral infections, as environmental factors, significantly influence the onset and progression of Type 1 Diabetes Mellitus (T1DM). The novel coronavirus, in particular, may cause more complex immune disruptions in children, potentially leading to the development of T1DM. This study aims to analyze the impact of the virus on the onset and progression of T1DM by comparing clinical indicators of newly diagnosed T1DM children in Southwest China before and after the pandemic.
Methods
A retrospective analysis was conducted on children initially diagnosed with diabetes in our hospital in 2019 and 2024. Differences in age of onset, glycated hemoglobin levels, and diabetes antibody levels were examined, and their association with COVID-19 infection was analyzed.
Results
In 2019, 87 children were newly diagnosed, compared to 142 in 2024. The proportion of female children was 59. 78% and 59. 15%, respectively. The age of onset was 7. 40 ± 3. 94 years and 8. 13 ± 4. 18 years, respectively. Glycated hemoglobin levels were 12. 93% ± 2. 49% and 12. 54% ± 2. 48%, respectively. The proportion of children presenting with ketoacidosis at diagnosis was 59. 78% and 80. 99%, respectively. Among the 2024 cohort, 61. 27% had a history of COVID-19 infection, with an average of 2 years between infection and diabetes diagnosis; 7. 04% had a history of mumps virus infection. Antibody testing (GADA, IAA, INS, ZnT8, IA-2Ab) revealed that in 2019, 63. 22% of patients tested positive for only one antibody, with 45. 98% positive for GADA alone, 41. 38% positive for two or more antibodies, and 29. 89% positive for IA-2Ab. In 2024, 48. 23% tested positive for only one antibody, with 3. 53% positive for GADA alone, 51. 77% positive for two or more antibodies, and 77. 65% positive for IA-2Ab.
Conclusion
The incidence of newly diagnosed T1DM in children increased significantly before and after the COVID-19 pandemic, closely related to COVID-19 infection. Although there were no significant changes in the age of onset, glycated hemoglobin levels, or gender distribution, there were substantial differences in the types and proportions of antibodies, with a more pronounced coexistence of multiple antibodies. This suggests that viral infections may cause pancreatic islet damage through different immune mechanisms, providing clinical evidence for further research into the immune mechanisms of T1DM.

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P429

JOINT1691

Socioeconomic status, modifiable factors, and risk of microvascular complications in individuals with type 2 diabetes: a cohort study from the UK biobank

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Background
Diabetes is a prevalent chronic condition that can lead to microvascular complications, which significantly affect patients' health and quality of life. Socioeconomic status (SES) is associated with an increased risk of chronic metabolic diseases and may influence the progression of diabetes. This study aims to investigate whether lower SES was associated with an increased risk of diabetic microvascular complications, and analyze the potential mediating role of several modifiable factors.
Methods
The study included 11, 309 patients with type 2 diabetes at baseline from the UK Biobank cohort. SES was grouped based on income, education, and employment status by using the latent class analysis. The primary endpoint was the occurrence of diabetic microvascular complications, including diabetic nephropathy, diabetic neuropathy, and diabetic retinopathy, which were identified through electronic health records. Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for diabetic microvascular complications. Mediation analysis was applied to explore potential mediators between SES and diabetic microvascular complications.
Results
During a median follow-up of 12. 2 years, 2, 043 cases of diabetic microvascular complications were recorded. Compared to participants with high SES, those with low SES had a HR of 1. 75 (95% CI: 1. 53, 2. 01) for total microvascular complications, a HR of 2. 11 (95% CI: 1. 74, 2. 55) for diabetic nephropathy, a HR of 1. 40 (95% CI: 1. 14, 1. 72) for diabetic retinopathy, and a HR of 1. 79 (95% CI:

1. 32, 2. 43) for diabetic neuropathy, respectively. Mediation analysis indicated that alcohol consumption, body mass index, triglycerides, high-density lipoprotein cholesterol, and glycated hemoglobin mediated the association between SES and total microvascular complications, with mediation percentages of 1. 3% (95% CI: 0. 3%, 3. 0%), 12. 2% (95% CI: 8. 4%, 17. 0%), 4. 4% (95% CI: 2. 4%, 7. 0%), 10. 9% (95% CI: 7. 1%, 16. 0%), and 10. 8% (95% CI: 7. 4%, 16. 0%), respectively. Body mass index, high-density lipoprotein cholesterol, and glycated hemoglobin also mediated the association between SES and individual microvascular complications ($P < 0.05$).
Conclusions
Our study indicated that lower SES was associated with an increased risk of microvascular complications in patients with type 2 diabetes, in which obesity-related indicators and glycated hemoglobin played important mediating roles. SES is relatively difficult to change, and efforts are suggested be made through other approaches such as increasing financial support for patients of low SES and enhancing weight and blood glucose management to prevent or reduce the occurrence of diabetic microvascular complications.

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P430

JOINT3925

Challenges in the diabetes transition clinic: a 10-year experience at a tertiary care hospital

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Introduction
Adolescents, particularly those with chronic conditions, face heightened demands and challenges as they transition into adulthood, especially in the social and professional spheres, along with an increasing need of autonomy. Studies show that this transition often leads to deteriorating glycemic control and increased loss to follow-up in adolescents with diabetes. To address these concerns, our center established a Diabetes Transition clinic to ensure continuity of care, treatment adherence, and optimal metabolic control.
Objectives
To characterize the patients with diabetes who attended the Diabetes Transition clinic of a tertiary care hospital.
Methods
Retrospective study of all patients with diabetes who transitioned from the Pediatric to the Adult Diabetes clinic from January 2015 to December 2024. Data were collected from the patients' medical records. Statistical analysis was performed using SPSS.
Results
A total of 96 patients were transitioned from the Pediatric Diabetes clinic to the Adult Diabetes one during this period. 52. 1% ($n = 50$) were female, median age at diabetes diagnosis was 10 years (1-17) and median age at the time of transition was 19 years (18-22). 91. 7% ($n = 88$) of patients had type 1 diabetes (T1D), 5. 2% ($n = 5$) had type 2 diabetes, one patient had MODY type 3, one patient had diabetes secondary to cystic fibrosis and one patient had diabetes secondary to congenital generalized lipodystrophy type 1. Mean HbA1c levels before transition and at 1, 3 and 5 years post-transition were 8. 68 ± 1. 88%, 8. 47 ± 1. 84% ($P = 0.98$), 7. 87 ± 1. 64% ($P = 0.10$) and 7. 94 ± 1. 45% ($P = 0.11$), respectively. Mean time in range (TIR) of the T1D patients was 44. 3 ± 15. 3% pretransition and 40. 1 ± 14. 7% 1 year post-transition ($P = 0.24$). Currently, 79. 2% ($n = 76$) of patients remain in care at our Adult Diabetes clinic. Of the remaining patients, 12 were lost to follow-up, 7 elected to be transferred to other centers and the one with cystic fibrosis died from non-diabetes-related complications.
Conclusion
Unlike trends reported in the literature, in our study of the last 10 years of our Diabetes Transition clinic, mean HbA1c and TIR did not exhibit statistically significant differences in the years post-transition. These findings highlight the role of our multidisciplinary approach in supporting young adults with diabetes through this critical transition period. Nevertheless, implementing a more structured transition process, initiated earlier in adolescence, could further enhance patient engagement, improve long-term metabolic outcomes and reduce loss to follow-up.

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P431

JOINT2017

Evaluation of emergency department admission reasons and associated factors in pediatric patients diagnosed with type 1 diabetes mellitus

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Objective
The diverse clinical presentations, increasing prevalence and incidence rates of type 1 diabetes mellitus (T1DM) have escalated the need for emergency department (ED) visits and hospital admissions. This study aimed to evaluate the characteristics and distributions of all ED visits—both diabetes-related and unrelated, requiring or not requiring hospital admission—among pediatric patients diagnosed with T1DM.
Materials and Methods
This retrospective study included 201 pediatric and adolescent patients who had been followed with a T1DM diagnosis for at least one year and presented to the Pediatric Emergency Department of Ankara Etlik City Hospital between October 1, 2022, and March 1, 2024. Patient data included sociodemographic characteristics, details of diabetes diagnosis and management, ED visit information, and laboratory findings.
Results
Among a total of 201 patients, 92 (46%) were using continuous glucose monitoring (CGM) devices, and 17 (8. 5%) were using insulin pumps. The mean HbA1c level over the past year was 8. 75 ± 2. 51%, and 61 patients (29. 4%) had not undergone an HbA1c measurement within the last three months. Between October 2022 and March 2024, there were a total of 345 ED visits, 50. 4% of which were diabetes-related, while 49. 6% were due to non-diabetes-related causes. Vomiting was the most common presenting complaint. Regarding the most recent ED visits, 15. 9% ($n = 32$) were due to hyperglycemia, 11. 4% ($n = 23$) due to ketosis, 26. 4% ($n = 53$) due to diabetic ketoacidosis (DKA), 13. 9% ($n = 28$) due to hypoglycemia, 26. 9% ($n = 54$) due to infections, and 5. 5% ($n = 11$) due to other reasons. Patients presenting with DKA had higher mean ages, higher diabetes diagnosis ages, higher daily insulin doses, and higher mean HbA1c levels compared to those with other diabetes-related presentations ($P < 0.001$). The CGM usage rate among DKA patients ($n = 8$; 15. 1%) was significantly lower than that of patients presenting with other diabetes-related conditions ($P < 0.001$). Patients with lower basal insulin percentages, those using antidepressant therapy, and those who were diagnosed with diabetes during a DKA episode had a higher likelihood of developing DKA during periods of illness.
Conclusion
Our study found that the clinical reasons for ED visits among pediatric patients with T1DM were closely associated with their metabolic control status and demographic characteristics. The majority of diabetes-related visits were accompanied by infections. Diabetes education for patients and caregivers should emphasize the importance of glycemic regulation during periods of illness. Regular follow-ups in collaboration with diabetes care teams are essential for improving diabetes management and reducing the long-term burden on emergency services.

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P432

JOINT2095

Investigation of lower urinary tract symptoms and their effects on quality of life in patients using sglt-2 (sodium-glucose cotransporter-2) inhibitors

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Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are oral antidiabetic agents that have gained attention for their beneficial effects on glucose control, as well as their cardio-renal and metabolic benefits in managing diabetes mellitus. As diabetes prevalence increases, the use of these medications is expected to rise. This study aimed to assess the impact of SGLT-2 inhibitors on lower urinary tract symptoms (LUTS) and quality of life in patients with type 2 diabetes, a topic that has been limitedly explored. Conducted at the Department of Endocrinology, Başkent University Faculty of Medicine (October 2023-May 2024), the study included 210 participants—105 patients using SGLT-2 inhibitors and 105 using other non-insulin antidiabetic agents. The subjects were evaluated separately by sex using the FLUTS/MLUTS questionnaires, validated in both international and Turkish contexts. Additional data on comorbidities, medication use, fluid intake, and body mass index were also collected. Statistical analysis was performed using independent samples t-test, Mann-Whitney U test, Chi-square/Fisher's Exact test, and Spearman's correlation coefficient, with significance set at $P < 0.05$. The results revealed an increase in urinary frequency in male patients using SGLT-2 inhibitors ($P = 0.015$), but no significant differences in

voiding, storage, or nocturia complaints compared to the control group ($p > 0.05$). In female patients, no significant effects of SGLT-2 inhibitors on voiding, storage, or incontinence complaints were observed ($p > 0.05$). However, an increase in voiding discomfort was noted in the group using dapagliflozin among females ($P = 0.048$). This study is the first to evaluate the effects of SGLT-2 inhibitors on LUTS separately by sex and against a control group. It provides new insights, showing an increase in urinary frequency in male patients after more than six weeks of drug use. Additionally, the persistent urinary frequency in male patients using SGLT-2 inhibitors for over a year suggests that pollakiuria may continue long-term. The study also explored the relationship between SGLT-2 inhibitors and incontinence, contributing a novel perspective on their effect on voiding and storage phases. Our findings offer valuable insights into the use of SGLT-2 inhibitors and highlight the need for further research in larger populations to deepen our understanding of their impact on LUTS and optimize drug use in clinical practice.

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P433

JOINT2206

Comparison of metabolic control in children with type 1 diabetes using reimbursed, self-funded intermittent, and self-funded continuous CGM

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Aim
Although children with type 1 diabetes facing significant financial constraints are provided with reimbursed continuous glucose monitoring (CGM) systems in Turkiye, many individuals with diabetes continue to encounter socioeconomic barriers to accessing CGM technology. To mitigate these challenges, we encourage families experiencing financial difficulties to wear sensors just before their routine follow-up visits. This approach aims to enhance patient/parents' awareness and facilitate more accurate treatment decisions. This study aims to assess differences in metabolic control among patients utilizing reimbursed CGMs, self-funded intermittent CGMs, and self-funded continuous CGMs.
Methods
Between 2021 and 2023, data from 207 CGM users were collected from CareLink, LibreView, and Clarity databases. Patients were excluded if they were in honeymoon period, used insulin pumps, had less than 14 days of CGM data, fewer than two CGMs annually, fewer than two HbA1c tests per year, or missed follow-ups. The final cohort was divided into three groups: reimbursed users (Group-1), self-funded intermittent users (Group-2), and self-funded continuous users (Group-3). Intermittent users were defined as those using sensors at least twice (10-14 days period) a year. Each group was evaluated for pre- and post-CGM one-year averages of HbA1c and anthropometric data, also groups were compared with each other in terms of one-year averages of TIR, TAR, TBR, CV.
Results
A total of 147 patients (Group-1, $n = 49$; Group-2, $n = 43$; Group-3, $n = 55$) were included. Pre-CGM HbA1c levels were significantly higher in Group-1 compared to Groups 2 and 3 ($P < 0.001$) (Table). One year after CGM use, Group-1 still had the poorest metabolic control, but it was the only group to show a significant decrease in HbA1c. Group-3 had the lowest post-CGM HbA1c ($P < 0.0001$). Although Group-3 had higher TIR value compared to Group-2, there is no statistical significance was found ($P = 0,075$).
Conclusion
Patients with poor metabolic control benefit most from CGM systems and should be prioritized for support, regardless of glycaemic outcomes. Although not statically significant and less than those using continuous CGM, individuals using intermittent CGM showed a minimal decrease in one-year average HbA1c.

Table 1: Comparison of pre-post CGM Hba1c, TIR, TAR, TBR and CV between groups

	Group-1 ($n = 49$)	Group-2 ($n = 43$)	Group-3 ($n = 55$)	p
Hba1c(%), mean±SD	9. 27±2. 03	7. 72±2. 43	7. 48±1. 44	**0. 0005**
Post-CGM Hba1c(%), mean±SD	8. 45±1. 22	7. 57±1. 08	7. 05±0. 76	**<0. 0001**
TIR(%), mean±SD	40. 49±16. 44	54. 13±17. 83	61. 37±14. 57	**<0. 0001**
TAR(%), mean±SD	55. 58±17. 67	40. 15±18. 85	33. 55±14. 00	**<0. 0001**
TBR(%), mean±SD	2. 6(0-13. 0)	3. 6(0-18. 3)	3. 2(0-12. 0)	0. 075
CV(%), mean±SD	39. 14±8. 75	40. 15±7. 11	38. 16±7. 38	0. 45
Change in Hba1c	**-0. 82***	-0. 15	-0. 43	

*$P = 0.0023$

Keywords: CGM, type-1 diabetes, metabolic control

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P434

JOINT3412

An Unusual case of late-onset ipex syndrome

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Introduction
IPEX syndrome is a primary immunodeficiency caused by hemizygous mutations in the *FOXP3*, which encodes a key transcription factor essential for thymus-derived regulatory T cells to maintain immune tolerance. It is typically characterized by systemic autoimmunity beginning in the first year of life. This syndrome is defined by a triad of enteropathy, endocrinopathy, and eczematous dermatitis. Early diagnosis and treatment are crucial for preventing complications.
Case
A 4-year-2-month-old male patient was referred for hyperglycemia. Previous history revealed hematuria, proteinuria and thrombocytopenia at 2. 5 years. ANA and anti-dsDNA antibodies were positive, renal biopsy suggesting Class 5 lupus nephritis led to treatment with pulse steroids, intravenous immunoglobulin(IVIG) , cyclophosphamide, azathioprine and hydroxychloroquine. In addition, recurrent pancytopenia, and later, recurrent thrombocytopenia and arthritis in the left knee was treated with MPZ, eventually he developed hyperglycemia for which insulin lispro was started. The patient was referred to our clinic for management of hyperglycemia. There was no history of consanguinity, however, two maternal uncles had a history of diabetes with onset at 10 years of age. The patient's height and weight were normal, and systemic examinations were unremarkable. Investigations revealed elevated HbA1c, negative autoantibodies for diabetes, thyroid and celiac disease, normal liver, kidney, and thyroid functions, and anemia. Insulin glargine was added to the treatment. There was a progressive increase in HbA1c since the initiation of insulin(baseline: 4. 2%; 3rd months: 5. 2%; 18th: 10. 9%), and the family history of insulin-dependent diabetes in two uncles, thus genetic diabetes was suspected. Next-generation sequencing identified a hemizygous mutation in *FOXP3*. Further exploration of the uncles' medical history revealed that one uncle was diagnosed with diabetes at age 11, and chronic diarrhea and microcytic anemia at age 14; while the other uncle developed diabetes at age 8, chronic diarrhea at age 11, thrombocytopenia at age 15, and adrenal insufficiency at age 18. Genetic testing confirmed the *FOXP3* hemizygous mutation in the uncles, heterozygous in the mother. IVIG and fluconazole prophylaxis were initiated. High-resolution HLA samples were sent for the patient and siblings to assess suitability for HSCT.
Conclusion
IPEX syndrome presents with neonatal diabetes as well as early-onset enteropathy and eczema. However, it may have an atypical presentation, and should be considered in cases of diabetes of unknown etiology, especially associated with other autoimmune disorders, even when onset is after the first year of life, and is not accompanied by enteropathy/eczema.

Keywords: Autoimmune polyendocrinopathy, diabetes, nephropathy, arthritis, thrombocytopenia

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P435

JOINT257

Transforming youth diabetes care: the role of tellmi in providing digital mental health support in NHS somerset UK

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Background
Young people with diabetes face significant physical and mental health challenges that are often overlooked or mismanaged. Tellmi is a novel digital peer-support mental health app designed for individuals from age 11. Tellmi offers youths unlimited, anonymous, and pre-moderated peer support, organised by age groups. For high-risk comments, real-time trained counsellors actively intervene to provide appropriate support.
Methods
This qualitative study aimed to explore the lived experiences of youths with diabetes through interviews with participants recruited via Tellmi. As part of this project, the Tellmi app was adapted to enhance diabetes-specific support. Additions included 32 diabetes validated resources and services, such as a Diabetes Sucks Portal offering direct access to the Somerset NHS Children's Diabetes Nurses helpline. New content addressed topics like recognising diabetes symptoms, mental health, sexual health, and students' rights at school, codeveloped with NHS Somerset, paediatric diabetes clinicians, psychologists from Somerset Foundation Trust and the Tellmi team with input from youths with diabetes who tested and approved the questions. Promotional materials were also designed by young people with diabetes, ensuring a collaborative, youth-focused approach.
Results
7 participants (2M, 5 F) were recruited (age13-20 yrs). Findings revealed that a lack of awareness among healthcare providers often led to missed opportunities for timely diagnosis. For girls, symptoms such as weight loss were frequently misinterpreted as disordered eating, contributing to the later development of eating disorders. Participants also revealed that schools lack understanding of the complexities of diabetes management. All participants reported experiencing mental health issues, including anxiety, depression, self-harm and suicidal ideation. While some participants had accessed Child and Adolescent Mental Health Services (CAMHS), many expressed a preference for informal, peer-based support such as the Tellmi app. Tellmi was praised for allowing young people to both give and receive support within a community. Participants found this model effective in addressing feelings of isolation and in providing practical advice and emotional reassurance.
Conclusions
These findings highlight the urgent need to integrate psychological support into the diagnostic and management processes of diabetes for young people. This research underscores the importance of holistic, patient-centered approaches to diabetes care. Improving education for healthcare providers, caregivers, and schools could facilitate earlier diagnosis and reduce the long-term physical, mental, and economic costs of diabetes. Integrating psychological support as a standard part of diabetes care, and leveraging innovative novel digital tools like Tellmi, offers a promising pathway to improving outcomes for young people with diabetes.

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P436

JOINT2811

The relationship of iron homeostasis and biochemical biomarkers according to therapeutic management in patients with type 2 diabetes

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Introduction
Iron, as an essential micronutrient, crucially modulates insulin sensitivity, impacting various processes in glucose homeostasis. The mechanisms involved in this interaction are crucial for developing targeted therapeutic interventions to address metabolic disorders.
The aim of the present study was to investigate the correlation of iron homeostasis factors with hematological and biochemical markers in patients with T2DM taking into consideration the treatment schema.
Methodology
400 subjects were included, 200 with T2DM: 100 in metformin treatment (PMET), 100 in GLP1 analogs treatment (PGLP), 100 control with prediabetes (PDC), and 100 healthy controls (C). Also, iron homeostasis markers were assessed: Iron (Fe), ferritin (Ferr), hepcidin (Eps), transferrin, transferrin saturation (TSAT), Total Iron Binding Capacity (TIBC), hematological and biochemical indices and HbA1C%. Statistical Analysis was performed by SPSS. Informed consent were acquired from all the participants
Results
Higher levels of BMI, WBC, transferrin, total and LDL cholesterol, and CRP were observed in PMET and PGLP compared to the C and PDC ($P < 0.001$). Also, diabetic patients showed a significant decrease in iron, hepcidin, and TSAT compared to C and PDC ($P < 0.001$). Regarding the differences between the therapeutic schemes, PGLP1 showed significantly increased BMI, fasting glucose, urinary microalbumin, and direct bilirubin, and had significantly lower platelet and alkaline phosphatase (ALP) levels, compared to PMET. PMET showed increased mean platelet volume and decreased HDL levels, compared to C only ($P = 0.026$), while their hepcidin was decreased compared to both C and PDC ($p \leq 0.0001$). PGLP1 showed significantly reduced hepcidin and increased considerably uric acid, compared to the PDC ($P = 0.005$ and $P = 0.046$, respectively) and reduced considerably HDL, ALP, and direct bilirubin compared to both the C and PDC ($p \leq 0.0001$). At the same time, the PDC and both diabetic groups had higher levels of BMI, fasting sugar, HbA1c %, red blood cell distribution range, hematocrit, triglycerides, urea, uric acid, creatinine, and pyruvate transaminase, compared to the control group ($p \leq 0.045$). Statistical analysis in all patients with diabetes according to fasting glucose levels showed that subjects with >100 to 130mg/dL had higher total iron-binding capacity ($P = 0.026$), transferrin ($P = 0.021$), transferrin/ferritin ratio ($P = 0.05$), platelets ($P = 0.026$) as compared to normal fasting glucose levels ≤100mg/Dl
Conclusion
Diabetic patients show disturbed iron homeostasis and a mild inflammatory state. These are associated with an increase and hyperfunction of PLTs, and hyperlipidemia reflecting cardiovascular risk, mainly in patients with uncontrolled diabetes.

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P437

JOINT2088

Monogenic diabetes: results from targeted sequencing in lithuania during 2017-2022

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Introduction
Monogenic diabetes (MD) is a rare form of diabetes caused by single-gene defects. Maturity-onset diabetes of the young (MODY) has well-established diagnostic guidelines in children and adolescents, but individuals over 25 are often overlooked despite the importance of molecular diagnosis for personalized treatment and family risk assessment. The "Genetic Diabetes in Lithuania" project identified GCK, HNF1A, and HNF4A as the most common MODY subtypes in Lithuanian patients up to age 25, leading to the integration of targeted genetic sequencing into clinical practice since 2017. This study aimed to analyze genetic sequencing results from a targeted MD gene panel in patients with non-autoimmune diabetes at our diabetes center from 2017 to 2022.
Methods
We analyzed data of 51 patient (females $n = 31$ (60, 8%)) who had confirmed MODY diagnosis after targeted sequencing. The total number of patients suspected of MODY was 301, either because of negative autoimmune markers, diabetes in family history, or slight hyperglycemia, with no need for insulin treatment. Patient's age was not considered a selection criterion for genetic counseling. Targeted gene (*GCK*, *HNF1A*, *HNF4A*) panel was used during 2017-2022. The values presented as median (min;max), unless stated otherwise.
Results
The median age of patients was 23.5 (7;74) years; the median duration of diabetes was 6.0 (2;55) years at the analysis. The median age at diabetes diagnosis was 18.3 (4;68) years. Twenty-nine (56, 9%) patients had confirmed MODY diagnosis up to the age of 25 years. Twenty-five (86, 2%) of them were diagnosed with *GCK*, 3 (10, 3%) – *HNF1A*, 1 (3, 4%) – *HNF4A* mutations. 65, 5% ($n = 19$) had positive family history for diabetes, either MD or type 1, or type 2 diabetes. Twenty-two (43, 1%) of patients were diagnosed with MODY after the age of 25, with *GCK* most frequently - 17 patients (77, 3%), followed by *HNF1A* – 4 (18, 2%), and *HNF4A* – 1 (4, 5%). Eighteen (81, 8%) patients had positive family history for diabetes.
Conclusions
This study demonstrated a high diagnostic yield (17.9%) for MODY among patients referred for genetic testing, with *GCK* mutations identified as the most prevalent etiology. Furthermore, the findings underscore the necessity of critically evaluating selection criteria for MD genetic testing, as over 40% of diagnosed

cases were older than 25 years, including individuals in their late 40s and 50s. These results suggest that expanding genetic screening criteria may facilitate the identification of previously undiagnosed cases of MD, contributing to improved clinical management and risk stratification.

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P438

JOINT3508

Maturity-onset diabetes of the young type 10 with a rare insulin gene mutation in a 35-year-old male

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Introduction
Maturity-onset diabetes of the young type 10 (MODY 10) is a very rare monogenic form of diabetes caused by mutations in the insulin gene, leading to impaired insulin synthesis or secretion. This condition presents with early-onset hyperglycemia, often before age 25, and follows an autosomal dominant inheritance. MODY 10 requires precise genetic diagnosis and tailored management strategies.
Methods
We present the case of a 35-year-old patient diagnosed with MODY 10, followed-up in the Endocrinology Department of our hospital.
Results
The patient presented to the Emergency Department with nausea, vomiting and weight loss. Hyperglycemia was detected, leading to a diabetes diagnosis. The patient had a low body mass index of 18kg/m^2. His family history included a mother diagnosed with diabetes at the same age and requiring insulin therapy a decade later. Initial tests revealed a C-peptide level of 0. 8ng/mL, while autoantibodies (GAD, ICA, IA2 and insulin antibodies) were negative. Considering the family history and clinical presentation, MODY 3 was initially suspected, as it is the most common subtype. However, genetic testing was negative. He was treated with basal insulin, oral antidiabetic drugs, and later with fast-acting insulin. After several years without a clear diagnosis while maintaining a C-peptide of 1. 2ng/mL, a comprehensive genetic panel (next-generation sequencing) was performed. The results identified a heterozygous mutation in the insulin gene, c. 130G > A, p. (Gly44Arg), very rare in population databases (MAF gnomAD 0, 002%), confirming the diagnosis of MODY 10. The patient was than referred to genetic counselling and currently maintains good metabolic control on glargine insulin, metformin, dapagliflozin and sitagliptin, with an HbA1c of 6. 3% and maintaining partial pancreatic function (C-peptide 1. 14ng/mL).
Conclusion
Underweight MODY patients are often misdiagnosed as type 1 diabetes, particularly when C-peptide levels are low and insulin therapy is required at diagnosis. However, MODY diagnosis should be considered in the presence of family history, negative autoantibodies and C-peptide above 0. 6ng/mL, even with an atypical age of onset. This rare mutation underscores the importance of extensive genetic testing in atypical diabetes cases. Referral to genetic counselling is essential to identify affected family members.

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P439

JOINT2874

The association between metabolic score for insulin resistance and acanthosis nigricans in overweight and obese individuals: a cross-sectional study

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Background
Acanthosis nigricans (AN) is a common skin manifestation associated with insulin resistance in overweight and obese individuals. Although previous studies have suggested a relationship between insulin resistance and AN development, the association between different surrogate insulin resistance indices and AN remains unclear. This study aimed to investigate the differential associations of three commonly used insulin resistance indices (HOMA-IR, TYG-BMI, and METS-IR) with AN occurrence in overweight and obese individuals.
Methods
This cross-sectional study included 1, 077 patients (age $\geq$ 18 years, BMI $\geq$24 kg/m^2) from the Department of Endocrinology, Shanghai Tenth People's Hospital, between May 2010 and October 2021. Participants were stratified into two groups: AN (n = 446) and non-AN (n = 631). Insulin resistance indices were calculated and associations with AN were assessed using multivariate logistic regression, adjusting for potential confounders, including sex, age, waist circumference, family history of obesity, blood pressure, hormonal levels, liver enzymes, and uric acid. Predictive performance was assessed using receiver operating characteristic (ROC) curves.
Results
Patients with AN exhibited significantly higher insulin resistance indices compared to those without AN (HOMA-IR: 7. 11 $\pm$ 3. 37 vs. 5. 37 $\pm$ 3. 09; TYG-BMI: 319. 54 $\pm$ 43. 13 vs. 293. 85 $\pm$ 49. 00; METS-IR: 57. 74 $\pm$ 9. 20 vs. 52. 19 $\pm$ 9. 33, P $<$ 0. 05). Multivariable-adjusted models demonstrated significant positive associations between each index and AN occurrence, with an adjusted odds ratio (OR) of 1. 10 (95% CI: 1. 02 - 1. 18) for HOMA-IR, 1. 13 (95% CI: 1. 04 - 1. 21) for TYG-BMI/10 and 2. 09 (95% CI: 1. 44 - 3. 04) for METS-IR. Quartile analysis demonstrated a striking dose-response relationship, showing a progressive increase in the risk of AN across insulin resistance index quartiles, with METS-IR showing the most pronounced association (Q4 vs. Q1: Or = 5. 19, 95% CI: [2. 18 - 12. 36], P for trend $<$ 0. 001). ROC analysis confirmed the superior predictive performance of METS-IR (AUC = 0. 670) compared with HOMA-IR and TYG-BMI.
Conclusion
Although HOMA-IR and TYG-BMI were significantly associated with AN occurrence, METS-IR demonstrated the strongest predictive ability for AN risk in overweight and obese individuals.

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P440

JOINT1988

Time in tight range during ramadan intermittent fasting in adolescents and young adults with diabetes: are the new CGM targets met?

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Background
Time in tight range (TITR) is a novel glycemic metric assessing normoglycemia in individuals with diabetes.
Aim
To assess the attainability of the TITR (70–140 mg/dL) target in youth with diabetes using different treatment strategies during Ramadan fasting.
Methods
This prospective study included 276 non-insulin-treated type 2 diabetes mellitus (T2DM) and 426 patients with type 1 diabetes mellitus (T1DM) who were categorized into: multiple daily injections [MDI] + intermittently scanned CGM (isCGM), sensor augmented pump (SAP) and advanced hybrid closed loop (AHCL).
Results
At the end of Ramadan, the mean TITR was 42. 3 $\pm$ 6. 6% for all T1DM patients and 63. 5 $\pm$ 4. 0% in T2DM (P $<$ 0. 001). The highest TITR was in T2DM group together with T1DM on AHCL (62. 3 $\pm$ 11. 6%), followed by SAP group (37. 7 $\pm$ 5. 7%) and MDI + isCGM group (23. 6 $\pm$ 5. 9%, P $<$ 0. 001). Hypoglycemic episodes as shown by time below range (TBR) $<$70 mg/dL and TBR $<$54 mg/dL were minimal during Ramadan in AHCL group in comparison to before Ramadan (2. 6 $\pm$ 0. 7 vs 2. 9 $\pm$ 0. 9%; P = 0. 061 and 0. 4 $\pm$ 0. 1 vs 0. 5 $\pm$ 0. 1%, P = 0. 561, respectively) with a lower coefficient of variation (CoV) (P $<$ 0. 001) than other T1DM participants.
Conclusion
At the end of Ramadan, TITR was decreased in patients with T1DM except those using AHCL who had similar levels to non-insulin-treated T2DM patients. Advanced technology has the potential for achieving tight glycemic targets, along with a reduction in CoV, without increasing hypoglycemic risk compared with other insulin treatment modalities.

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P441

JOINT1149

Phenotypic variation of fasting glucose in GCK-related hyperglycaemia

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Introduction
Heterozygous inactivating variants in *GCK* cause *GCK*-related hyperglycaemia (GCK-MODY), presenting with lifelong mild fasting hyperglycaemia. While different *GCK* variants have substantially variable functional effects on glucokinase activity *In vitro*, no specific variant has been linked to a distinct human phenotype. We hypothesized that the differences in enzyme activity might translate into variant-specific effects on fasting glucose in humans. This study aimed to assess how each *GCK* variant influences fasting plasma glucose and identify other factors that further modulate glucose levels.
Methods
We investigated *GCK* variants classified as pathogenic or likely pathogenic, identified in at least three carriers and two non-carrier relatives in the FINNMODY/Botnia study. We analysed how these variants and other factors influence fasting plasma glucose (FPG) and, in a subgroup, 2-hour plasma glucose (2PG) during an OGTT.
Results
The preliminary analyses of ten *GCK* variants (60 carriers, 37 non-carriers) suggested that each variant had a distinct effect on FPG (effect 1. 09-3. 03 mmol/l, FPG range 5. 1-10. 1 mmol/l) and 2PG (data for 8 variants, effect 1. 09-8. 36 mmol/l, 2PG range 4. 4-19. 4 mmol/l). Among the carriers, FPG was strongly correlated with 2PG ($P = 0.00039$) and fasting insulin ($P = 3.35e-05$). HbA1c correlated more strongly with FPG than with 2PG. Surprisingly, metabolic factors such as BMI or lipids showed no significant correlation with FPG or 2PG.
Interpretation
Each GCK variant demonstrated a distinctive effect on plasma glucose. Beyond the *GCK* variant, individual factors might further modify glucose levels. To assess this, we are performing GWAS genotyping to calculate a polygenic risk score for type 2 diabetes.

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P442

JOINT2660

Glycemic control in people living with type 1 diabetes using the medtronic minimed™ 780 system: results from the galaxy service in greece

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Background
The Galaxy project supports healthcare providers in managing clinical and device data for people with diabetes.
Objective
This analysis examines glycemic control, insulin use, and device settings in adults with Type 1 Diabetes (T1D) using the MiniMed™ 780G system across three hospitals in Greece.
Methods
Device data from the two weeks preceding the most recent clinic visit were used. Sensor usage below 70% excluded subjects from the analysis. Subgroups were formed based on pump settings, and comparative analyses were applied.
Results
Data from 99 adults were analyzed (age 43. 6 ± 14. 8 years, 66. 7% female). Mean HbA1c was 7. 2 ± 1. 5%, with 43. 5% having HbA1c <7%. Mean Glucose Management Indicator (GMI) was 6. 9 ± 0. 5. Median Time in Range (TIR) was 76. 3 (69. 9-83. 0)% and Time Below Range was 1. 2 (0. 6-2. 0)% (Figure 1). No significant differences in glycemic metrics were observed in subgroup analysis by age, sex, BMI, diabetes duration, or presence of complications. However, the optimal pump settings group (glucose target = 100mg/dL and Active Insulin Time = 2 hours)had lower GMI and higher Time in Tight Range (6. 7 ± 0. 2% vs. 7. 0 ± 0. 3%, $P = 0.032$, 54. 1% vs. 46. 3%, $P = 0.009$) without significant TBR difference. TIR was higher in the optimal settings group (81 [74. 8-82. 8]% vs. 76 [71. 7-84. 5]%), though the difference was not statistically significant ($P = 0.2$).
Conclusion
These findings provide a comprehensive overview of the demographics, clinical profiles, and glycemic control of MiniMed™ 780G users in Greece and they are essential for understanding the impact of the system on type 1 diabetes management.

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P443

JOINT2698

Application of an extended NGS gene panel in 573 monogenic diabetes mellitus referrals

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Introduction
Monogenic Diabetes (MD) constitutes a genetically and clinically distinct group of diabetes mellitus (DM) that includes Maturity Onset Diabetes of the Young (MODY), Neonatal Diabetes Mellitus (NDM) and Syndromic DM. The utilization of Next Generation Sequencing (NGS) with extended gene panels in the diagnostic routine of patients with suspected MD, gives the opportunity to identify rare MODY subtypes and syndromic forms of MD.
Patients and Methods
Genetic analysis was performed in 573 Greek unrelated patients with clinical suspicion of monogenic diabetes beyond infancy. A targeted gene panel (tNGS) was designed including originally the genes *GCK, HNF1A, HNF4A, HNF1B, INS, ABCC8, KCNJ11, NEUROD1, PDX1* whereas the genes *INSR, WFS1* and *CEL* were added later. All referrals were tested for the original panel and 421 for the extended. Confirmation of the detected variants and segregation analysis was performed employing Sanger Sequencing. For the identification of the *MT-TL1* m. 3243A>G variant, Sanger sequencing was carried out in 3 different tissues derived from 2 patients (peripheral blood, urine, buccal swab) to evaluate varying levels of heteroplasmy.
Results
Out of 573 tested patients, 167 were found to carry variants in genes associated with frequent and rare MODY subtypes alongside syndromic forms of MD. As expected, the most frequent MODY subtypes were *GCK* (67/573) and *HNF1A* (39/573) followed by *ABCC8* (18/573), *HNF4A* (8/573) and *HNF1B* (8/573). We identified 9/573 patients with heterozygous variants in rare MODY genes, *KCNJ11*($n = 5$) and *INS* ($n = 4$). Variants in syndromic genes were identified in 18/423 patients: *WFS1* ($n = 12$), *INSR* ($n = 2$), *CEL* ($n = 3$), *MT-TL1* m. 3243A>G ($n = 1$), most of the patients presenting with diabetes only (Table 1).
Discussion
In our cohort, frequent MODY subtypes were identified in 24. 4% of tested patients and rare MODY subtypes in 1. 6%. Variants in syndromic monogenic diabetes genes were identified in 4. 2% of the referrals. Multiple gene screening in

Table 1: Patients with variants in syndromic genes

Genes	No. Patients	Zygosity	Extra-pancreatic/ Syndromic features
CEL	3	heterozygous	Pancreatic exocrine dysfunction ($n = 1$)
INSR	2	heterozygous	Hyperinsulinemia ($n = 1$), Hypertriglyceridemia ($n = 1$)
WFS1	12	9 heterozygous	Family history of vision loss ($n = 1$)
		2 compound-heterozygous	Bilateral nuclear cataract ($n = 1$)
		1 homozygous	Optic atrophy + deafness
MT-TL1 m. 3243A>G	1	heteroplasmic	hearing loss + myopathy + gastrointestinal problems

MD patients, through expanded gene panels even in patients lacking typical features, provides early diagnosis of potential comorbidities, diseases progression prognosis and family genetic counseling.

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P444

JOINT1678

Body composition in T1DM: a comparison of patients using advanced hybrid closed-loop systems vs. multiple daily injections/patch pumps

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Background and Aims
Limited research exist on the effects of Advanced Hybrid Closed Loop (AHCL) systems on body composition in individuals with type 1 diabetes mellitus (T1DM). This cross-sectional study aimed to compare body composition between patients using AHCL systems (MiniMed 780G® or T:slim X2 Control-IQ®) and those using multiple daily injections (MDI) or patch pumps.
Methods
Patients who had been using the same AHCL system for at least one year ($n = 24$) were compared to those using MDI ($n = 13$) or patch pumps ($n = 8$) combined with a continuous glucose monitoring (CGM) sensor (grouped together as the MDI/patch group, $n = 21$). MDI users recorded their fast-acting insulin doses with smartpens. Exclusion criteria were conditions affecting body composition and HbA1c >69 mmol/mol. Body composition was assessed using bioelectrical impedance analysis (BIA), three-point skinfold thickness (measured with a plicometer), and handgrip strength (measured with a dynamometer).
Results
A total of 45 patients (mean age: 37 ± 11 years) were included. There were no significant differences between the AHCL and MDI/patch groups in terms of sex, age, BMI, waist circumference, estimated glomerular filtration rate (eGFR), International Physical Activity Questionnaire (IPAQ) score, or HbA1c (52 ± 8 vs. 52 ± 8; $P = 0.932$). BIA revealed no significant differences in fat mass percentage ($P = 0.752$), fat mass ($P = 0.912$), fat-free mass ($P = 0.433$), body cell mass ($P = 0.554$), total body water ($P = 0.446$), or phase angle ($P = 0.998$) between the AHCL and MDI/patch groups. Similarly, skinfold thickness and handgrip strength did not differ significantly between groups. AHCL users had significantly higher time in range (TIR: 72 ± 8% vs. 56 ± 16%; $P = 0.001$) and time in tight range (TITR: 46 ± 11% vs. 35 ± 12%; $P = 0.007$), along with lower time above range (TAR), time below range (TBR), and glucose management indicator (GMI) compared to MDI/patch users. The mean per-kilogram total daily insulin dose did not differ significantly between groups (0.62 ± 0.14 U/kg in AHCL users vs. 0.58 ± 0.18 U/kg in MDI/patch users; $P = 0.422$) and was positively correlated with body cell mass percentage ($r = 0.328$, $P = 0.039$). Fat mass percentage, in addition to its established associations with sex, BMI, physical activity, and suprailiac skinfold thickness, showed a positive correlation with total cholesterol ($r = 0.359$, $P = 0.015$) and LDL cholesterol ($r = 0.333$, $P = 0.025$).
Conclusions
Compared to MDI/patch therapy, AHCL systems were associated with improved glucose profile parameters without significant differences in body composition or insulin dosage. Higher total and LDL cholesterol levels were associated with higher fat mass percentage.

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P445

JOINT3878

Exploring pancreatic diabetes: key features and diagnostic insights from 145 patients

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Introduction
Pancreatic diabetes, or Type 3c diabetes by the ADA, is secondary form of diabetes caused by primary pancreatic disorders damaging the Islets of Langerhans, leading to endocrine dysfunction of the pancreas. Often misdiagnosed as Type 1 or Type 2 diabetes, it presents certain characteristics that make it markedly different in terms of causes, clinical presentation, treatment, and prognosis.
Objective
The aim of our study is to highlight the various clinical, biological, and morphological aspects that can suggest the diagnosis of pancreatic diabetes in certain patients.
Patients and Methods
Descriptive retrospective study, including 145 patients hospitalized in our department for newly diagnosed diabetes between September 2018 and December 2024.
Results
The study included 106 men and 39 women, with a sex ratio of 2.79. The average age was 48 years, and 37.5% had a family history of diabetes. Some patients reported toxic habits, including smoking. Clinically, the average BMI was 20.4, with an average weight of 60 kg. The duration of diabetes did not exceed one year in any of the patients, with an average weight loss of 14.6 kg. Biologically, an elevated CA 19-9 level was found in 37.5% of cases. All patients underwent a CT scan, which identified pancreatic tumor lesions with varying locations.
Conclusion
Pancreatic diabetes, although previously considered rare, is increasing in adults in their fifties, presenting with rapid onset of diabetes and significant weight loss. Suspecting this condition requires further appropriate investigations to confirm the diagnosis.

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P446

JOINT462

Renoprotective effects of dipeptidyl peptidase-4 inhibitors in diabetic kidney disease: a meta-analysis of randomized controlled trials

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Background and Objectives
The first clinically evident feature of renal involvement in diabetic kidney disease (DKD) is albuminuria and higher levels are associated with increased risk of chronic kidney disease (CKD) progression, thus treatments aimed at reducing albuminuria delay CKD progression. The incretin effect, mediated by glucagon-like peptide-1 (GLP-1), reduces kidney inflammation, fibrosis, and albuminuria, and its degradation is prevented by dipeptidyl peptidase-4 inhibitors (DPP4I) that are used in the treatment of type 2 DM. Renal effects of DPP4I include reduction in albuminuria and glomerulosclerosis. Given the potential of DPP4I in delaying the DKD progression, there is a need to summarize and review the current evidence.
Method
Computerized literature search of PubMed, CENTRAL, and ClinicalTrials.gov was done from inception to October 2024. Adults diagnosed with DM and any type of DPP4I evaluated for DKD were included. Primary outcomes included changes in urine albumin to creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR). Secondary outcomes included change in renal biomarkers for CKD progression including neutrophil gelatinase-associated lipocalin (NGAL), renal endpoints (doubling of serum creatinine, progression to ESRD, initiation of RRT, and renal related death). Subgroup analysis was done to examine differences in the effect estimates and heterogeneity by follow-up period and specific DPP4I used.
Results
870 references were identified from the electronic search. 13 RCTs were included in the meta-analysis. The risk of bias of the studies were low to moderate. Meta-analysis showed significant reduction in UACR after treatment with DPP4I compared to control (7 RCTs, 20,689 participants, MD -11.06 mg/g Crea, 95% CI -21.37 to -0.75), however with high heterogeneity ($I2 = 77\%$). Subgroup analysis based on follow-up period showed decrease in the heterogeneity in the subgroup with a follow-up period of 12-24 weeks ($Chi2 = 3.12$, $I2 = 0\%$) with significant decrease in UACR favoring DPP4I treatment (5 RCTs, 365 participants, MD -13.36 mg/g Crea, 95% CI -20.19 to -6.52). Results showed no significant difference in change in eGFR and NGAL between treatment and control groups. None of the results evaluating the secondary outcomes were eligible for quantitative synthesis and failed to show difference between treatment and control.

Conclusion
This study found significant reduction of albuminuria with DPP4I treatment in patients with DKD, particularly in a short follow-up period of 6-12 months, suggesting DPP4I may be beneficial in delaying DKD progression. Limitations include a short follow-up period of the included RCTs precluding assessment of further effects of DPP4I on the prespecified renal endpoints.

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P448

JOINT3069

Subcutaneous insulin aspart in treatment of children with mild and moderate diabetic ketoacidosis

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Objectives
To evaluate the effects and safety of subcutaneous injections of rapid-acting aspart insulin for treatment of uncomplicated mild and moderate DKA in children and also to determine the times to resolution of DKA.
Study Design
Prospective, single-arm, uncontrolled study of children and adolescents with DKA in 2022.
Setting
Hamadan University teaching hospital.
Data collected
Age, sex, clinical/laboratory parameters including severity of dehydration and diabetic-ketoacidosis, time to recover from DKA, hospitalization's duration, complications, blood glucose, sodium, potassium, creatinine, urine ketones. Patients were admitted to the pediatric endocrinology unit outside the PICU where appropriate nursing care and access to laboratory test results were available. Based on the degree of dehydration, fluid deficit was replaced by sodium chloride 0. 45%. Insulin aspart 0. 15 units/kg subcutaneous was injected every 2 hours in the hospital outside ICU. Blood glucose was measured hourly and blood gases every 2 hours. Ketoacidosis was considered resolved when the patient did not have nausea/vomiting, was conscious, and could eat, and blood glucose was <250 mg/dL, pH was >7.30, and/or HCO3 was >15 mmol/l.
Results
A total of 25 DKA patients (mean age 11. 06 ± 3.89, range 4-17 years, 60% female) were included in the study. Sixteen of the participants (64%) had type 1 diabetes. Overall, 13 (52%) cases had mild ketoacidosis (average pH = 7. 25), and 12 (48%) cases had moderate ketoacidosis (average pH = 7. 15). The average time to resolution of ketoacidosis was 11. 24 hours. Mean duration of hospitalization was 2. 3 days. All but one patient met DKA recovery criteria without complications. Mild cases compared to moderate cases of DKA had a shorter duration to resolution of DKA ($P = 0.04$(. There were no electrolyte disturbances, hypoglycemic events, readmissions and deaths or other adverse events.
Conclusion
Subcutaneous rapid-acting insulin aspart is an effective, safe, and convenient alternative to intravenous infusion of regular insulin for children and adolescent with uncomplicated mild and moderate DKA.

Keywords: : Aspart; diabetic ketoacidosis; rapid-acting insulin; subcutaneous insulin.

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P449

JOINT614

Characteristics of maturity-onset diabetes of the young: a single-center experience from a tertiary referral hospital

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Introduction
Maturity-Onset Diabetes of the Young (MODY) is characterized by diabetes in two or more generations of a family, typically affecting individuals under the age of 25, with a normal body weight and no insulin resistance. The main mechanism underlying MODY is a defect in insulin secretion. Identifying the specific MODY type is essential for patient management and treatment. This study aimed to assess the demographic and biochemical features of patients who underwent MODY genetic analysis, identify the most common MODY mutations, and explore associated clinical characteristics.
Materials and Methods
A retrospective analysis was conducted on 162 patients who underwent MODY genetic testing between 2022 and 2024. Data from 129 patients, including demographic, biochemical, and genetic information, were analyzed to determine MODY types and mutations.
Results
The average age of the 129 patients included in the study was 34. 06 ± 9.45 years. Of the patients, 66 (51. 2%) were female. The average body mass index (BMI) was 29. 26 ± 7.01 kg/m^2, and the mean duration of diabetes was 5. 83 ± 7.46 years. Diabetic complications included retinopathy (7. 8%), nephropathy (7%), and neuropathy (9. 3%). Treatment regimens varied: 58. 1% were on metformin, 4. 7% on GLP-1 analogues, 14. 7% on gliclazide, 18. 6% on SGLT2 inhibitors, 21. 7% on DPP-4 inhibitors, and 52. 7% on insulin. The mean C-peptide level was 2. 86 ± 1.70 ng/ml. A family history of diabetes was noted in 79. 1% of patients. At admission, mean HbA1c was 8. 93 ± 3.81%, with fasting plasma glucose at 213. 7 ± 88.5 mg/dL, creatinine at 0. 74 ± 0.18 mg/dL, and triglycerides at 247. 7 ± 232.3 mg/dL. The control HbA1c was 4. 36 ± 4.03%. MODY was diagnosed in 34. 1% of patients, with additional diagnoses of hyperinsulinemic hypoglycemia (5 patients) and Wolfram syndrome (1 patient). Among the MODY patients, 11 (25%) were diagnosed with type 12, 7 (15. 9%) with type 3, 7 (15. 9%) with type 8, 6 (13. 6%) with type 2, 3 (6. 8%) with type 1, 2 (4. 5%) with type 7, 2 (4. 5%) with type 10, 2 (4. 5%) with type 11, 1 with type 6, 1 with type 9, 1 with type 13, and 1 with type 14. The most frequent mutations were found in the ABCC8, HNF1A, CEL, GCK, INS, and HNF4A genes.
Conclusion
Selecting appropriate patients for MODY genetic testing is crucial for avoiding unnecessary tests and ensuring effective diabetes management. Given ethnic differences in MODY types, large-scale national studies could contribute significantly to understanding its genetic and clinical variability.

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P450

JOINT2650

Progression and outcomes of prediabetes in children and adolescents: insights from an indian perspective

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Background
Type 2 diabetes mellitus (T2 DM) is a leading cause of morbidity and mortality in children. Identification in the early-stage lead to better outcome and lesser intervention. Risk factors predisposed to progression of pre-diabetes needs to be identified.
Aim
To identify the course and outcomes the progression from prediabetes to Type 2 Diabetes Mellitus (T2 DM) in Indian children and adolescents.
Methodology
90 Indian children and adolescent (Boys 68. 9%, Mean age 13. 2 ± 3.3 years) were followed up. Baseline fasting blood glucose (FBS) and 2 Hours oral glucose tolerance test after 1. 75gm/kg glucose (OGTT) was done to identify pre-diabetes in children. Metabolic profiles were also analyzed. At the last follow-up they were again evaluated for glycemic profile and other metabolic complications.
Result
A total of 90 children were followed up for a mean duration of 2. 3 ± 1.7 years. Of these, 60 children (66. 7%) were cured, while 30 children (33. 3%) remained dysglycemic. Among the 30 dysglycemic children, 8. 9% progressed to diabetes, while 24. 4% remained prediabetic. Children with a family history of diabetes had an odds ratio of 2. 8 for progression to diabetes. The cured group showed a significant reduction in BMI SDS ($P = 0.008$) and percentage BMI ($P = 0.02$) compared to the disease group.

Conclusion
The findings indicate that a family history of diabetes may be a significant predictor for the progression of prediabetes in Indian children. Furthermore, a reduction in BMI SDS is linked to the potential resolution of prediabetes.

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P451

JOINT2504

From pediatric to adult diabetes care: experience of the organized transition process of youth with type 1 diabetes

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Introduction
The transition from pediatric to adult diabetes care is a critical phase for youth with type 1 diabetes (T1D), as it significantly impacts long-term health outcomes. The main aim of this study was to implement a structured transition process for adolescents with T1D to adult diabetes care.
Methods
Adolescents up to 18 years of age were enrolled in a transition program designed to facilitate their referral from pediatric to adult healthcare service. Patients under the care of the diabetes outpatient clinic in Greater Poland were referred to the Department of Pediatric Diabetes for final hospitalization before adulthood. The hospitalization included collection of data from therapy-supporting devices, laboratory tests, and assessment of Health-Related Quality of Life (HRQoL) using the validated KIDSCREEN-27 questionnaire and diabetes distress (DD) using the age-specific Problems Areas in Diabetes questionnaire (PAID). The stay at the hospital was concluded with the issuance of a Diabetes Care Information Card, a referral, and the scheduling of the first visit to the adult diabetes clinic.
Results
The study cohort comprised 68 patients (37 boys) with a mean T1D duration of 8 years. Most patients were treated with CSII ($n = 47$), and all used CGM for blood glucose monitoring. The mean TIR and HbA1c were 60% and 7, 3%, respectively. Participants exhibited significantly lower scores on the physical well-being dimension in comparison to scores on the remaining four dimensions in the KIDSCREEN-27 questionnaire. Girls reported notably lower scores on all dimensions of HRQoL than boys. T1D duration <5 years was associated with the worst scores on physical and psychological well-being dimensions while scoring on autonomy and parental relation dimension was the lowest among those with T1D duration between 5 to 10 years. Almost 12% ($n = 8$) of youth reported high levels of DD measured via PAID; it mainly concerned girls (62%, $n = 5$). A slight increase in DD levels was noticed, along with a decrease in TIR values. Around 14% of adolescents with TIR $<70\%$ had a mean score above 40, suggesting high emotional distress regarding the disease. Eight youths from the uncontrol group had a mean score of less than 10, which may suggest denial. The mean PAID score was comparable between both sexes.
Conclusion
Youth with T1D have insufficient metabolic control of the disease. HRQoL is decreased, mainly in the physical well-being dimension. DD is quite a common issue, especially among those with higher TIR values.

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P452

JOINT1539

Evaluation of the performance of continuous glucose monitoring in the treatment of patients with congenital hyperinsulinism

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Introduction
Continuous glucose monitoring (CGM) is a promising but unvalidated tool for the management of patients with congenital hyperinsulinism (CHI).
Objective
To assess the accuracy and performance of CGM in the management of patients with CHI.
Patients and Methods
Monocentric, retrospective, observational and analytic study. Inclusion criteria: patients diagnosed with CHI using CGM in hospital and/or outpatient settings. Data collection was conducted through medical record reviews and sensor downloads. For hospitalized patients, blood glucose measurements (BGM) were taken every 2-8 hours (depending on the clinical condition); the measurements performed to verify extreme sensor values were also recorded. For outpatients, BGM for hypoglycaemia-checking or calibration were collected. Only paired measurements taken within 3 minutes or less were included. Pairs performed to confirm the resolution of hypoglycaemic episodes were excluded. Families were surveyed regarding their experience with CGM. Statistical analysis was performed using XLMiner Analysis ToolPak.
Results
Data from two years of follow-up (2022-2024).
Discussion/Conclusions
CGM effectively prevents severe events and facilitates real-time decision-making in CHI patients. A CGM glucose threshold of 65 mg/dL is proposed, requiring capillary confirmation for values ≤ 65 mg/dL. Trend arrow analysis may optimize this, posing a goal for future studies.

Table 1: Data from two years of follow-up (2022-2024).

CGM	Patient	Age (months)	n of pairs of data	Origin
Dexcom G6	P1	2	45	Hospitalized
			1	Outpatient
	P3	61	3	Outpatient
	P4	35. 2	17	Outpatient
	P5	0. 67	87	Hospitalized
	P6	41. 4	1	Outpatient
	P7	149. 6	13	Outpatient
	P8	26. 4	58	Outpatient
Dexcom G7	P2	0. 56	33	Hospitalized
Libre2	P3	61	27	Outpatient
	P9	96. 6	62	Outpatient
Total		**Median / IQR**	347	165 Hospitalized
		35.2 / 59		182 Outpatient
Pearson's correlation test		**R**	**p**	**n of pairs of data**
Total		0. 94	**<0. 05**	347
Glucose ≤70 mg/dl		0. 20	**0. 02**	124
Glucose ≤50 mg/dL		-0. 24	0. 31	20
MARD		**%**		**n of pairs of data**
Total		16. 1		347
Glucose <70 mg/dl (all sensors)		14. 4		115
Libre2 (all glucose values)		11. 7		89
Libre2 (Glucose <70 mg/dl)		17. 1		16
Dexcom G6 (all glucose values)		15. 6		278
DexcomvG6 (Glucose <70 mg/dl)		13. 7		107

Hypoglycaemia detection (≤70 mg/dL): CGM identified 124 episodes, of which 91 were confirmed by capillary glucose (Sensitivity = 79. 1%, Specificity = 85. 8%, PPV = 73. 4%, NPV = 89. 2%). All hypoglycaemia episodes ≤50 mg/dL were detected with a minimum CGM threshold of ≤65 mg/dL (Sensitivity = 100%, Specificity = 74. 4%, PPV = 7. 5%, NPV = 100%). All participants reported satisfaction with CGM use and declined its removal.

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P453

JOINT3556

Turning back the metabolic disturbances - results of treating two brothers with Berardinelli Seip syndrome with leptin analogue for five months

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Background
Berardinelli-Seip syndrome is a rare autosomal recessive disease, causing generalized lipodystrophy. Affected individuals cannot store fat subcutaneously and thus have very low leptin level and are always hungry. Accumulation of visceral fat in the liver, spleen and skeletal muscles causes

insulin resistance and leads to the development of metabolic syndrome and type 2 diabetes. Fat accumulation in the liver may cause liver fibrosis and failure. The metabolic disturbances are difficult to treat without addressing leptin deficiency. Treatment with leptin analogue was previously not used for children in Sweden.

Aim

To present five months treatment results with leptin analogue in two brothers with severe phenotype of generalized lipodystrophy.

Materials

Patients were followed at the Queen Silvia Children's Hospital since diagnosis. Data on disease history, growth and laboratory values were collected from the hospital records. Informed consent was obtained from the parents.

Results

Both patients have type 2 lipodystrophy caused by BSCL-2 mutation, causing complete absence of the subcutaneous fat. Treatment with leptin analogue was started in July 2024, at the age of 9 yrs and 7 yrs. At the start of the treatment both patients had severe insulin resistance with acanthosis nigricans and have developed type 2 diabetes, treated with maximal doses of metformin and SGLT2 inhibitor, as well as lipid lowering drugs and angiotensin receptor inhibitors for microalbuminuria. Fat accumulation caused severe liver enlargement and fibrosis, meeting criteria of clinical liver cirrhosis. The older brother had developed hypertriglyceridemia and myocardial hypertrophy and was treated with combination of lipid lowering and cardioprotective drugs. Both patients had their tonsils and adenoids removed due to obstructive sleep apnea.

Conclusion

Treatment with leptin analogue was safe and effective in reducing the accumulation of visceral fat and reversing the metabolic abnormalities in children with type 2 generalized lipodystrophy.

Table 1:

	Patient 9 yrs old					Patient 7 yrs old				
	Max	Baseline	1 mon	3 mon	5 mon	Max	Baseline	1 mon	3 mon	5 mon
Weight (kg)		61	59, 4	57	54		56, 2	54, 1	52, 5	51, 7
BMI		23, 6	22, 8	21, 6	20, 6		23, 6	22, 4	21, 5	21, 2
Waist (cm)		94	91	90	86		90	83, 5	86, 5	80, 5
HbA1c mmol/mol (%)	76 (9, 1)	48 (6, 5)	41 (5, 9)	38 (5, 7)	35 (5, 4)	61 (7, 7)	41 (5, 9)	38 (5, 7)	33 (5, 2)	29 (4, 8)
Fasting insulin (ref 2, 7-17 mIE/l)	130	83	17	6, 2	7, 4	160	66	12	4, 4	8
Trigly-cerides (ref 0, 5-2, 2 mol/l)	19	3, 5	1, 3	0, 69	0, 85	3, 4	1, 5	0, 75	0. 52	0, 72

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P454

JOINT258

Driving data-driven impact through digital innovation: a collaborative case study between action4diabetes and correlaid's data4good initiatives

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Background

The utilisation of data is revolutionising the operations and impact of non-profit organisations (NGOs) worldwide. The effectiveness of NGOs is increasingly contingent upon their capacity to collect, analyze, and apply data at every level of their operations. Action4Diabetes (A4D) is a UK diabetes charity that is making sustainable and scalable progress in the battle to provide quality type 1 diabetes healthcare in emerging countries across South-East Asia (SEA). CorrelAid is a nonprofit organization of data scientists dedicated to improving the world through the application of data science. CorrelAid e. V. is the registered nonprofit association behind the CorrelAid community. CorrelAid and A4D have collaborated to develop a centralized database in the public cloud, which provides access to all historical data in a single repository.

Methods

A4D is exchanging data with the local hospitals in the programme on a monthly basis via Microsoft Excel files. A preprocessing pipeline was implemented to account for differences between files from different hospitals and differences over time for the same hospital. The pipeline extracts the patient and medical product data in a standardized and unified manner, rendering it suitable for storage in a database. The data is anonymized and subsequently uploaded to a secure storage in the public cloud, where it is processed and stored in a centralized database. An error reporting system is in place to monitor the pipeline's progress and alert in the event of critical errors or data quality issues.

Results

The public cloud database provides access to all historical data for the years 2017 to 2023. The database encompasses six countries, 31 clinics, and approximately 1, 000 patients along with their monthly medical data. Furthermore, the database contains information about the distribution and usage of approximately 200 medical products.

Conclusions

The formulation of a data strategy and the implementation of a centralized database solution for healthcare data is a challenging but achievable objective when approached in a cost-effective manner, particularly when utilizing services from modern public cloud providers. The subsequent stages of the process entail the identification of initial use cases that build upon the data, the implementation of dashboards and reports that facilitate access to the data, the automation of the data pipeline to ingest newly arriving data without manual intervention, and the establishment of a data governance strategy to oversee data content, structure, usage, and safety.

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P455

JOINT608

SGLT-2 Inhibitor-induced erythrocytosis and risk of coronary artery disease in type 2 diabetes - a nationwide cohort study

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Purpose of Study

Therapy of type 2 diabetes (T2D) with SGLT-2 inhibitors can lead to increased risk of new-onset erythrocytosis. On the other hand, studies conducted in pre-SGLT-2i era showed that incident erythrocytosis in non-diabetic individuals heightens cardiovascular risk. The aim of this investigation was to assess cardiovascular risk in persons who develop SGLT-2i-induced erythrocytosis.

Methods

This was a retrospective nationwide cohort study of US Veterans with T2D who received care between 3/2013–12/2023. Inclusion criteria were complete medical records data, normal baseline hematocrit (Hct) $<$ 50. 0% within 1 year before the study start, adequate adherence with SGLT-2i, no testosterone prescription, and no history of erythrocytosis or cardiovascular disease. We identified 2 groups of patients: control (no record of SGLT-2i use) and new SGLT-2i users; in all patients we followed hematocrit for 1 year to identify those who developed new erythrocytosis defined as hematocrit $\geq$ 50%. Primary endpoint was odds ratio (OR) of incident non-fatal coronary artery disease (CAD) calculated by logistic regression model adjusted for case-mix.

Results

We identified 691104 patients mostly males (94. 5%) and Caucasians (Whites 70. 2% and Blacks 19. 4%) with mean age 65. 7yrs. The SGLT-2i use for 1 year

Study Outcomes	Control, Hct $<$ 50% (n = 605311)	Control, Hct $\geq$ 50% (n = 14516)	SGLT-2i, Hct $<$ 50% (n = 63698)	SGLT-2i, Hct $\geq$ 50% (n = 7579)
HbA1c, % (Mean $\pm$ SD): At baseline	6.9 $\pm$ 1.4	6.9 $\pm$ 1.6	8.3 $\pm$ 1.5	8.4 $\pm$ 1.5
Δ after 1 yr	-0.05 $\pm$ 1.1	-0.04 $\pm$ 1.2	-0.91 $\pm$ 1.5	-1.06 $\pm$ 1.6
Hct, % (Mean $\pm$ SD): At baseline	41.6 $\pm$ 4.2	46.5 $\pm$ 3.1	41.7 $\pm$ 3.8	46.1 $\pm$ 2.5
Δ after 1 yr	-0.3 $\pm$ 3.3	2.4 $\pm$ 4.3	2.0 $\pm$ 3.2	4.4 $\pm$ 3.2
CAD event OR (95% CI), adjusted	1.0 (ref)	1.76 (1.47, 2.10)	0.98 (0.90, 1.06)	1.36 (1.10, 1.66)

resulted in significant HbA1c reduction and hematocrit increase compared with the control group (Table). In adjusted analyses, absolute incidence of erythrocytosis was about 5. 0-fold higher ($P < 0.0001$) in SGLT-2i-treated than in control patients (10. 6% vs 2. 3%). In the models adjusted for baseline hematocrit, HbA1c, age, ethnicity, sex, BMI, eGFR, sleep apnea, concomitant hypoglycemic agent use, and smoking status, new erythrocytosis was associated with equally higher probability of incident CAD in control and SGLT-2i-treated patients (Table).

Conclusion

For the first time, we demonstrated that in a large T2D cohort, a new diagnosis of erythrocytosis is associated with incident CAD and SGLT-2i therapy does not offer cardiovascular protection in such patients. Considering markedly increased erythrocytosis incidence in the SGLT-2i-treated patients which in turn can lead to larger number of cardiovascular events, we recommend implementation of strategies to monitor hematocrit trends in T2D patients and particularly in individuals starting gliflozin therapy.

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Endocrine Related Cancer

P10

JOINT1372

Validation of prognostic biomarkers in adrenocortical carcinoma through a Next-Generation Sequencing in real-life setting

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Background

Adrenocortical carcinoma (ACC) is a rare aggressive malignancy with heterogenous clinical outcomes. Our previous research demonstrated that targeted DNA-based biomarkers assessed on paraffin-embedded (FFPE) samples can improve prognostic classification.

Aim

To investigate the feasibility in real-life setting of a Next-Generation Sequencing (NGS) service for prognostic classification of ACC in two European centres (Queen Elizabeth Hospital Birmingham (QEHB), UK, and IRCCS Sant'Orsola Polyclinic, Bologna, Italy).

Methods

A total of 43 patients with ACC were enrolled, who underwent adrenalectomy at QEHB ($n=23$) or IRCCS Sant'Orsola Polyclinic ($n=20$), including a previously published retrospective cohort ($n=10$; surgery date 2012–2020) and an independent validation cohort ($n=33$; surgery date 2002–2024). Tumour DNA was extracted from FFPE tissue using a Qiagen DNA protocol and quantified by Qubit fluorometer. A targeted NGS platform for 10 ACC-specific genes (*ATM, APC, RB1, MEN1, CDK4, NF1, ZNRF3, TERT* promoter, *TP53* and *CTNNB1*) was developed and validated using the retrospective cohort and commercially available DNA control (HD827, Horizon Oncospan). Sequencing was performed using an Illumina platform. The variant allele frequency (VAF) threshold was validated at 5% at QEHB and 10% at IRCCS Sant'Orsola Polyclinic. We assessed predicted turnaround time (TAT) and costing of implementing this NGS service within a routine laboratory setting.

Results

After 11 cases were excluded due to low quality DNA, the final cohort consisted in 32 patients (25F/7M, average age 50yrs). In the retrospective cohort ($n=6$), all previously identified somatic variants (i.e. in *RB1, MEN1, ZNRF3, CTNNB1* and *NF1)* were confirmed. Two more variants were detected in the added TERT promotor region c.−146.C>T and c.−124C>T. In the validation cohort, 36 variants were reported in 14/26 patients (53.8%). Pathogenic/likely pathogenic variants (52.8% of total variants) were detected in *TP53* (22.2%, mean VAF 50.6%), *NF1* (19.4%, mean VAF 41.73%), *CTNNB1* (p.Ser45Pro, mean VAF 62.3%, 11.1%), with variants of uncertain significance found in *TERT, APC, MEN1, NF1* and *ZNRF3* (13.9%). The predicted TAT for the validation cohort was 21 calendar days from sample receipt to final report, with an average 1.5 hours reporting time per case. There was no relevant difference for full costings between the two centres (€200–250 per sample).

Conclusions

Our proposed ACC-specific NGS service was reliable, feasible and cost-effective for most cases allowing implementation in real-life clinical setting. Most detected variants have shown strong evidence for clinical significance, prognostic value and/or represent potential drug targets (NF1), potentially facilitating personalised management of patients with ACC.

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P11

JOINT2851

ACCacia, a novel machine-learning approach for adrenocortical carcinomas molecular classification in routine care

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Background

Transcriptomic classification can differentiate adrenocortical adenomas (C2 cluster) from carcinomas (C1A and C1B clusters, respectively associated with bad and better prognosis). 3'-RNAseq allows for transcriptomic analysis on formlain-fixed and paraffin-embedded (FFPE) tissue -even on highly degraded RNA- though at the cost of missing data on up to 50% of transcripts. Our goal was to build a routine-compatible predictor using cutting edge models and techniques to answer this challenge.

Material and methods
ACCacia includes two modules: (I) a *prediction module* using denoising auto-encoder (DAE) and random forest models for C1A/C1B/C2 classification, and (ii) a *novelty detection module* using DAE reconstruction error and isolated trees to identify potential situations of inapplicability (i.e. non adrenocortical tumors). ACCacia was trained on 88 adrenocortical samples (28 C1A, 28 C1B, 32 C2) and its performance evaluated by multiple cross-validation. An additional dataset of 28 pituitary tumors was used as a test set for novelty detection.
Results
ACCacia maintains $>$ 99% accuracy and adequate calibration up till 50% of missing data. Its two novelty detection metrics perfectly discriminate the pituitary tumor dataset from the adrenal tumor dataset (AUC ROC $=1$). Two validation cohorts, retrospective ($n=360$) and prospective ($n > 28$), are currently being set up and will enable us to better assess the diagnostic and prognostic value of this tool.
Conclusion
ACCacia enables robust and specific prediction of the molecular class of adrenocortical tumors based on 3'-RNAseq transcriptomic data in a routine-compatible way.

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P12

JOINT1284

Measurement of circulating cell-free DNA concentrations for differential diagnosis of adrenal masses: a pilot study

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Background
Ruling out malignancy in adrenal masses (AM) is a clinical challenge. We demonstrated that circulating cell-free DNA concentrations (ccfDNA-C) are higher in patients with adrenocortical carcinoma (ACC) compared to healthy subjects (HS). However, ccfDNA-C have not been compared among different types of AM.
Objectives
To assess the potential role of ccfDNA-C for AM differentiation.
Methods
We enrolled 97 adult patients (58 females) with a final diagnosis of adrenocortical adenoma (ACA, $n=61$), other benign AM (OB, $n=7$), ACC ($n=17$), pheochromocytoma ($n=6$) or adrenal metastases from other primary tumours (MET, $n=6$: 2 renal cell cancer, 1 melanoma, 1 unknown primary, 1 leiomyosarcoma, 1 papillary thyroid cancer). Blood samples, clinical, hormonal and radiological data were collected at first clinic review. AM with heterogeneous radiological appearance or plain Hounsfield Units >10 and not associated with overt adrenal hormone excess were labelled as "undefined AM" ($n=35/92$, 18 ACA, 4 ACC, 7 OB, 6 MET). ccfDNA was isolated with a commercial kit and ccfDNA-C were measured with fluorometer. Tumour size adjusted univariate analysis was conducted to assess ccfDNA-C distribution. We tested the diagnostic performance of our previously published HS-derived cut-off (>0.146 ng/μL) with logistic regression, positive (PPV) and negative predictive value (NPV) for ACC recognition.
Results
Unadjusted statistics showed higher ccfDNA-C in ACC than each group within the entire cohort ($P=0.003$ vs ACA, $P=0.055$ vs OB, $P=0.001$ vs MET, $P=0.042$ vs pheochromocytoma), but not within undefined AM ($P=0.129$ vs ACA, $P=0.075$ vs OB, $P=0.004$ vs MET). Tumour size-adjusted univariate analysis showed that ccfDNA-C were higher in ACC than each group in the entire cohort ($P=0.039$ vs ACA, $P=0.005$ vs OB, $P=0.003$ vs MET, $P=0.021$ vs pheochromocytoma) but also within undefined AM ($P<0.001$ vs ACA, $P<0.001$ vs OB, $P<0.001$ vs MET). In the entire cohort, the ccfDNA-C HS-derived cut-off was confirmed to predict ACC and showed Odds Ratio 14.982 (95% Confidence of Interval: 3.888–57.741), $P<0.001$. HS-derived cut-off predicted ACC with PPV $=42.4\%$ and NPV $=95.3\%$ in the entire cohort and with PPV $=44.4\%$ and NPV $=100\%$ in the undefined cohort. Approximately the same cut-off ($\geqq 0.148$ ng/μL) was confirmed by Receiver-Operating Characteristic curve analysis showing sensitivity 82.4% and specificity 76.2% with same PPV and NPV as the HS-derived cut-off.
Conclusions
High ccfDNA-C in AM seem to be ACC-specific, and our ccfDNA-C HS-derived cut-off is useful for ACC discrimination. Further studies with larger cohorts of malignant adrenal lesions are needed to confirm our results.

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P456

JOINT2410

Quantitative analysis of [^{18}F]fluorocholine-PET acquisition times in patients with histopathologically proven primary hyperparathyroidism

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Background/Aim
[^{18}F]fluorocholine-PET has emerged to a diagnostic tool of first choice in the localization of a culprit parathyroid gland in primary hyperparathyroidism. The aim of this analysis was to retrospectively compare quantitative radioligand uptake of parathyroid adenomas and non-target organs, target to background ratios and the diagnostic accuracy of [^{18}F]fluorocholine-PET at different scan times.
Methodology
All operated patients with primary hyperparathyroidism who preoperatively underwent [^{18}F]fluorocholine-PET scan at LMU Hospital between November 2020 and December 2024 were included. A visual qualitative and a semiquantitative (SUV_{mean} and SUV_{max}) analysis of histopathologically proven parathyroid adenomas and non-target organs were applied. Quantitative values are reported with median and interquartile range. The radioligand uptake and target to background ratios were then compared between three acquisition times (early: 15-24 min, intermediate: 25-54 min, late: 55-94 min) using the Kruskal-Wallis test.
Results
A total of 101 patients were included in the study. Histopathological reports revealed a single parathyroid adenoma in 89 patients. Sixteen hyperplastic glands were identified in six patients (one of whom carried a MEN1 germline variant). One patient presented with a parathyroid carcinoma. In 3 cases, no parathyroid tissue was found in the histopathological examination. 50 patients were scanned at an early, 33 at an intermediate and 19 at a late acquisition time. Overall, the visual analysis showed a very good detection rate of 91. 08% with no significant difference between the groups ($P = 0.953$). In the quantitative analysis, the median SUV_{max} of the 108 histologically proven lesions was highest in the late acquisition group, although statistical significance was not reached (4. 0(2. 2) vs. 4. 0(1. 9) and 5. 1(2. 7); $P = 0.163$). Similarly, the median adenoma to mediastinal blood pool ratio was highest in the late acquisition group (3. 63(2. 47) vs. 4. 14(2. 58) vs. 5. 89(5. 91)), with significant differences between the early and late acquisition ($P = 0.002$) and the intermediate and late acquisition ($P = 0.012$).
Conclusion
[^{18}F]fluorocholine-PET is a reliable diagnostic tool in the detection of adenoma in patients with primary hyperparathyroidism. The [^{18}F]fluorocholine uptake of the parathyroid adenomas was strongest at late acquisition times. However, the present study found no significant difference in detection rate between the early and late acquisition groups.

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P458

JOINT191

Evolution of small (=4 cm) adrenal lesions diagnosed as adrenocortical carcinomas: a5 multicenter retrospective cohort study

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Background

Adrenocortical carcinomas (ACC) are rarely diagnosed in patients with adrenal tumors ≤4 cm, potentially representing a missed opportunity for an earlier intervention.

Aims

We aimed to characterize clinical, biochemical, and imaging presentation of patients with adrenal lesions ≤4cm eventually diagnosed as ACC.

Methodology

We present an interim analysis of an ongoing A5 multicenter retrospective cohort study (1998-2024) that included adults with adrenal tumors ≤4 cm, subsequently diagnosed as ACC. We evaluated clinical and hormonal presentation, imaging characteristics at initial and latest imaging prior to ACC diagnosis, and staging at the time of ACC diagnosis. Reference standard was histopathology after adrenalectomy or biopsy, or imaging of metastatic adrenal mass with biochemical evidence of hormone excess.

Results

At the time of interim analysis, 118 patients (65% women) with ACC diagnosed at a median age of 52 years (range, 19-83) were included. Reasons for initial imaging were unrelated to adrenal mass (70, 59%), hormone excess (19, 16%), extra-adrenal malignancy staging (19, 16%), compressive symptoms (5, 4%), and genetic screening (3, 3%). At initial imaging, median tumor size was 25 mm (range 4-40), with unenhanced mass attenuation of 31 (range 17-95). Among 33 patients (28%) suspected of having ACC, 25 (21%) underwent adrenalectomy shortly thereafter. Meanwhile, 71 patients (60%) had follow-up imaging at a median of 21 months (range 0. 9-149) showing a median tumor growth rate of 13 mm/year (range 0-198), a median tumor size of 44 mm (range 10-270), and unenhanced mass attenuation of 31 HU (18-50). At the time of ACC diagnosis, 61 patients (52%) had stage I, 21 (18%) stage II, 19 (16%) stage III, and 3 (3%) stage IV disease. Clinical features of overt hormone excess were observed in 40 patients (34%), 50% presenting with Cushing syndrome, 37% with hyperandrogenism, 30% with mineralocorticoid excess, and hyperestrogenism in 2. 5%. Biochemical hormone excess was present in 62 patients (52%) including hypercortisolism in 28 (45%), combined hypercortisolism-hyperandrogenism in 19 (31%), hyperandrogenism in 7 (11%), mineralocorticoid excess in 7 (11%), combined hypercortisolism-mineralocorticoid excess in 1 (2%), and isolated hyperestrogenism in 1 (2%).

Conclusion

We show that ACC was suspected only in 28% at the time of initial imaging, despite indeterminate imaging characteristics, potentially because of false reassurance of smaller tumor size. We further show a variable tumor growth rate, with a median of 13 mm/year. Clinicians need to be aware of the possibility of ACC in smaller indeterminate adrenal tumors.

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P459

JOINT1757

Plasma concentrations of selected growth factors as a potential tool for detecting recurrence in endocrine tumors - a pilot study

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Introduction

The current standard of care for patients with endocrine neoplasms emphasizes the personalization of diagnostic and therapeutic approaches. Several key time points are critical, including the early detection of recurrence following radical surgery. While thyroglobulin is used for thyroid cancer and calcitonin for medullary thyroid cancer, robust tumor markers are unfortunately unavailable for other types of endocrine neoplasms, such as neuroendocrine tumors and pheochromocytomas. It appears that certain growth factors involved in tumorigenesis could potentially serve as useful markers for detecting recurrence of these tumors. The aim of this study is to determine whether any of the selected growth factors (TNF-α, Fascin, VEGF, Galectin-1, Galectin-3, and FGF), measured in the serum of patients with disseminated endocrine neoplasms, could serve as potential markers for recurrence.

Methods

The study included 43 patients with disseminated endocrine neoplasms (30 with neuroendocrine tumors (NET), 6 with medullary thyroid cancer (MTC), and 7 with adrenal neoplasms) and 25 healthy controls. Serum levels of TNF-α, Fascin, VEGF, Galectin-1, Galectin-3, and FGF were measured in all patients and healthy controls using ELISA assays. The biochemical analysis results were compared across the different patient subsets with various endocrine neoplasms and the control group.

Results

A comparison of all patients with disseminated endocrine neoplasms and the control group revealed significant differences in TNF-α levels (2. 88 vs. 0. 93 [ng/mL], $P = 0.008$). When comparing the concentrations of the measured factors between subgroups (classified by tumor type) and the control group, differences were found for TNF-α ($P = 0.007$) and Fascin ($P = 0.035$). For Fascin, significant differences were observed between MTC patients and those with adrenal neoplasms (0. 52 vs. 5. 28 [ng/mL], $P = 0.048$), as well as between MTC and NET patients (0. 52 vs. 5. 59 [ng/mL], $P = 0.007$). The difference between NET patients and controls was nearly significant (5. 59 vs. 3. 67 [ng/mL], $P = 0.076$). For TNF-α, significant differences were found between NET patients and controls (2. 88 vs. 0. 03 [ng/mL], $P = 0.005$) as well as between MTC patients and controls (2. 77 vs. 0. 93 [ng/mL], $P = 0.004$).

Conclusion

Plasma concentrations of selected growth factors (TNF-α, Fascin) differ between healthy individuals and those with disseminated endocrine neoplasms. Further research is needed to evaluate their potential in detecting recurrence of NET and MTC.

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P460

JOINT2949

Molecular characterization of circulating tumor cells (CTCs) in sporadic medullary thyroid carcinoma (spMTC) patients

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Objectives

Distant metastases (DM) and/or biochemical persistent disease (BPD) in MTC, adversely affect disease prognosis. Calcitonin and CEA doubling-times (DTs) are the main prognostic indicators. Liquid-biopsy based on CTCs enrichment and molecular characterization is a non-invasive tool providing information about tumor biology and molecular identity. The aim of this study was molecular characterization of CTCs in

spMTC with DM and/or BPD using epithelial, mesenchymal and MTC-specific markers while a droplet-digital polymerase chain reaction (ddPCR) was performed to detect in CTC-derived genomic (g)DNA the most common somatic mutation in spMTC (*RET*-M918T).

Methods

Twelve spMTC patients (DM:7, BPD:5) carrying somatic mutations in *RET* ($n = 7$, *RET*-M918T=4/7) and *HRAS* ($n = 5$) were included. Peripheral blood (10mL-EDTA) was obtained every 3-6 months depending on disease progression. In total of 53 samples, CTCs enrichment by EpCAM-based positive immunomagnetic selection (EpCam-IMS) was performed following our previous announcement where EpCam-IMS proved to be superior to the size-based Parsortix microfluidics system. CTCs gene expression analysis was based on RT-qPCR for epithelial (*CK-8, CK-18, CK-19*), mesenchymal (*Vimentin-VIM*), MTC-specific (*Calcitonin-CALCA*) and chemokine-receptor markers (*CXCR4*). A ddPCR assay was developed to detect the *RET*-M918T. Calcitonin, CEA DTs and disease status according to RECIST, were recorded.

Results

During a mean f-up of 24. 6 months (range 12-39) Calcitonin and CEA DTs were >24 months. Structural disease progression (SDP) was documented in four patients (2/4 harboring *RET*-M918T). Overexpression of *CALCA* was detected in 10 samples related to 8 patients, including those with SDP, at time-points 1-6 months before calcitonin levels showed a mean percentage increase from the preceding time point of 28. 65±24. 23% vs 14. 09±8. 59%, $P = 0.058$, which was observed in 11 samples without *CALCA* overexpression. *CXCR4* was overexpressed in 5 samples related to 3 patients (2/3 with SDP). In 2/17 samples related to *RET*-M918T patients the mutation was detected by ddPCR at time-points 6 months before SDP was documented, albeit calcitonin and CEA were slightly increased; the samples related at the time-point of SDP documentation were found negative. Epithelial markers were expressed in 8/53 (15. 1%) samples, while *VIM* in 22/53 (41. 5%).

Conclusions

Molecular characterization of CTCs in progressive spMTC, may add valuable information in disease monitoring. *CALCA* and *CXCR4* expression in CTCs as well as gDNA detection by ddPCR may be used as ancillary biomarkers towards efficient therapeutic management and precision medicine implementation. Increased expression of *VIM* advocates towards an epithelial to mesenchymal transition-EMT process. Larger patients' series and for longer follow-up periods should be studied to validate these Results

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P461

JOINT1122

20 Years of pediatric thyroid cancer experience at a tertiary care center

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Objectives

Thyroid cancer is a rare malignancy in the pediatric population, however recently the incidence has been increasing. This study describes the presentation, management and outcomes of patients seen at our centre over the last twenty-two years.

Methods

A retrospective chart review of 42 patients was conducted and statistical analysis performed. Inclusion criteria: Diagnosis of thyroid cancer, age less than 18 years at diagnosis, managed at the Stollery Children's Hospital between 2002-2024. There were no exclusion criteria. The presentation, investigations, management, and follow-up data were collected.

Results

Patients' age at diagnosis ranged from 5 to 17 years, with a median of 15. 7 years and an average follow-up time of 10 years (+/- 6 years). Thirty-five patients (83%) had papillary carcinoma, five (12%) had follicular carcinoma, one (2%) had medullary carcinoma, and one (2%) was diagnosed with non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Three patients were found to have hereditary cancer syndromes including DICER1, PTEN Hamartoma Tumour Syndrome and MEN2. Metastatic disease was identified in twenty-five patients (60%) at presentation, including 22/25 involving lymph nodes and 3/25 distant lung metastases. 8/42 patients (19%) had extrathyroidal extension and 15/42 patients (36%) had lymphovascular invasion. Molecular testing was not conducted routinely but is becoming more utilized. One patient's pathology was indeterminate but demonstrated a PAX8/PPARG mutation. This prompted surgery, resulting in confirmation of follicular carcinoma. Two patients with distant lung metastases and persistent disease were tested. NTRK3 and RET gene variants were identified, both of which are associated with aggressive disease. All patients underwent thyroidectomy. Data describing postoperative parathyroid function was available in 12/42 (29%) patients. 7/12 (58%) developed hypoparathyroidism, of which 4/7 (57%) cases were permanent. Data regarding laryngeal nerve function was available in 14/42 (33%) patients. Acquired laryngeal nerve dysfunction resulting in permanent vocal cord paralysis was diagnosed in 2/14 (14%) patients. Radioactive iodine was used for 38/42 (90%) patients. No patient deaths were reported.

Conclusion

Pediatric thyroid cancer has a high burden of disease. The mortality rate is low but there is significant morbidity associated with treatment. Molecular studies are becoming an essential tool in management of thyroid cancer.

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P462

JOINT1083

Exploring SDHA variants: navigating predisposition and incidental findings

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Background

Multigene panel testing (MGPT) is increasingly employed in oncology, leading to identification of numerous pathogenic/likely pathogenic (P/lP) variants in the *SDHA* gene. This includes incidental findings in patients with non-*SDHA*-associated tumours, creating challenges for clinical interpretation.

Aim

This study aimed to determine the prevalence and potential role of *SDHA* P/lP variants in the development of both *SDHA*-associated and non-*SDHA*-associated tumours.

Methods

A cohort of 1699 cancer patients who underwent MGPT from 2021 to 2023 was screened for suspected heritability. Tumours were categorized into *SDHA*-associated types (gastrointestinal stromal tumour, phaeochromocytoma-paraganglioma, renal cancer, neuroblastoma, pituitary adenoma; $n = 62$) and non-*SDHA*-associated types (endocrine tumours, hereditary breast-ovarian cancer syndrome, and other tumours; $n = 1637$). Controls were drawn from the gnomAD non-cancer database ($n = 134,187$). Comprehensive analyses included next-generation sequencing, RNA characterization, and loss of heterozygosity (LOH) studies by immunohistochemistry. Additionally, somatic *SDHA* sequence and copy number variations in 10, 463 pan-cancer and 7988 breast tumour samples were examined through The Cancer Genome Atlas datasets.

Results

Germline *SDHA* P/lP variants were significantly enriched in *SDHA*-associated tumour group compared to controls (5. 41x, $P = 0.05$), but their prevalence in patients with other tumour types was low (0. 23–1. 57x, $p > 0.05$). LOH was absent in non-*SDHA*-associated tumours with germline variants. Somatic *SDHA* alterations, including heterozygous and homozygous deletions, were identified in 1–4% of non-*SDHA*-associated tumours. In breast cancer, heterozygous *SDHA* copy number loss was linked to worse overall and relapse-free survival (hazard ratio=1. 55 and 1. 48, respectively; $P < 0.05$).

Conclusion

Germline *SDHA* P/lP variants predispose to *SDHA*-associated tumours, supporting their role in these cancers. While SDHA rarely contributes to non-*SDHA*-associated tumours, somatic *SDHA* deletions in breast cancer may act as disease modifiers, influencing progression and prognosis.

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P463

JOINT1493

Variable redifferentiation effect of larotrectinib for NTRK fusion-positive pediatric papillary thyroid carcinoma and disease outcomes off therapy

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Background
Few data exist regarding larotrectinib therapy in pediatric *NTRK* fusion-positive papillary thyroid cancer (PTC), especially its effects on redifferentiation in radioactive iodine-refractory (RAIR) disease. Our objective was to describe redifferentiation effects and disease outcomes in pediatric patients with stage 2 PTC following treatment with larotrectinib ± RAI.
Methods
This was a retrospective case series at a tertiary cancer center of patients <19 years with *NTRK* fusion-positive PTC and RAIR pulmonary metastases treated with larotrectinib and considered for ^{131}I therapy. Tumor response was assessed utilizing RECIST 1. 1.
Results
Four patients with pediatric PTC (ages 6-16 years at diagnosis; 50% female) and lung metastases considered RAIR were treated with larotrectinib 100 mg BID for a median of 14 months (range 6-30 months). Treatment was well tolerated, except for grade 3 hypocalcemia in one patient with pre-existing hypoparathyroidism, and tumor response (-25 to -100%) occurred in all patients. On diagnostic ^{123}I thyroid scans, any RAI uptake was identified in only 2/4 patients, but therapeutic ^{131}I did not cause an incremental tumor response in the two patients treated despite robust pulmonary uptake on the post-therapy scans. After stopping larotrectinib, all patients had stable structural disease after a mean follow-up of 38 months (range 26-48 months).
Conclusion
Although larotrectinib can have a redifferentiation effect in pediatric *NTRK* fusion-positive PTC, therapy with ^{131}I may not lead to an incremental benefit in children with established RAIR disease. Structural disease progression does not occur after cessation of larotrectinib, suggesting that it can be safely stopped in this population.

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P464

JOINT1293

Radiogenomics pilot study in adrenocortical carcinoma: assessing the relationship between genetic background and computerized tomography texture

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Background
Adrenocortical carcinoma (ACC) is an aggressive cancer with heterogeneous prognosis and few therapeutic options. Somatic genetic alterations have been demonstrated to predict clinical outcomes and have been highlighted as possible therapeutic targets. Radiomics has been used for the prediction of clinically relevant mutations, but not in ACC.
Aim
To predict the presence of key pathogenic gene variants in ACC using radiomics features.
Methods
We retrospectively enrolled 37 ACC patients (25 females) who underwent adrenalectomy at Queen Elizabeth Hospital Birmingham (Birmingham, United Kingdom) and IRCCS Sant'Orsola Malpighi Polyclinic (Bologna, Italy) from 2013 to 2023 with available pre-surgery portal-phase computerized tomography. Targeted Next Generation Sequencing was performed on formalin-fixed paraffin-embed samples using customised panels that included 10 ACC-specific genes (*TP53, RB1, CDK4, CTNNB1, APC, ZNRF3, MEN1, TERT, ATM* and *NF1*) designed and assembled in both centres. Sequencing was performed with routinely available techniques at each centre (i. e. Illumina). Radiomics was performed with LifeX software (Lito©, FR). After standardization, features selection was conducted with U Mann Whitney followed by Spearman correlation to avoid collinearity. Predictive models based on radiomics features for the prediction of most frequently mutated genes and mutated beta-catenin pathway genes (BCPG: *CTNNB1, ZNRF3, APC*), mutated tumour suppressor genes (TSG: *TP53, RB1, CDK4*), mutated chromatin remodeling genes (CRG: *MEN1, TERT*), *NF1* and *ATM* were formulated through logistic regression and their diagnostic performances were evaluated with Receiver Operator Characteristic (ROC) curve analysis and negative (NPV) and positive (PPV) predictive factor.
Results
Wild type genotype was observed in 20 samples (54. 1%). Mutations were detected for BCPG (n = 9 (24. 3%): *CTNNB1*=5 (13. 5%), *ZNRF3*=3 (8. 1%), *APC*=2 (5. 4%)), TSG (n = 9 (24. 3%): *TP53* =7 (18. 9%), *RB1*=2 (5. 4%)), CRG (n = 5: *MEN1*=4 (10. 8%), *TERT*=1 (2. 7%)), *NF1* (n = 4 (10. 8%)). BCPG mutations (P = 0. 020) were predicted by Inverse Variance (Odds ratio (OR)=0. 171 (95% Confidence Interval (95% CI) =0. 034-0. 846), P = 0. 030), Normalised Grey Level Non-Uniformity (Or = 0. 084 (95% CI=0. 007-0. 983), P = 0. 048), with sensitivity=88. 9%, specificity=79. 6%, NPV=81. 3%, PPV=60%. *CTNNB1* mutations (P = 0. 002) were predicted by Inverse Variance (Or = 0. 181 (95% CI=0. 039-0. 836), P = 0. 029) and Normalised Grey Level Non-Uniformity (Or = 0. 082 (95% CI=0. 007-0. 959), P = 0. 046), with sensitivity=100%, specificity=81. 8%, NPV=100%, PPV=45. 5%. *NF1* mutations (P = 0. 032) were predicted by Difference Entropy (OR=3. 014 (95% CI=1. 000-9. 079), P = 0. 050), with sensitivity=100%, specificity=72. 7%, NPV=100%, PPV=30. 8%.
Conclusion
We present the first radiogenomics study in ACC so far. Radiomics could be a swift and cost-effective analysis useful for early recognition of somatic mutations in BCPG, especially in genes *CTNNB1* and *NF1*. Larger studies might be required to further investigate variant predictions.

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P465

JOINT1158

Increased serum visfatin in neuroendocrine tumors shows promise as a diagnostic biomarker: a single-center, cross-sectional study

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Introduction
Neuroendocrine Tumors (NETs) remain a problematic area in endocrine oncology, due to their non-specific symptoms and the lack of reliable biomarkers. They are often diagnosed late, which leads to poor disease outcomes. Visfatin, an adipocytokine initially researched in metabolic disorders, has been linked with angiogenesis and tumorigenesis in various neoplasms. However, no studies in NETs were previously conducted. In this study, we aimed to analyze serum visfatin concentrations as a diagnostic biomarker in patients with NETs.
Material and Methods
We conducted a single-center, cross-sectional study of 77 patients with NETs (33 pancreatic and 44 small intestinal NETs) and 29 controls without NET diagnosis. Serum visfatin levels were measured using ELISA. Patient demographics and clinical characteristics were recorded for patient recruitment, with data on sex, age, NETs primary site, and WHO grade used for subsequent analyses. Group

comparisons were performed using Mann-Whitney U and Kruskal-Wallis tests. Spearman's rank correlation and multiple linear regression were used to compare the association between visfatin, and patient and tumor characteristics. ROC curve analysis evaluated visfatin's diagnostic performance in distinguishing NETs patients and controls. Statistical analyses were conducted in Python using pandas, NumPy, SciPy, scikit-learn.
Results
Serum visfatin concentrations were significantly higher in patients with NETs compared to controls (median[IQR]: 6. 94[2. 11-236. 17] vs 1. 59[1. 1-9. 24] ng/ml, $P = 0.0233$). ROC curve analysis showed moderate diagnostic performance (AUC = 0. 68), with concentrations above 2. 11 ng/mL providing a sensitivity of 75. 3% and specificity of 58. 6%. In patients with NETs, visfatin levels did not differ between WHO grades (G1 vs G2, $P = 0.31$), primary sites (pancreas vs small intestine, $P = 0.95$), sex ($P = 0.89$), age ($P = 0.13$), and when stratified by both primary site and grade ($P = 0.178$). Multiple linear regression confirmed no association between visfatin and age, sex, NETs primary site, and grade (R-squared = 0. 036, $p > 0.2$ for all variables).
Conclusion
This is the first study to evaluate potential utility of serum visfatin as a diagnostic biomarker in NETs. Serum visfatin concentrations show moderate discriminatory ability between subjects with and without NETs, and appear independent of other tumor and patient characteristics. Further research should involve larger study groups and assess visfatin's utility alongside and compared to other NETs biomarkers.
Keywords: Neuroendocrine neoplasms, visfatin, biomarkers, eNAMPT, PBEF1
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P466

JOINT2626

A comparison of clinical and hormonal characteristics in patients with paraneoplastic cushing's syndrome and in those with cushing's disease

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Introduction
The differential diagnosis between Cushing's disease (CD) and ectopic (paraneoplastic) Cushing's syndrome (ECS) is frequently difficult, notably when bilateral inferior petrosal sinus sampling is unavailable or a pituitary incidentaloma is visualized. We present a comparison between patients diagnosed with CD and ECS and our experience in their diagnosis in a tertiary center of Endocrinology.
Patients and Methods
This retrospective study identified 27 patients diagnosed with CD [78% females, mean age 37. 5 years (10-65)] and 21patients with ECS [67% females, mean age 50 years (18-74)] evaluated in our department between 1997-2024. Data on clinical presentation and hormonal workup were analyzed; 85% of CD and 90% of ECS patients were confirmed histologically.
Results
CD patients had 16 (59%) microadenomas and 11 (41%) macroadenomas. Causes of ECS: neuroendocrine tumors in 12 patients (57%); medullary thyroid cancer in 5 patients (24%); lymphoma in 1 patient; thalamic tumor 1 patient, unknown primary tumor in 2 cases (10%). Almost all the ECS and only 63% of CD patients presented with typical cushingoid appearance. In ECS more frequent were hypertension (81% vs 67%, $P < 0.05$) and hypokalemia (range 1. 65-3. 2 mmol/l) in 72% vs 0%, while in CD patients more frequently were found overweight/obesity (78% vs 50%, $P < 0.001$) and osteoporosis/osteopenia (40. 7% vs 24%, $P < 0.05$), while dyslipidemia (81% in ECS vs 74%) and prediabetes/diabetes (52% in ECS vs 48%) were non-significantly different. ECS patients had higher median morning cortisol level 46 vs 22 μg/dL, $P < 0.001$, higher late night serum cortisol 18. 7 vs 15 mg/dL, $P < 0.05$, higher ACTH [141 pg/mL (range 35-1221) vs 77 pg/mL (range 21-201), $P < 0.05$], higher UFC levels (5. 97 vs 1. 59 xULN, $P < 0.05$). Levels in ECS patients overlapped with those in CD in 57% of cases for morning cortisol, 50% for late night cortisol, 72% for ACTH. Inadequate cortisol suppression (<50% reduction) after high dose dexamethasone (DST, 8mg/day for 2 days) was recorded in 93% of ECS patients, but also in 47. 6% of 21 CD patients (in 44. 5% of those with macroadenomas and in 41% of those with microadenomas). Extensive imaging identified the primary tumor in 71. 4% of ECS patients.
Conclusion
Patients with ECS had higher prevalence of hypertension and hypokalemia and lower prevalence of obesity and osteoporosis compared with patients with CD. ECS patients had significantly higher morning and late-night serum cortisol, ACTH and UFC levels. High dose DST had 93% sensitivity but only 52% specificity for ECS. Management of ACTH-dependent CS needs a multi-disciplinary approach.
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P467

JOINT88

Long-term persistence of glycemic dysregulation in patients with a history of pheochromocytoma/paraganglioma

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Introduction
Pheochromocytomas and paragangliomas (PPGLs) are relatively rare endocrine tumours often characterized by excess catecholamine production. Catecholamine-induced cardiometabolic complications substantially contribute to increased morbidity and mortality in PPGL patients prior to surgical resection. Hyperglycemia driven by catecholamines can lead to the onset or worsening of diabetes mellitus, while elevated plasma norepinephrine levels have been associated with higher HbA1c and reduced body weight in PPGL patients. Despite these acute findings, the long-term cardiometabolic outcomes following PPGL resection remain insufficiently studied. This study aimed to explore biomarkers indicative of a persistent higher cardiometabolic risk in PPGL patients.
Methods
We conducted a retrospective analysis of a multicentre cohort of patients with PPGLs enrolled in the prospective **ProsPheo**study and the **ENS@T registry**. Cardiometabolic risk factors including glycemic status, dyslipidemia and BMI, were evaluated at the time of PPGL diagnosis and during follow-up. To further assess long-term outcomes after successful PPGL resection, patients with a history of resected PPGL (without recurrence) were compared to a control group of individuals with non-functioning adrenal adenomas (NFAA) [with normal aldosterone-renin ratios, normal 1 mg dexamethasone suppression testing, and non-elevated plasma levels of (nor)metanephrines and 3-methoxytyramine].
Results
A total of 259 individuals were included: patients with a present PPGL or a history of PPGL ($n = 188$), a metastatic PPGL ($n = 27$), or a pathogenic variant in a PPGL susceptibility gene without prior PPGL history ($n = 44$). Mean HbA1c levels were lowest in the susceptibility gene carrier group (5. 4%, SD 0. 5%) and similar in patients with a present PPGL (5. 6%, SD 0. 6%), a history of PPGL (5. 6%, SD 0. 4%) or metastatic PPGL (5. 6%, SD 0. 8%). In patients with a history of PPGL (without recurrence) and ≥12 months post-surgery follow-up ($n = 113$), mean HbA1c levels (5. 6%, SD 0. 4%) and the

prevalence of hyperglycemic disorders were significantly higher than in a control group with non-functioning adrenal adenomas (NFAA; $n = 76$) of similar age and BMI (HbA1c 5. 5%, SD 0. 4%; $P = 0.004$). Pre-surgery HbA1c was higher in catecholamine-secreting PPGLs compared to non-secreting PPGLs (5. 8% vs. 5. 3%; $P = 0.02$), but this difference was not observed during follow-up (5. 6% vs. 5. 5%; $P = 0.56$). No significant differences were found between groups regarding other cardiometabolic risk factors or laboratory parameters, including BMI, cholesterol, triglycerides, eGFR, and NT-proBNP levels.

Conclusions

The primary conclusion of this study is that chronic hyperglycemia persists long-term following successful PPGL resection.

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P468

JOINT1154

[^{68}Ga]Ga-DOTA-exendin-4 PET/CT for the localization of insulinoma: results of an international, dual-center, retrospective, open-label real-world imaging study

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Introduction

Benign insulinomas are the main cause of endogenous hyperinsulinemic hypoglycemia (EHH) in adults, with surgery as the only cure. Pancreas-preserving procedures are preferred, making precise localization crucial. Recent studies indicate that GLP-1R imaging, such as [^{68}Ga]Ga-DOTA-exendin-4 (^{68}Ga-Ex4) PET/CT, outperforms conventional imaging in identifying insulinomas.

Aim

The goal of this study was to generate real-life data for the detection rate of insulinoma with ^{68}Ga-Ex4 PET/CT in patients with negative/inconclusive workup on prior conventional imaging.

Material and Methods

In this retrospective, real-life, dual-center imaging study, patients with biochemically proven EHH and/or a positive Whipple triad underwent ^{68}Ga-Ex4 PET/CT at two tertiary centers between April 2017 and March 2024. Endpoints: ^{68}Ga-Ex4 PET/CT detection rate after inconclusive conventional workup (gold standard: histology) and impact on patient management.

Results

Hundred one patients were enrolled, of which 63 (62%) received conventional workup prior to ^{68}Ga-Ex4 PET/CT. ^{68}Ga-Ex4 PET/CT was positive in 26 out of the 35 patients with negative conventional workup leading to a PET/CT detection rate of 74% in this challenging patient group. 22/26 (85%) patients with positive results only with ^{68}Ga-Ex4 PET/CT were confirmed by histology for either Insulinoma (21 cases) or nesidioblastosis (1 case).

Conclusions

In a real-life setting; ^{68}Ga-Ex4 PET/CT effectively detects insulinomas and nesidioblastosis in patients with inconclusive conventional workup, achieving a 74% detection rate. Histology confirmed insulinomas or nesidioblastosis in all operated patients with positive ^{68}Ga-Ex4 PET/CT results, highlighting its impact on patient management.

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P469

JOINT3401

Phenotypic and genotypic characteristics of patients with MEN2 in france: preliminary features from the MEN2 french database

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Introduction

Multiple Endocrine Neoplasia type 2 (MEN2) is a rare disease caused by activating mutations of the *RET* proto-oncogene. MEN2 is responsible for predisposition to develop endocrine tumors including medullary thyroid carcinoma (MTC) and pheochromocytomas (PHEO)[1]. MEN2 is characterized by a genotype-phenotype correlation, as evidenced by the phenotypic differences of the two main entities: MEN2A, mainly linked to codon 634 mutations, associates CMT, PHEO, less frequently primary hyperparathyroidism, while MEN2B linked to codon 918 mutation associates CMT, PHEO and cutaneous-mucosal, digestive and bone manifestations[2]. This genotype-phenotype correlation is the basis of international recommendations for monitoring and management (prophylactic and curative) of MEN2 patients[3]. Despite this genotype-phenotype correlation, MEN2 is characterized by intra- and inter-family variability for patients carrying the same *RET* variant, particularly concerning CMT. The aim of this study is to conduct a retrospective analysis of the clinical, biological, and genetic characteristics of MEN2 patients in France to better understand the natural history of the disease and identify modifiers of disease progression.

Patients and Methods

Between November 2022 and October 2023, we collected retrospective data from MEN2 patients followed at four tertiary centres in France.

Results

We established a cohort of 748 patients from 335 families. The *RET* variant was available for 734 patients (98%), mainly located on exons 10 ($n = 142$, 19%), 11 ($n = 278$, 38%), and 14 ($n = 163$, 22%). The mean age at molecular diagnosis was 45. 4 years for index cases and 26. 8 years for relatives. A total of 393 of 467 patients (84%) had undergone surgery for MTC, with 283 localized diseases (pTxN0) at diagnosis, 96 locally advanced (pTxN1), and 7 metastatic (pTxNxM1) . After a median follow-up of 12 years, 199 of 304 patients were in remission (65%), 87 had residual disease (29%), and 18 had died (6%). A total of 30% (137/449) of patients benefited from pheochromocytoma surgery, including 91 patients with bilateral adrenal involvement (66%).

Conclusion

This study confirms the feasibility of national epidemiological and genetic data collection. This future database will help identify modifiers of disease progression to better understand phenotypic variability and to tailor the management of MEN2 patients.

Conflict of interest

None

Fundings

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P470

JOINT1762

Individual dosimetry in radionuclide therapy (RLT) of NET using [177Lu]Lu-DOTA-TATE or [177Lu/90Y]-DOTA-TATE mixture - effect on total administered RLT activity

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Introduction
Radioligand therapy (RLT) targeting somatostatin receptors is an effective treatment for disseminated neuroendocrine tumors(NETs) that express these receptors. Individual dosimetry of critical organs ensures safety and, in some cases, allows for an increased radiation dose during therapy, potentially leading to better treatment outcomes. The DUONEN multicenter randomized clinical trial aims to evaluate the effect of individual dosimetry on the efficacy and safety of RLT with [177Lu]Lu-DOTA-TATE or a mixture of [177Lu/90Y]-DOTA-TATE in patients with NET.
Materials and Methods
Adult patients with advanced, unresectable, well-differentiated(G1 and G2) NETs, who are progressing on long-acting somatostatin analogues, are randomized into four arms:
- Arm A: Treated with [177Lu]Lu-DOTA-TATE at a constant radioactivity of 7400MBq per cycle
- Arm B: Treated with a mixture of [177Lu/90Y]-DOTA-TATE, initially in a 3700:1850MBq/MBq ratio, with the [90Y]Y-DOTA-TATE dose adjusted in each cycle based on individual dosimetry to maintain the highest possible radiation dose in tumor tissue
- Arm C: Similar to Arm B, but with the radioactivity of [177Lu]Lu-DOTA-TATE adjusted according to dosimetry, while the radioactivity of [90Y]Y-DOTA-TATE remains constant
- Arm D: The first dose is analogous to arm A, with subsequent doses individualized based on dosimetry

The overall dose limits for four cycles of RLT are $<$23Gy for the kidneys and $<$2Gy for the red bone marrow.

Results
By now dosimetry was performed for 115cycles of RLT in 40patients (10 per arm) using QDose software based on 4 SPECT/CT scans and 5 blood samples. In all arms, the doses to the red bone marrow did not exceed the critical limits, with most cases being considerably lower. There was significant variability in the individual doses absorbed by the kidneys. The average dose for kidneys equaled 0. 64 Gy/GBq (SD 0. 19) in arms A and D whereas in arms B and C 0. 76 Gy/GBq (SD 0. 29), and 3. 26 Gy/GBq (SD 1. 26) for [177Lu]Lu-DOTA-TATE and [90Y]Y-DOTA-TATE, respectively. Considering the standard activity of 7. 4GBq in the first cycle, the activity in subsequent cycles could be increased by more than 10% in 60% of cases and decreased in about 15% of cases.
Conclusion
Individual dosimetry may play an important role in RLT, leading to significant dose adjustments in subsequent cycles of treatment for most patients. This approach frequently allows for significant dose increases in subsequent cycles of [177Lu]Lu-DOTA-TATE therapy and suggested dose reductions in the arms using mixtures of [177Lu/90Y]-DOTA-TATE.
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P471

JOINT3591

Thyroid carcinoma in children and adolescents - subtypes and clinical evolution

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Introduction
The management of thyroid nodules in children is challenging. Moreover, the risk of malignancy for any nodule is higher than in adults.
Aim
To assess the subtypes of cancer in thyroid nodules in a pediatric population and to observe their clinical evolution.
Material and Methods
We retrieved from our endocrinology center database all the fine-needle aspiration (FNA) procedures and all the pathology results from total/subtotal thyroidectomies performed on $\leq$ 18-year old children between January 2020 and June 2024.
Results
There were 163 patients, of whom 39 (23. 92%) had thyroid malignancies. Of the 39 patients, the mean age at diagnosis was 14. 66 years (youngest -7, oldest – 18), with a girls/boys ratio – 33/6. 19 of them had preoperative FNA procedures: there were 4, 6 and 9 patients with Bethesda 4, 5 and 6 respectively. 35 patients had papillary thyroid carcinoma (PTC), 1 follicular carcinoma (FC) and 3 medullary thyroid carcinoma (MTC). Of the 35 patients with PTC, 17 had diffuse sclerosing PTC (48. 57%), 12 classic PTC (35. 29%), 2 follicular variant PTC (5. 88%), 2 trabecular PTC (5. 88%), 1 tall cell PTC (2. 94%) and 1 Warthin tumor (2. 94%). 18 (50%) and 3 (8. 33%) patients had cervical lymph node and pulmonary metastases respectively at diagnosis. The majority of patients with PTC (41. 66%) had an excellent biochemical and structural response after surgery and radioiodine therapy (RAI). Of the 3 patients with CMT, 2 of them had positive RET mutations for MEN 2A, and familial CMT, but unfortunately did not undergo prophylactic thyroidectomy, and only got surgery when calcitonin levels were already elevated and the thyroid tumor was detectable on ultrasound. The other patient had a positive de novo RET mutation (Met918), underwent 3 surgical interventions, and still has signs of residual disease and elevated calcitonin levels (400 mg/dl). None of the patients have had a thyroid carcinoma related death.
Conclusion
The most common type of carcinoma in these patients was diffuse sclerosing PTC (43. 58%). The clinical evolution of these patients varies according to malignancy subtype, the majority of them having a good clinical outcome. Children with familial MTC and positive RET mutations need better clinical monitoring and appropriate therapeutic intervention.
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P472

JOINT1288

Annual tumour surveillance screening for paediatric carriers of SDHX gene variants in family clinics at barts health NHS trust

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Background
Phaeochromocytomas and paragangliomas have an annual incidence of 0. 5-2 cases per million children, with 70-80% linked to inherited pathogenic variants in tumour suppressor genes[(1)]. An international consensus statement (2024) underscored the need for lifelong surveillance of asymptomatic variant carriers identified through family-based genetic testing, from childhood/early adulthood[(1)]. Surveillance enhances early detection and timely management of tumours.
Methods
This retrospective audit analysed uptake and outcomes of annual surveillance offered to young people identified through family-based genetic testing and referred to Barts Health NHS Trust from 2019-2024.
Results
The audit included a population of 55 individuals aged 5-19. Of these, 48 (87%) had heterozygous variants in *SDHB*, 4 (7%) in *SDHD*, and 1 (2%) in each of *SDHA*, *SDHC*, and *TMEM127*. Of those aged under 10, each year, an average of 92% (range 82-100%) attended clinic reviews (face-to-face/telephone), 75% (range 42-93%) undertook 24-hour urinary metanephrine screening, and 94% (range 83-100%) attended for ultrasound neck/abdomen/pelvis. Of those aged 10 and over, each year, 85% (range 50-100%) attended clinic reviews (face-to-face/telephone), 82% (range 76-91%) had plasma metanephrines tested and 84% (range 75-91%) attended MRI scans (alternating MRI abdomen/pelvis and MRI

neck/thorax/abdomen/pelvis). During the audit period, 2 patients, both *SDHB* variant carriers, had lesions identified on first surveillance. The first was diagnosed with a retroperitoneal paraganglioma (20x23x27mm) at age 8. 7, suspected following an elevated 24-hour urinary normetadrenaline/creatinine ratio at 851nmol/mol (normal <300nmol/mol), and confirmed by MRI. The second was diagnosed with a left adrenal phaeochromocytoma (28x22mm) at age 16. 9, detected on MRI. They had raised plasma normetanephrine at 1308pmol/l (normal <775pmol/l). Alpha-blocked resection was followed by 6-monthly imaging and plasma metanephrines for 5 and 1 years respectively. No recurrences/metastases have since been identified. Over this period, 27 of 202 scans conducted (ultrasound/MRI) showed unrelated incidental findings (22 individuals). 10 underwent further investigations and 1 required treatment. Work is ongoing to understand patient experiences and the psychological impact of screening on patients and their families.

Discussion

Within our cohort, the annual screening programme demonstrates good compliance and is effective at detecting lesions early. Since screening revealed pathology in children under 10, this supports early surveillance for variant carriers identified through family-based genetic testing.

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P473

JOINT1984

USP10 as a multifaceted therapeutic target in adrenocortical tumors: implications for tumor biology and steroidogenesis

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Adrenocortical carcinoma (ACC) is a rare and aggressive endocrine malignancy with an incidence of one case per million people per year and a 5-year overall survival rate of less than 35%. Currently, complete surgical resection is the only curative treatment, while mitotane, an adrenolytic drug, remains the sole approved systemic therapeutic option besides platinum-based chemotherapy. Given these limitations, there is an urgent need for innovative therapeutic approaches. The ubiquitin-proteasome system (UPS) is an essential cellular machinery that regulates protein stability and is known to be hijacked by tumor cells to exploit signaling pathways and sustain highly proliferative states. However, the role of deubiquitinases (DUBs) in adrenocortical tumors remains poorly understood. Analyzing publicly available datasets, we prioritized DUBs associated with patient survival in ACC and its most relevant signaling pathways. Among these, USP10 emerged as a particularly compelling candidate in follow-up *In vitro* studies. Analysis of Immunohistochemical staining of USP10 on tissue microarrays (TMAs; n: number of single cores) revealed significantly higher USP10 expression in ACC ($n = 645$; $P < 0.001$) and adrenocortical adenomas ($n = 128$; $P < 0.01$) compared to normal adrenal gland ($n = 42$). Subsequential analysis of adenomas by hormonal status showed an increased USP10 expression in cortisol-producing adenomas ($n = 95$) compared to hormonally inactive adenomas ($n = 12$; $P < 0.001$), which is in line with its distinct zone-specific expression we observed in the normal adrenal cortex. So far, we were able to obtain complete clinical datasets for 121 ACC specimens, allowing correlations between USP10 expression and clinical outcomes, including survival, chemotherapy response, hormonal status, and pathological tumor markers. Interestingly, subgroup analysis for hormonal activity showed no significant difference in USP10 expression in ACC. However, treatment with an USP10-specific inhibitor resulted in a significant reduction in cell proliferation in ACC cell lines. Combining USP10 inhibition with cisplatin elicited a synergistic anti-tumor effect, likely through interference with DNA damage response. Therefore, our preliminary analyses indicate that USP10 dysregulation in ACC might be linked to its malignant phenotype rather than hormonal activity. Subsequent *In vitro* experiments using LC-MS-based steroid profiling and immunoblotting of steroid biosynthesis enzymes in ACC cell lines following USP10 inhibition provided further insight into USP10's influence on hormone production. In conclusion, our findings show evidence for USP10 dysregulation in adrenocortical tumors. Its multifaceted role in tumor biology, including DNA damage response and steroidogenesis, suggests a complex contribution to tumorigenesis, with potential clinical implications for diagnosis and treatment.

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P474

JOINT78

Pediatric and adolescent von hippel-lindau disease: tumor profiles, genotype-phenotype correlations, and a comparison with adults

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Background

Data on pediatric/adolescent von Hippel-Lindau (VHL) disease is sparse, and comprehensive studies detailing the phenotype of all associated neoplasms are lacking. Their current surveillance/management recommendations rely on expert opinion or extrapolation from adults, not individualized to the mutation type.

Objectives

The study aimed to characterize the childhood/adolescent-onset VHL disease phenotype, compare it to adult-onset disease and identify genotype-phenotype correlations.

Methods

This was a retrospective review of children/adolescents (≤19 years) and adults (≥20 years) with VHL disease from a single endocrine center (2000-2024). The diagnosis was based on either clinical criteria (15%, per the guidelines) or genetic confirmation (85%: 66% missense, 19% truncating variants). Only neoplasms diagnosed until 19 years of age were included in the childhood/adolescent group and compared with the last follow-up of adults. The demographic, clinical, anatomical/functional imaging, operative details, histopathology (operated patients) for each VHL-associated neoplasm, and genetics were noted.

Results

Twenty-six children/adolescents (median age at diagnosis 15. 5 years) were identified. By age 19 years, 81% developed pheochromocytoma/paraganglioma (PPGL, of which 10% head and neck PGL), 42% central nervous system hemangioblastoma (CNS-HB), 31% each retinal RHB and pancreatic neuroendocrine tumor (PNET), while none had endolymphatic sac tumor/renal cell carcinoma. At diagnosis, all those with PPGLs were symptomatic (median size 4. 5 cm, 52 lesions). CNS-HBs showed female preponderance, with a high disease burden (60% symptomatic, 50% synchronous in ≥2/3 components of the neuroaxis) and surgical requirement by age 19. Two pediatric patients needed surgery for a symptomatic PNET before the recommended surveillance initiation age (15 years). Two children/adolescents developed polycythemia during follow-up. Compared to adults ($n = 39$), pediatric/adolescent PPGL patients had significantly higher plasma free-normetanephrine (median 1099. 5 vs 2513. 5 pg/mL), more bilateral (47% vs 76%) and extra-adrenal (19% vs 48%) disease by 19 years, and an 8. 3-fold higher operative-site recurrence over a similar follow-up duration (median 108 months: adults, 75 months: children/adolescents) independent of cortical-sparing surgery. Other neoplasms' frequency and burden by 19 years resembled adults. Childhood/adolescent PPGLs occurred predominantly (16/17 cases) and PNETs exclusively, with missense variants. Codon 167 missense variants were associated with synchronous bilateral pheochromocytomas.

Conclusion

In pediatric/adolescent VHL disease, we report a severe phenotype, more extensive (PPGL) or comparable to adults. Our findings support head and neck PGL and earlier PNET surveillance in pediatric/adolescent protocols. The occurrence of childhood/adolescent PPGLs and PNETs almost exclusively with missense variants suggests the genotype may guide the pediatric surveillance strategy for these neoplasms.

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P475

JOINT2481

Treatment of lung neuroendocrine tumors with ^{177}Lu-DOTATATE: experience from a tertiary oncology centre

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Background
PRRT with ^{177}Lu-DOTATATE is approved for the treatment of metastatic or unresectable, progressive, well-differentiated, SSTR-positive gastroenteropancreatic neuroendocrine tumors (NETs). Although controlled randomized trials are lacking, several studies have shown that PRRT is also effective for SSTR-positive lung NETs. Our study aimed to evaluate the efficacy and safety of ^{177}Lu-DOTATATE PRRT in patients with lung NETs.
Materials and Methods
We retrospectively selected patients with metastatic and/or unresectable lung NET who completed treatment with ^{177}Lu-DOTATATE PRRT at a tertiary oncology center, between 2011 and 2023. Response rates, progression-free survival (PFS), overall survival (OS), and toxicity were assessed.
Results
Twenty-two patients were identified (mean age 63. 1 ± 11. 4 years; 18, 82% men): 12 (55%) with atypical carcinoids, 9 (41%) with typical carcinoids, and 1 (4%) unclassified. Eighteen (82%) patients had hepatic metastasis, 15 (68%), bone metastasis, 9 (41%), lymph node metastasis, and 7 (32%), other. Fourteen patients (64%) were symptomatic, 5 (36%) of whom had carcinoid syndrome. Most patients were previously treated with somatostatin analogs (17; 77%) and chemotherapy (12; 55%). All patients were treated due to disease progression: 19 patients received 3 cycles of ^{177}Lu-DOTATATE and 4, 4 cycles, with a median cumulative activity of 19. 7 GBq (range, 14. 4-29. 6). Median follow-up time after the first cycle was 45 months (range: 7-147), with 16 (73%) deaths recorded. Median PFS was 19 months (95%CI 10-28) and median OS was 46 months (95%CI 38-53). Objective response rate was 32% (7 patients), with all responses documented as partial. Stable disease was described in 7 (32%) patients, yielding a disease control rate of 64%. Of the 14 symptomatic patients, 5 (36%) showed improvement after PRRT, 3 (21%) experienced worsening symptoms, and 6 (43%), no change. There were no cases of clinically significant (grade 3/4) hematologic, hepatic, or renal toxicity. Previous treatment with somatostatin analogs was associated with longer PFS and the presence of respiratory symptoms, with shorter PFS.
Conclusions
^{177}Lu-DOTATATE PRRT seems to be a valuable treatment option for advanced progressive lung NET, with a minimal risk of toxicity. Randomized prospective studies are needed to validate these findings.

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P476

JOINT1905

MiR-191-5p represents a potential personalized diagnostic and therapeutic tool in the pathophysiological interplay between obesity and prostate cancer

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Prostate cancer (PCa) is a major cause of male cancer-related mortality worldwide, emphasising the need for non-invasive diagnostic and prognostic biomarkers and therapeutic targets for this pathology. MicroRNAs (miRNAs) have emerged as promising diagnostic and therapeutic tools for various pathologies. In this study, we investigated the microRNA landscape in plasma samples from PCa patients and explored their potential diagnostic and therapeutic value. Initially, the miRNome of plasma samples from an discovery cohort of healthy subjects (n = 18) and PCa patients (n = 19) was determined using an Affymetrix-miRNA array. Subsequently, the major changes were validated in an independent and ample validation cohort [n = 202 (91 healthy subjects, and 111 PCa patients)] by quantitative real-time PCR. In addition, *in silico* and *In vitro* approaches were performed on normal (RWPE-1 and PNT-2) and tumour (LNCaP, DU145, and PC-3) prostate cell models. The results from the discovery cohort revealed that the expression of 104 miRNAs was significantly altered. Among these, miR-191-5p emerged as a particularly noteworthy candidate due to its potential clinical utility and its role in the pathophysiology of PCa. Specifically, miR-191-5p levels were significantly elevated in PCa patients, highlighting a potential diagnostic value particularly within the Grey Zone of PSA (range of 3 to 10 ng/mL), wherein PSA sensitivity and specificity for diagnosing PCa is limited. Notably, the diagnostic capacity of miR-191-5p was further enhanced in PCa patients with obesity (BMI > 30). Then, a bioinformatics approach was employed, using diverse tools to identify potential targets regulated by miR-191-5p, which showed 13 potential oncogenic targets. Further analyses in PCa cell models in response to miR-191-5p overexpression identified *TMOD2*, a migration-related gene, as the most consistently decreased target. Furthermore, *TMOD2* levels were also confirmed to be modulated by miR-191-5p by using a novelty miRNA-target interaction blocker. Altogether, our findings demonstrate that miR-191-5p may serve as a novel and effective personalised diagnostic biomarker in PCa, particularly among patients with obesity, and as a potential therapeutic tool worth to be explored in PCa patients.

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P477

JOINT1683

DICER1 syndrome: clinical and endocrinological manifestations in pediatric patients followed in a third-level hospital

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Introduction
DICER1 syndrome (DS) is a genetic condition that predisposes individuals to benign and malignant neoplasms. It is caused by pathogenic variants of the DICER1 gene, inherited in an autosomal dominant manner, with low penetrance. The DICER1 protein promotes the maturation of microRNAs, which regulate post-transcriptional mRNA expression.
Objective
To describe the clinical, biochemical and genetic characteristics of a group of pediatric patients with DS diagnosed and followed in the endocrine service at a single tertiary center
Methods
A retrospective descriptive study was conducted. Molecular studies consisted of exonic sequencing of the DICER1 gene in peripheral blood leukocytes and tumor tissue. The variables analyzed were: age at diagnosis, sex, inheritance, associated pathology, and clinical characteristics of endocrine involvement.
Results
Seventeen patients were included, 12 girls (70%). The median age was 13. 8 years (range 1. 9-16. 2). The median follow-up time was 3 years (IQR 0. 67-5). Sixteen patients had pathogenic variants in the germline (94%). The family study was performed in 14 patients, of which 10/7 families were hereditary and 4 were de novo. The associated pathologies were: thyroid gland involvement (n = 16; 94%), ovarian Sertoli-Leydig cell tumor (n = 5; 29%), uterine cervical rhabdomyosarcoma (n = 3; 18%), cystic nephroma (n = 3; 18%), anaplastic renal sarcoma (n = 1; 6%), pulmonary cyst (n = 1; 6%), lymph node sarcoidosis (n = 1; 6%) Regarding thyroid pathology, the first clinical manifestations were: cervical mass (n = 10; 62. 5%) and ultrasound finding (n = 6; 37. 5%). The histological diagnoses were: multinodular goiter (MNG) (n = 13; 81. 2%), papillary thyroid carcinoma, follicular subtype (n = 5; 31. 2%), and follicular adenoma (n = 2; 12. 5%). All patients had normal thyroid function and negative antithyroid antibodies. Regarding ovarian Sertoli-Leydig cell tumors, the clinical manifestations in prepubertal patients (n = 2) were abdominal distension and mass, and in pubertal patients (n = 3), menstrual cycle alteration (n = 3) and clinical-biochemical signs of virilization (n = 1). Histology in prepubertal patients was undifferentiated, and in pubertal patients, it was moderately differentiated. In 4 cases, the location was unilateral. All with associated thyroid pathology. Uterine rhabdomyosarcoma presented with gynecological bleeding (n = 3) and was associated with Sertoli-Leydig cell tumor (n = 1) and thyroid pathology (n = 3).

Discussion
According to the literature, DS presented during childhood and adolescence, with predominance in girls and a familial inheritance pattern. Thyroid involvement was the most frequent. Sertoli-Leydig cell tumors in prepubertal patients showed histological features of worse prognosis. Lymph node sarcoidosis was not previously reported in association with DS. The diagnosis of DS is crucial for patient follow- up and detection of affected family members.

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P478

JOINT1599

Frequency and phenotypic spectrum of DICER1 syndrome among children and adolescents with thyroid cancer

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Purpose
DICER1 syndrome is an autosomal dominant familial tumor syndrome predisposing various benign or malignant tumors with incomplete penetrance and variable expressivity. Mutations in DICER1 on chromosome 14q32. 13 lead to truncated protein, impaired microRNA production, and dysregulated gene expression, resulting in tumor formation. DICER1 syndrome is associated with early-onset multinodular goiter and differentiated thyroid carcinoma. This study aimed to investigate the frequency of DICER1 mutations in patients with thyroid cancer and the clinical phenotypes of patients with DICER1 syndrome.
Methods
This study included 16 patients from 8 families with DICER1 syndrome through targeted gene panel sequencing or Sanger sequencing of DICER1. The targeted gene panel included 172 genes associated with hereditary tumor syndromes. Genetic testing was conducted for patients with a clinical features of DICER1 syndrome such as pleuropulmonary blastoma (PPB), ovarian Sertoli-Leydig cell tumors, early-onset thyroid cancer, or family history of DICER1 syndrome. Clinical phenotypes and mutation spectrum of the patients were reviewed retrospectively.
Results
Mutations in DICER1 were found in 7 probands with childhood-onset differentiated thyroid cancer, one with PPB, and two with rhabdomyosarcoma by targeted panel sequencing, and the other 6 first-degree relatives of DICER1 syndrome were diagnosed by Sanger sequencing. The mean age at diagnosis was 12. 4 years for probands and 26. 8 years for family members. Associated tumors included PPB ($n = 4$), thyroid carcinoma ($n = 6$), ovarian Sertoli-Leydig cell tumors ($n = 1$), cystic nephroma ($n = 1$), embryonal rhabdomyosarcoma ($n = 2$) , and ectomesenchymoma ($n = 1$). Genetic analysis identified 9 nonsense mutations from 3 pedigrees, 5 frameshift mutations from 3 pedigrees, and 2 splice site mutations from 2 pedigrees, including three novel variants: c. 3747del (p. K1249Nfs*9), c. 1376+2T>C, and c. 3689del (p. Q1230Rfs*9).
Conclusions
Pediatric patients with thyroid cancer and associated tumors should be evaluated for DICER1 syndrome with family screening. Given the association of endocrine organ tumors with DICER1 syndrome, pediatric endocrinologists should be aware of the disease's clinical spectrum to provide proper management and reduce its morbidities.

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P479

JOINT2731

Cabozantinib in advanced adrenocortical carcinoma – first preliminary results of the prospective phase II caboACC study

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Background
Adrenocortical carcinoma (ACC) is a rare malignancy with a poor prognosis in advanced stages and limited therapeutic options. In a retrospective analysis, we previously observed clinical activity of the multityrosine kinase inhibitor cabozantinib (cabo; Kroiss, J. Clin. Endocrinol. Metab, 2020). A recently published phase II study conducted in parallel with this trial reported that 13 out of 18 patients with advanced ACC achieved progression-free survival at four months (Campbell, *Lancet Oncol.*, 2024).
Objective
To prospectively evaluate the clinical activity of cabo in patients with unresectable/metastatic ACC after failure of standard-of-care therapy.
Study Design
The prospective, open-label, multicenter, single-arm, phase II study (NCT03612232) followed a two-stage accrual design. Patients received oral cabo at an initial dose of 60 mg/d. Tumor response was evaluated radiologically every 8 weeks. To minimize potential drug-drug interactions, patients with mitotane plasma concentration >5 mg/l were excluded.
Primary Outcome Measure
The proportion of patients with progression-free survival after four months of treatment.
Results
Of 45 patients screened, 37 were enrolled, with 36 undergoing at least one follow-up imaging. Two patients discontinued cabo due to treatment-related toxicity despite stable disease prior to primary endpoint assessment. Among 34 evaluable patients, 14 (41. 2%) met the primary endpoint, maintaining stable disease for at least four months (preliminary data). The median duration of treatment was 22 weeks. Two patients achieved partial remission, and four additional patients experienced disease control for more than ten months. No new safety aspects were detected.
Conclusion
This investigator-initiated study confirms the promising clinical activity of cabo in heavily pre-treated ACC patients in a patient population larger than both previous retrospective and prospective studies combined. The lower response rate compared to the smaller parallel study may be due to differences in disease characteristics, prior treatments, and the larger sample size. Cabo may have greater efficacy in earlier lines of treatment for advanced ACC or in combination regimens, such as with immunotherapy.
Outlook
Secondary endpoints, markers of response and the potential impact of prior treatment, including interaction with prior mitotane, are currently under investigation.
Funding
This study was sponsored by the University Hospital of Würzburg and funded by Ipsen Pharma. The study team was solely responsible for the study conduct and interpretation of the data.

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P480

JOINT499

Rare occurrence of thyroid paraganglioma in the context of SDHB mutation: a case report

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Background
Thyroid paragangliomas (PGL) are rare neuroendocrine tumors, with nearly 75 cases reported globally. Arising from extra-adrenal paraganglia of the autonomic nervous system, they often present as slow-growing solitary thyroid nodules. While generally indolent and treatable through surgical excision, their malignant potential remains uncertain, necessitating long-term follow-up. Succinate Dehydrogenase Complex Subunit B (SDHB)-related thyroid PGL are exceptionally uncommon, with limited literature and no established guidelines for their management. The SDHB gene is inherited in an autosomal dominant manner and is associated with poor prognosis and increased metastatic potential.
Objectives
This case report aims to present the clinical course of a rare thyroid -SDHB related paraganglioma.
Methods-Results
The patient is a 54-year-old woman who underwent surgery for a thyroid nodule in 2016. Histopathological analysis of the thyroidectomy specimen unexpectedly revealed a paraganglioma, with a Ki-67 proliferation index of $<1\%$. The patient had normal laboratory (plasma and 24-h urinary catecholamines) and imaging (neck-thorax-abdomen MRI/CT scan) results post-thyroidectomy. She was subsequently referred to our department after genetic testing identified a pathogenic mutation in the SDHB gene. Her family history includes a daughter with a benign Warthin's tumor, another daughter who died from metastatic urothelial carcinoma, a third healthy daughter and a nephew with a carotid body paraganglioma. Genetic testing of her two living children was negative for pathogenic SDHB mutations. Follow-up tests of the patient in May 2024 including MRI of both neck and abdomen were normal and Positron Emission Tomography (PET) scanning with Ga-68 and 18F-FDG revealed no pathological uptake. The patient remains under close observation, without evidence of recurrence or metastasis, 9 years after surgery.
Conclusion
Thyroid paragangliomas remain exceptionally rare and represent a diagnostic challenge due to the limited data available. Vigilance is crucial, as these tumors may present with subtle symptoms or go unnoticed. The absence of guidelines and research, especially in the context of SDHB mutations, highlights the need for further investigation.

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P481

JOINT494

Chromogranin a and pancreatic polypeptide are not suitable for the screening of pancreatic neuroendocrine tumors in MEN1 - a long-term follow-up study

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Introduction
In patients with multiple endocrine neoplasia type 1 (MEN1) followed up at ENETS centers of Excellence, chromogranin A (CgA) and pancreatic polypeptide (PP) are widely used screening tools for pancreatic neuroendocrine tumours (panNETs). However, previous studies demonstrated conflicting results regarding their performance in MEN1 and the follow-up protocol can be questioned. This study aims to bring clarity to the question by investigating a well-characterized MEN1 cohort that, in addition to biomarker screening, underwent both somatostatin receptor positron emission tomography/computed tomography (SSTR PET/CT) and conventional imaging for the detection of panNETs. We studied the impact of long-term biomarker follow-up on the clinical management of panNETs in MEN1.
Methods
The study cohort consisted of 58 MEN1 patients from a European reference center for rare endocrine condition, all of whom underwent both SSTR PET/CT and conventional imaging of the pancreas in addition to long-term biomarker screening. We calculated sensitivity and specificity of CgA and PP for diagnosing any panNET, panNETs $\geq$ 20 mm, and metastatic panNETs, with pancreatic imaging as the reference standard. The longitudinal impact of 10-year annual biomarker measurements on clinical management was analyzed from electronic patient records.
Results
The sensitivity of CgA for diagnosing any panNET, $\geq$ 20 mm panNET, and metastatic panNET was 35%, 30%, and 60%, respectively. The sensitivity of PP for the same categories was 23%, 33%, and 0%, respectively. The area under the curve (AUC) in receiver operator characteristics analysis for CgA was 0. 30 (95% CI 0. 09-0. 51) for any panNET, 0. 49 (95% CI 0. 09-0. 51) for $\geq$ 20 mm panNET, and 0. 69 (95% CI 0. 42-0. 95) for metastatic panNET. The AUC for PP in detecting metastatic panNETs was 0. 28 (95% CI 0. 11-0. 46). Biomarker performance was poor and did not detect any new panNETs, or clinically significant panNETs (tumours $>$ 20 mm in size). Annual biomarker measurements during 514 patient-years of follow-up did not affect the clinical management of panNETs.
Conclusion
CgA and PP are not helpful in diagnosing panNETs in patients with MEN1. Long-term biomarker measurements did not impact clinical management of panNETs. The findings question the clinical value of using CgA and PP for the screening of panNETs in MEN1. Practice should change and other diagnostic methods prioritized instead.

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P482

JOINT431

Ectopic adrenocorticotrophic hormone secreting bronchial carcinoid: a retrospective study from a tertiary center

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Introduction
Adrenocorticotropic hormone (ACTH)- producing extra-pituitary tumors are 8-18% of endogenous cushing's syndrome, and their frequency is often under-estimated. This low frequency poses a challenge to acquiring experience in their management.
Methods
A retrospective study was undertaken at a tertiary center in Lucknow. Cases were identified through the Hospital Information System from 2000 to 2024. A cohort of eleven cases of bronchial carcinoid-secreting ACTH was retrieved. The biochemical parameters, hormonal profile, localization studies, medical and surgical treatment, and outcomes were analyzed. Data are presented as median with inter-quartile range (IQR) and percentage.
Results
Out of 11 patients, men constituted 70%. The median age of presentation was 28 years (IQR-26-43). Clinically all patients had cushingoid features and hyperpigmentation, hypokalaemia(63. 6%), hypertension(63. 6%), diabetes(72. 7%), fractures(9%), low bone mass(54. 5%) of patients. The median values of endocrine investigations are mentioned in Table 1. Localization study- Inferior petrosal sinus sampling median ratio of central to periphery was 0. 96 (IQR-0. 85-1. 08). Computed tomography and DOTANOC scan had localized lesions to right lung (54. 5%) and left lung(45. 5%). Ketoconazole usage prior to surgery in 54.

Table 1: Endocrine Investigations

Patient No	8am cortisol (nmol/l)	11pm cortisol (nmol/l)	ACTH (pmol/l)	LNSC (nmol/l)	Urinary free cortisol (mg/dl)	ONDST (nmol/l)	LDDST (nmol/l)	HDDST (nmol/l)
1	892	-	147.5	-	1234	512	-	720
2	618	1043	96.7	-	2475	618	789	894
3	817	-	40	-	120	516	555	-
4	704	941	20.7	-	2012	701	-	107
5	1173	1007	54.4	-	1554	-	927	773
6	748	693	29	52.8	-	621	-	528
7	1073	880	27.9	70	-	512	588	249
8	1288	1202	43	106	-		1161	562
9	938	578	40	64	-	657	524	755
10	826	719	196.4	54	-	985	886	952
Median	886	880	40	59	1554	619.5	688.5	641
IQR 1	748	706	27.9	45.85	677	513	531.75	292.5
IQR 3	1073	1025	96.7	79	2243.5	690	916.75	803.25

5%. Surgical excision through thoracotomy in all patients. Re-surgery was required in 27. 3%. Bilateral adrenalectomy was done in 18. 2%. Remission achieved in 81. 8% in a median duration of 28 months(IQR 3-75)(1 is lost to follow-up). No patient received antitumor treatment.
Conclusion
Ectopic cushing's syndrome is an uncommon clinical syndrome that is associated with significant morbidity and mortality. Antitumor treatment and control of hypercortisolism is equally important and therefore a multi-disciplinary approach.

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P483

JOINT2573

Medullary thyroid carcinoma and c-cell hyperplasia in patients affected with neurofibromatosis type 1

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Background
Neurofibromatosis type 1 (NF1) is an autosomal dominant cancer predisposition syndrome caused by NF1 gene mutations. Although medullary thyroid carcinoma (MTC) is not typically associated with NF1, several case reports suggest a higher prevalence of C-cell disease in this syndrome. On the other hand, somatic NF1 mutations may drive MTC in some rare cases, when mutations in RET or RAS are not present.
Methods
Clinical data from 421 adult NF1 patients, being followed up at the Medical Genetics and Endocrinology Units at our Institution, were retrospectively retrieved, selecting only those who underwent at least one Ctn measurement. Patients with confirmed elevated Ctn values ($\geq$ 10 pg/mL) were referred for thyroid surgery, either immediately or after a positive calcium stimulation test (Ctn peak above the threshold for MTC or C-cell hyperplasia, CCH). Somatic nucleic acids were extracted from 5 formalin-fixed paraffin-embedded thyroid tissue samples, with histologically proven C-cell disease, for molecular characterization by Next Generation Sequencing (NGS).
Results
The study included 384 NF1 patients, with 332/384 testing negative after Ctn screening and 52/384 (13. 5%) with hypercalcitoninemia (median Ctn 14. 1, IQR 12. 1–18. 4 pg/mL). No statistically significant differences were found between the two groups except for male sex (P = 0. 002). After repeating Ctn measurement, 20/52 patients showed persistently elevated levels and two of them were directly referred for thyroid surgery. Nine out of 20 patients were placed under active surveillance, with mean Ctn levels not significantly changing over a median period of 32. 1 months (IQR 21–37). Calcium stimulation test was performed in 9 patients with hypercalcitoninemia, excluding C-cell disease in 2 cases but resulting positive in 7 of them. Overall, 14 NF1 patients (3. 6%) underwent thyroid surgery, with 50% of cases having a suspicious C-cell disease. Among the latter, MTC was found in 2 patients, nodular CCH in 4 (coexisting with follicular thyroid adenoma in 1 case) and thyroid follicular nodular disease in the other one. The NGS analysis identified at least one acquired somatic mutation in the NF1 gene in both cases of MTC and in 3 available cases of CCH, whereas no pathogenic mutation involving RET or RAS was found.
Conclusions
Hypercalcitoninemia is a relatively common finding in patients with NF1 and underlies a possible higher combined prevalence of MTC/CCH (1. 6%) than the general population. The molecular basis of this association is most likely to be found in NF1 gene loss of heterozygosity in thyroid C-cells.

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P484

JOINT2766

Thyroid and pituitary dysfunction after total body irradiation as conditioning therapy of haematopoietic stem cell transplantation during childhood

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Introduction
The endocrine system is commonly affected by chemotherapy and irradiation prior to allogeneic haematopoietic stem cell transplantation (HSCT) during childhood. Our aim was to analyse the incidence of thyroid and pituitary dysfunctions in paediatric survivors of HSCT, following total body irradiation (TBI) as conditioning therapy.
Objective
We analysed thyroid and pituitary dysfunctions in a cohort of paediatric patients who underwent TBI prior to HSCT.
Material and methods
This retrospective study included paediatric patients who underwent HSCT and received TBI, with a minimum follow-up of 24 months, followed-up at our endocrine late-effects clinic. We excluded patients who received cervical radiotherapy from the thyroid analysis and those who received central nervous system radiotherapy from the pituitary analysis. Statistical analysis was performed with IBM SPSS.
Results
We analysed data from 161 paediatric survivors who underwent HSCT and included 31 patients who received TBI as part of their conditioning therapy. The mean age of HSCT was 11. 0$\pm$5. 0 years and 51. 6%(n = 16) patients were male. The most prevalent haematological disease was acute lymphoblastic leukaemia (ALL), accounting for 48. 4% (n = 15) of cases. The median dose of TBI therapy was 10. 8 Gy (IQR 5. 7). The incidence of thyroid dysfunction in this cohort was 61. 3% (n = 19). The mean follow-up time was 21 $\pm$ 7 years. During follow-up, 12 (38. 7%) patients developed hypothyroidism, with a median time to diagnosis of 14 years (IQR 22) after TBI. Thyroid antibodies were negative in all patients tested (n = 31). Thyroid nodules were diagnosed in 21 (67. 7%) patients, with an average time after TBI of 16 years (IQR 7). The cumulative incidence of thyroid nodules increased over time, being 16%, 35%, and 52% after 10, 15, and 20 years, respectively. Papillary thyroid carcinoma was diagnosed in 7 (22, 6%) patients, with a median age at diagnosis of 26. 5 years (IQR 7). The median time to malignancy diagnosis was 21 years (IQR 13) post-TBI. One patient presented with both papillary and follicular carcinoma. We didn't observe any pituitary dysfunction following TBI, including any puberty disorders.
Conclusion
These findings underlight the importance of long-term thyroid monitoring in paediatric HSCT survivors submitted to TBI. The majority of these patients were diagnosed with thyroid nodules, and its incidence increased throughout their follow-up. The low dose of radiation may explain the absence of pituitary disorders in these patients.

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P485

JOINT444

Pediatric papillary thyroid carcinoma as the first manifestation of undiagnosed hereditary tumor predisposition syndrome?

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Background
In children, papillary thyroid cancer (PTC) is generally sporadic and, rarely, part of an unrecognized hereditary tumor predisposition syndrome (HTPS). The aim of our study was to report cases of PTC as the first manifestation of HTPS and to characterize the histologic variant, age at diagnosis, recurrence risk according to the American Thyroid Association (ATA 2015), and response to treatment.

Material and Methods
A retrospective, descriptive study was conducted in 88 pediatric patients who underwent total thyroidectomy for PTC. Seven patients with HTPS were identified. The diagnosis was made as follows: 5/63 by next generation sequencing (NGS) panel with PTC-related genes and fusions while in 2/25 patients the molecular study was requested based on clinical suspicion. Patients who were found to have HTPS before PTC diagnosis were excluded. The patients were classified according to the histological criteria, ATA recurrence risk, and dynamic risk stratification at final follow-up.
Results
Seven patients with HTPS in whom the first manifestation was PTC were identified. Three had DICER1 syndrome, two Lynch syndrome, and two PTEN syndrome. Of two patients diagnosed based on clinical suspicion, one had a history of cystic adenomatous malformation in the lung and the other had macrocephaly and developmental delay. DICER1 and PTEN syndrome were confirmed, respectively. Three patients with DICER1 syndrome had follicular variant of PTC: a 6-year-old girl with ATA high risk, and a 14-year-old girl and a 15-year-old boy with ATA low risk. Lynch syndrome (*MSH6* mutation) was diagnosed in two sisters whose mother had a history of thyroid cancer. The index case was a 12-year-old girl with a follicular variant of PTC with ATA low risk. A thyroid ultrasound was requested for the 16-year-old sister due to family history, and PTC of the classic variant with ATA intermediate risk was diagnosed. Two unrelated girls with PTEN Syndrome, aged 12 and 15 years, had a classic variant of PTC with ATA low risk. All patients had excellent response to treatment at the final follow-up (+/- 2 years).
Conclusions
The NGS panel enabled the identification of HTPS in children in whom PTC was the only or initial manifestation of the syndrome. In addition, a comprehensive medical history along with a thorough physical examination is essential to suspect the presence of HTPS in a patient presenting with PTC. Our study patients with PTC associated with HTPS primarily had ATA low-risk and responded well to treatment.

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P486

JOINT1935

The importance of assessing IDO1 activity when targeting tryptophanyl-tRNA synthetase (WARS) inhibition in medullary thyroid carcinoma (MTC)

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Medullary Thyroid Carcinoma (MTC) is an aggressive cancer associated with immunosuppression mediated by indoleamine 2, 3-dioxygenase 1 (IDO1), which IFN-gamma induces. IDO1 converts tryptophan (TRP) into kynurenine (KYN), promoting an immunosuppressive microenvironment. IDO1-producing tumor cells ensure their survival during TRP depletion by producing WARS, which binds TRP to tRNA. This mechanism has been described in some tumors but not yet in MTC. Thus, WARS inhibition could exert a cytotoxic effect on tumor cells. We aimed to: (1) evaluate IDO1 and WARS expression in MTC cells; (2) verify if IDO1 expression is associated with IDO1 activity; (3) assess the effect of WARS inhibition on cell viability.
Methods
TT cells (C634W) were cultured and incubated with IFN-gamma (50ng/mL) for 24h. The relative quantification of *IDO1* and *WARS* expression was determined by qPCR with SYBR_Green, using *TBP* for normalization and ΔΔCt. IDO1 activity was assessed by measuring TRP and KYN levels in the supernatant (KYN/TRP ratio) using HPLC. For WARS inhibition, tryptamine was applied at varying concentrations (0. 0001-100mM) to evaluate cell toxicity (MTT). Linear regression and ANOVA were used.
Results
TT cells constitutively express *WARS* but not *IDO1*. Both genes were induced by IFN-gamma (10-fold increase in WARS; CQ of 24. 8 for *IDO1* vs. undetectable in Control). *IDO1* was positively correlated with *WARS* ($r = 0.898$, $P < 0.05$). Interestingly, the KYN/TRP ratio was not altered by IFN-gamma (ratio 1. 8±0. 1 vs. 1. 5±0. 2 in Control), indicating that enzyme activity did not increase despite mRNA expression. Tryptamine reduced cell viability (IC50=5. 8mM), independently of IFN-gamma (IC50=5. 8mM). In conclusion, IFN-gamma induces *IDO1* and *WARS*; however, this does not necessarily lead to increased IDO1 activity. The cytotoxic effect of WARS inhibition may be enhanced in cases where IDO1 activity is present. This study highlights the importance of confirming IDO1 activity beyond its expression when designing treatment strategies that combine IDO1 and WARS inhibitors for MTC.

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P487

JOINT1870

Lipodystrophy in children following hematopoietic stem cell transplantation: analysis of prevalence, risk factors and response to conventional treatments

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Background
Hematopoietic stem cell transplantation (HSCT) has emerged as a rare cause of acquired lipodystrophy (AL). This condition, characterized by abnormal fat distribution and metabolic diseases, remains poorly described in pediatric patients.
Aim
Primary aim is to explore the incidence of AL in a large cohort of children treated with HSCT. Secondary aims are to evaluate the clinical and metabolic parameters in children with AL following HSCT and to describe the response to conventional management with a long-term follow up.
Methods
Among a total of 583 children with HSCT referred in the last 2 years to the endocrinology department of our tertiary Pediatric Hospital during the routinely follow up, we identified 6 cases (1%) of AL. All patients were monitored at six-monthly clinical visits with metabolic and endocrinological assessments, including leptin levels, during a follow up of 8-15 years. Liver/thyroid ultrasound scans were performed annually.
Results
Our patient group consists of 2 males and 4 females, all of whom were diagnosed with leukemia in childhood. Patients 1, 2, and 4 were diagnosed within the first two years of life. Four of six patients underwent a total body irradiation (TBI) as pre-transplant conditioning and all of them had a history of cutaneous graft-vs-host-disease (GVHD). Patient 3 underwent two HSCT due to disease relapse. The children presented with various metabolic symptoms, including hyperinsulinism, increased fasting and two-hour post-load glucose levels with a variable progression to T2D, severe dyslipidemia, and hepatic steatosis/steatohepatitis. Leptin levels range from a very low value of 1. 16 (patient 1) to a slightly elevated value of 21. 16 ng/ml (patient 6), with a mean value of 11. 8±10. 1 ng/ml. The BMI ranged from -3, 08 to +1, 08 SDS with a mean of +0, 58 SDS. The mean time from HSCT to AL diagnosis was 9. 8 years and the mean age at diagnosis of AL was 15. 25 years (range 9. 7 - 28. 3 years). The conventional treatment with metformin, GLP1 analogues, omega 3 fatty acids and lifestyle interventions showed a poor response. Despite treatment with metformin, patient 3 developed Type2Diabetes (T2D) treated with GLP-1 analogues with a partial response.
Conclusions
AL is a rare and severe complication of HSCT in children, increasingly recognized in association with TBI and GVHD. Long-term follow-up of metabolic health is crucial for early identification and management. Further research is needed to elucidate the risk factors and suggest other therapeutic strategies, including the use of metreleptin to improve metabolic control.

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P488

JOINT2839

Unraveling the role of autophagy in adrenocortical carcinoma

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Adrenocortical carcinoma (ACC) represents the second most lethal endocrine malignancy. This poor prognosis is mainly related to the difficulty in establishing an early diagnosis and the limited efficacy of mitotane which is the only approved pharmacological treatment. Autophagy, a dynamic cellular process that degrades and/or recycle various cellular components, plays a dual role in tumorigenesis by contributing for both cell survival and death. However, its role in adrenocortical tumors (ACT) remains largely unexplored. Therefore, we aimed to assess the expression of LC3, a central autophagy regulatory protein, in ACT, to verify its potential for ACC diagnosis. Additionally, we investigated the role of autophagy in ACC treatment. For that, the expression of LC3 was evaluated by immunohistochemistry (IHC) in paraffin-embedded tissues of ACC ($n = 10$) and adrenocortical adenoma (ACA) ($n = 15$). The LC3 dot-like staining pattern was evaluated by counting LC3-positive cells in tumor hot-spots, with at least 1000 cells analyzed per ACT case. In addition, to explore the role of autophagy in ACC treatment, the ACC cell-line (JIL-2266) was treated with mitotane either alone or in combination with bafilomycin, a late-stage autophagic flux inhibitor. Cellular density and expression of LC3I/II and p62 were assessed by Trypan-Blue assay and Western-Blot, respectively. LC3 dot-like staining was observed in all ACC and in 87% of ACA (13/15). The percentage of LC3 positive cells was significantly higher in ACC compared to ACA (ACC vs ACA: 13% vs 2%, $P<0.001$). Indeed, LC3 protein appears to be an excellent marker to differentiate ACC from ACA, with an area under ROC of 0. 900. *In vitro*, studies showed that mitotane treatment reduced ACC cell density and increased LC3-II levels compared to the vehicle. Moreover, LC3-II expression was even higher when cells were co-treated with mitotane and bafilomycin, compared to mitotane treatment alone. Our results suggest that autophagy play an important role in ACT. Indeed, LC3 dot-like expression, which has been correlated with autophagy induction, was present in most ACT. Notably, LC3 positive cells appear to be associated with malignancy in ACT. Additionally, our findings indicate that mitotane treatment modulates autophagy by the induction of autophagosome synthesis. Future research will validate these results in a larger ACT patients' cohort, along with more detailed mechanistic studies.

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P489

JOINT1303

Urinary steroid profiling by GC-MS as a diagnostic tool for evaluating malignancy of adrenocortical tumors – profile fit for purpose?

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Background - Aim
Adrenocortical carcinomas (ACC) are rare but aggressive cancers, and the ability to differentiate between these and benign adrenocortical adenomas (ACA) is essential. Current diagnostic workup in Denmark relies on clinical assessment, functional tests, and imaging, with urinary steroid profiling as a supplementary analysis. However, no consensus exists in terms of which steroids are relevant to include in such a profile. Thus, the first aim of this study was to systematically evaluate the literature to decide on an evidently ideal steroid profile for discriminating between benign and malignant adrenocortical tumors. Secondly, the aim was to perform a retrospective study to evaluate the diagnostic value of the ideal profile.
Methods
Our systematic review was performed according to the Cochrane Collaboration guidelines. The retrospective study was done according to local hospital guidelines including relevant ethical approvals.
Results
Based on our selection criteria, our systematic review identified twelve relevant original studies. Since not all studies evaluated the same steroids or employed comparable experimental approaches, we developed a scoring system to score the apparent significance of individual steroids for inclusion in an ideal profile. With this approach, we identified seven steroids with reported high diagnostic value. Five of the seven identified steroids were already part of our routine GC/MS-generated steroid profile based on 24h urine sampling. To evaluate the diagnostic value of the proposedly ideal profile, we added the two remaining steroids to our current profile and did a retrospective study (Dec 2022 until Oct 2024) employing data from patient medical records combined with historical GC/MS data. Due to recent implementation of GC/MS, the amount of data was limited to two ACC and 41 ACA patients. Thus, we are currently planning a larger prospective study. However, both ACA cases would have been identified employing the ideal profile.
Conclusion
A systematic review revealed seven steroids with high diagnostic potential for ACC. The diagnostic potential of these metabolites was confirmed by a small retrospective study. The retrospective study further indicated that five steroid metabolites were of especially high diagnostic value, however a larger study population is needed in order to confirm these findings.

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P490

JOINT2685

Exploration of the genomic clinical correlations of follicular differentiated thyroid cancer through a 56 gene panel next generation sequencing study

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Background
Follicular differentiated thyroid cancer (FDTC) is the most common endocrine cancer, globally. Next-generation sequencing (NGS) in thyroid cancer allows for high-throughput genetic sequencing with quick turnover. NGS Studies on papillary thyroid cancer are scanty from South East Asia. This study harnesses the power of Whole Exome Next-Generation Sequencing (WES) to unravel pan-exomic mutations in thyroid cancer samples. The primary objectives include correlating genomic changes with clinicopathologic features and unraveling the intricate mechanisms steering disease onset and progression.
Methods
We selected 22 FDTC cases. All of them underwent total thyroidectomy with neck dissection as needed. Tumour tissue samples extracted and paraffin embedded, were taken from exvivo specimens. Sample processing, DNA extraction, cDNA preparation and PCR amplification was performed. Mutation analysis with a thyroid cellular pathway specific 56-gene mutation panel using real-time PCR and ThyroSeq v2 on the Ion Torrent PGM sequencer was employed. Common single nucleotide polymorphisms (SNPs) with a minor allele frequency of >0.05 were excluded. Mutations were also manually checked using the Integrated Genomics Viewer v2. 4. 10 to filter out false positives.
Results
The analysis found mutations commonly in BRAF (16), CDKN2A (10), NRAS (7), PI3KCA (8), RET (4), RAS (13) and TP53 (3) genes. The common mutations found in the samples was RET (M918T), NRAS (Q61R), BRAF (V600E) and missense mutation in TP53 (c. 217 – c. 1178). A mutation has also been identified in KMT2D gene in two of the patient samples. BRAF, CDKN2A, PI3KCA were more common in papillary cancer. RAS, NRAS, RET mutations were common in follicular cancer. TP53 and KMT2D were seen only in poorly differentiated cancer.

Conclusion
NGS appears to be helpful in risk assessement, prognostication and study of tumour biology in clinical setting. More prospective studies are needed for its routine use at clinical level.

Key Words: Thyroid cancer; BRAF gene; RAS gene; Genomics; Mutation
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P491

JOINT214

Clinical implications of measuring muscle mass by computed tomography in neuroendocrine tumor patients

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Introduction
Sarcopenia is characterized by loss of skeletal muscle mass and quality, numerous studies have reported an association between sarcopenia and poor outcomes in various malignancies. There is limited data regarding lean body mass status in patients with neuroendocrine tumors (NETs). Skeletal muscle mass index (SMI), measured by computed tomography (CT) scans, is considered a gold standard for determining body composition in diagnosing sarcopenia.
Aim
To measure the prevalence of sarcopenia in patients newly diagnosed with intestinal and pancreatic NETs, evaluate its association with patient characteristics, and explore its potential impact on overall survival.
Methods
This retrospective cohort study reviewed the medical records of 145 patients diagnosed with intestinal or pancreatic NETs at Tel Aviv Sourasky Medical Center (TLVMC) from 2005 to 2020. CT scans, taken near the diagnosis date, were analyzed for the presence of sarcopenia. Abdominal CT slices, which displayed the cross-sectional area of Lumbar vertebra 3 (L3), were analyzed using Coreslicer software based on established cutoffs for sarcopenia diagnosis. Statistical methods, including survival analysis and Cox regression, were used to assess the adjusted risk factors of sarcopenia prevalence on overall survival.
Outcomes
Sarcopenia was identified in 41% of the cohort, with a significant association between sarcopenia and older age ($P = 0.013$). Sarcopenic patients also exhibited a higher prevalence of cardiovascular disease (19% vs. 5.8%, $P = 0.014$) and lower median body mass index (BMI: 25.3 vs. 27.5 kg/m^2, $P = 0.002$). Despite these associations, sarcopenia did not emerge as a significant predictor of overall survival. Weight loss was present in 17% of patients (median weight loss of 10.5 kg, IQR 6-17 kg), with 60% of those experiencing weight loss also diagnosed with sarcopenia. Additionally, the moderate correlation between BMI and skeletal muscle index ($R^2 = 0.44$, $P < 0.001$) highlights the limitations of BMI in reflecting muscle depletion in this cohort. These findings emphasize the need for muscle mass evaluation independent of BMI.
Conclusions
Sarcopenia is a prevalent and age-associated condition in NET patients, often coexisting with normal or elevated BMI. Its detection is crucial for early nutritional intervention, though it may not independently predict survival in heterogeneous NET populations. These findings underscore the importance of standardized sarcopenia assessment at diagnosis and encourage further research into its prognostic value in homogeneous NET subgroups.

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P492

JOINT1517

Selective early genetic screening for targetable gene fusions in papillary thyroid cancer (PTC) tissues

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PTC is characterized by a relatively low frequency of somatic mutations compared to other carcinomas, with BRAF-mutant tumors being the most common. Gene fusions are present in 15% of PTCs. PTC is associated with a very good prognosis, there are infrequent cases of recurrent or metastatic disease that require systemic therapy targeted to tumor's genomic characteristics. Given the risk of DNA degradation, genetic testing of paraffin-embedded tissue should ideally be performed as early as possible. High costs of these procedures make universal testing unfeasible. Patients who may benefit from genetic characterization of their tumor need to be preselected early, long before the tyrosine kinase inhibitors (TKI) therapy may be required. This is the preliminary study on selective genetic screening for targetable somatic mutations in PTC patients.
Material and Methods
Since mid-2022, we have performed next-generation sequencing (NGS) of tumor tissues from PTC patients with extensive nodal involvement, distant metastases, early recurrence, or requiring repeated surgeries. 40 such patients (15 M, 25 F, median age 45) were included. In each case, NGS was conducted to detect pathogenic variants of *AKT1, ALK, BRAF, CTNNB1, DDR2, EGFR, ERBB2, FGFR1, GNAS, HRAS, IDH1, IDH2, KRAS, MAP2K1, MET, NRAS, PIK3CA, RET, ROS1* and fusions of *ALK, AXL, BRAF, CCND1, EGFR, FGFR1, FGFR2, FGFR3, MET, NRG1, NTRK1, NTRK2, NTRK3, PPARG, RAF1, RET, ROS1, THADA*. The analysed variables included age, tumor characteristics (TNM, extranodal extension), categorised lymph node metastases size, repeated surgery, and remission status at latest follow-up. Statistical analyses were performed using the Mann-Whitney U test for continuous variables, and Chi-square or Fisher's exact tests for categorical variables.
Results
Among the 40 patients, 11 (27.5%) were identified with gene fusions [*CCDC6(1)-RET(12), NCOA(4)-RET(12), CCDC6(1)-RET(12), CCDC6(1)-RET(12), ETV6(4)-NTRK3(14), ERC1(17)-RET(12), TMEM9(5)-BRAF(9), NCO4(7)-RET(12), NCOA4(6)-RET(12), SQSTM1(5)-NTRK1(10)*] (2 M, 9 F; median age 35). In the no-fusion group (13 M, 16 F, median age 47), BRAF V600E was found in 22 patients, in 6 cases no pathogenic variants were detected, one sample was degraded. The fusion-positive group was significantly younger ($P = 0.007$). Lymph node metastases larger than 10 mm were more common in fusion-positive subjects ($P = 0.009$). No other significant differences in clinical course of PTC were observed.
Conclusions
Younger PTC patients with massive lymph node involvement, especially larger nodes, should be prioritized when considering the genetic screening of tumor tissues. Early genetic testing in these patients may identify actionable mutations or fusions, enabling timely targeted therapies.

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P493

JOINT338

Identifying the burden of hypothalamic syndrome in paediatric patients with craniopharyngioma in a single specialised centre cohort

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Background
Craniopharyngiomas are benign suprasellar tumours, approximately 4% of childhood brain tumours. Despite their WHO grade I classification, craniopharyngiomas have a high burden of morbidity due to their location and treatment-related sequelae, including Hypothalamic Syndrome (HS). HS is a rare but significant disorder, caused by tumour and/or treatment related injury to the hypothalamus, consisting of hypo/hyperphagia, hypothalamic obesity, pituitary dysfunction, sleep disturbance, behavioural changes and temperature disturbance, causing morbidity and reduced quality of life. This single specialised centre cohort study evaluates the burden of hypothalamic syndrome in paediatric patients with craniopharyngioma.

Method
A case notes review was undertaken for those diagnosed with craniopharyngioma <16 years old identified on the cancer registry at a single regional centre from 1/1/2014 to 1/1/2024. A data proforma was created after discussion with the multi-disciplinary team.
Results
19 patients were identified, median age at diagnosis 8 years (IQR 5-10 years), males: 10/19, 52. 6%, females 9/19, 47. 4%. All patients underwent neurosurgery, 7 recieved proton radiotherapy and 5 recieved photon radiotherapy. Patients were followed up for a median time of 6 years 3 months (range 1. 5-10. 3 years). All patients had at least 2 hormone deficiencies (growth hormone and adrenocorticotropic hormone deficiencies). 15/19 had four or more hormone deficiencies. 57. 9% of patients with craniopharyngioma had ≥3 symptoms of hypothalamic dysfunction. All patients were asked about appetite and hunger, and 8 patients reported hyperphagia, and 2 patients reported hypophagia. Of those with hyperphagia, half ($n = 4$) were diagnosed with hypothalamic obesity. Thirteen patients (68. 4%) reported sleep issues mainly difficulty falling asleep and snoring. Temperature dysregulation was only documented as having been discussed in two patients, one who reported feeling cold. Behavioural issues were documented as having been discussed in 17 patients (89. 5%), with 8 patients having behavioural issues, manifesting as anxiety in three patients. Mortality in this patient group was 0% at the time of this service evaluation. There was a significant burden of HS in this group, with the median number of features of hypothalamic syndrome 3, ranging from 1-5 symptoms of hypothalamic syndrome out of a total possible six features of HS.
Conclusion
Patients with craniopharyngioma are at very high risk of hypothalamic syndrome, necessitating close multidisciplinary team follow-up with specific questions about HS. This service evaluation identified areas requiring improvement in diagnosis and monitoring, including temperature dysregulation and behaviour. Implementation of a standardised hypothalamic syndrome checklist could improve recognition and monitoring of these challenging late effects.

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P494

JOINT1705

Multiple endocrine neoplasia 2B in two siblings with short stature, an uncommon association

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Introduction
Multiple endocrine neoplasia (MEN) is an autosomal dominant syndrome produced by mutations of the RET proto-oncogene and is characterized by a predisposition to the development of endocrine tumors. Subtype 2B (MEN 2B) is associated with the presence of medullary thyroid carcinoma (100%), pheochromocytoma (50%), mucosal neuromas, gastrointestinal symptoms, ocular alterations, marfanoid habitus, and tall stature.
Patients
Index case: Male, 3 years of age, referred for short stature. History of chronic constipation. Weight 15. 4 kg (pc 50-75), height 89. 5 cm (-2. 05 SD). Physical examination revealed everted upper eyelids, prominent lips, mucosal neuromas on the tongue, flat nose, large rotated ears, relative macrocephaly and body disproportion. Initial routine studies showed growth factors, thyroid profile, karyotype and growth hormone stimulation test, within normal limits. His 1-year-old sister was also referred for short stature (-3. 08 SD). Clinical examination showed prominent lips. Their mother had prominent lips too, and mucosal neuromas on the tongue. With clinical suspicion of MEN2B, calcitonin, thyroid ultrasound and RET gene study were requested. Total thyroidectomy was performed on the index case his sister and his mother without complications. Pathology reports medullary thyroid carcinoma in the three cases. The mother begins follow-up at an adult center.
Conclusions
Although one of the features that characterizes MEN2B is tall stature, cases of pediatric patients with short stature have been reported in the literature. Tha cause is still unknown. For this reason, it is important to keep it in mind in the presence of clinical stigmata as a differential diagnosis, since early prophylactic thyroidectomy (before one year of age) substantially modifies the prognosis of the disease.

	Calcitonine	Thyroid ultrasound	RET molecular study
Index case	9.47 pg/ml (RV: <11)	Solid nodular image 4×2×2 mm with microcalcifications	
Sister	37.2 pg/ml (RV: <11)	Normal	Phatogenic Variation Met918Thr Exon16 RET
Mother	593 pg/ml (RV: <5)	multinodular goiter with adenomegaly in the central compartment	

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P495

JOINT3308

Serum and cerebrospinal fluid hCG leves in children with beta hCG producing germ cell tumors

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Objective
A retrospective study was performed in children with beta-hCG-producing germ cell tumors (GCTs) under 18 years of age to evalute the levels of serum as well as cerabral spinal fluid(CSF) hCG.
Methods
From 2000 to 2023, 988 GCTs under 18 yeas of age were diagnosed in our hospital, in whom 60 children were beta-hCG-producing GCTs and were enrolled in our study. Serum hCG levels and hCG levels in cerabral spinal fluid(CSF) hCG were collected and comparaed between intracrinial and extracranial pateints.
Results
In 60 children, 53 males (88. 3%) and 7 females (11. 7%). The median age at presentation was 8. 7 years (range: 3. 2–14. 8 years). 49 were intracranial GCTs, while 11 were extracranial. All of the children with intracranial GCTs had increased levels of hCG in CSF, and CSF hCG levels had positive correlationship with serum hCG levels ($R=0.81$, $P<0.01$), however, 14 cases (32. 6%) exhibited CSF hCG levels lower than serum hCG levels at the same time. In children with extracranial GCTs, no one had increased hCG levels in CSF (<3 mIU/mL). No statistically significant differences of serum hCG levels were found between genders ($P=0.90$) or between intracranial and extracranial groups ($P=0.90$). Both serum and CSF hCG levels be found fluctuated during the course before treatment, occasionally dropping below the normal range (3 mIU/mL). 21 patients complished pathological diagnosis, in whom 10 were germinoma, 11 were non germinoma GCTs(NGGCTs). In 10 pathological diagnosed germinoma, 5 had serun and/or CSF hCG excreed 50mIU/mL, while in 11 NGGCTs only 6 had hCG levels more than 50mIU/mL.
Conclusion
hCG-secreting GCTs are more prevalent in males in children. Serum and CSF hCG level are valuable for diagnosis and localization of the tumors. Elevated CSF hCG levels reveal intracranial GCTs, however, CSF hCG levels lower than serum hCG can not rule out CNS lesions. Serum/CSF hCG levels are not always consistent with pathological diagnosis of HCG secreting GCTs in children. Nevertheless, due to the fluctuations of hCG levels during the course, multiple sampling at different time points may be necessary, espacially when the test of hCG was negtive.
Key words
endocrine complications, germ cell tumors, tumor markers/human chorionic gonadotropin, children, adolescents

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P496

JOINT3392

Prevalence and morphology of pineal gland calcifications in children with cranial germ cell tumors are different from normal chidren aged 0-15 years

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Background and Objectives
Pineal gland calcification is rare in children under 3 years old and the prevalence increase with age. However, in children with pineal region germ cell tumors (GCT), pineal gland calcification is common and may has features that be different from physiological calcifications. Prevalence as well as the characteristics of pineal gland calcification by head CT images in children with pineal region GCTs were studied and were compared with normal children aged 0-15 years.
Methods
During the period 2015-2023, 2749 normal children and 32 children with pineal region GCTs, who had head CT images and aged 0-15 years were enrolled and were analysed.
Results
In normal children, the incidence of pineal gland calcification was 10. 8%. The prevalence was 1. 1% in children aged 6 years and below, while 23. 2% in children aged 7-15 years ($P < 0.001$), and was 6. 2% in boys and 13% in girls respectively ($P < 0.001$). In children with pineal region GCTs, 96. 7% found pineal calcifications, more than normal children ($P < 0.001$). Pineal calcifications in GCTs had former significantly lower than that in normal children, and had special morphological features. The majority of pineal gland calcification in normal children was patchy (72. 7%), while in children with pineal region GCTs, the calcification morphology was mainly punctate + patchy (58. 6%) ($P < 0.001$), and all of the latter's calcification patterns were patchy or mixed.
Conclusion
In children aged 0-15 years, Physiologic pineal gland calcifications become increasingly prevalent with advancing age. Pineal gland calcification in children aged 6 and below is very rare, and attention should be paid to its pathological status. Compared with normal children, children with pineal region GCTs are more likely to develop pineal gland calcification, with a more diverse and extensive calcification morphology. When diagnosing intracranial germ cell tumors and brain MRI cannot accurately locate, cranial CT may provide key clues.
Keywords
Pineal Gland Calcification; CT; Physiological; GCTs
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P498

JOINT2682

Co-occurrence of burkitt lymphoma and follicular thyroid adenoma in a pediatric patient: a rare case report

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Background
Follicular thyroid adenomas, though benign, are rare in pediatric populations and may pose diagnostic and therapeutic challenges due to their potential overlap with malignancies. Burkitt lymphoma, a high-grade B-cell non-Hodgkin lymphoma, accounts for 30% of pediatric lymphomas and typically presents with rapidly enlarging lymph nodes or extranodal masses. The co-occurrence of these two distinct conditions in a pediatric patient is exceptionally rare and has not been previously reported, underscoring the need for careful evaluation and a multidisciplinary approach to management.
Clinical Case
We report the case of an 8-year-old male presenting with a one-year history of progressive cervical lymphadenopathy. Clinical examination revealed a 3. 5 cm firm, non-tender, poorly mobile submandibular lymph node conglomerate on the right side, along with smaller lymph nodes in the anterior cervical and submandibular regions bilaterally. The patient exhibited no systemic symptoms of infection or malignancy. Family history revealed malignancies on the maternal side, including intestinal, lung, and uterine cancers, raising concerns about genetic predispositions. Initial investigations, including ultrasonography and fine-needle aspiration biopsy (FNAB) of a thyroid nodule, suggested hyperplastic changes. Biochemical findings were significant for suppressed TSH: <0.01 mU/l (N 0. 4–3. 6) with elevated FT4: 25. 99 pmol/l (N 7. 87–20. 3), consistent with thyrotoxicosis. Despite antibiotic therapy, the lymphadenopathy persisted, prompting further imaging and evaluation. Subsequent histopathological analysis of a resected thyroid nodule and adjacent lymph nodes revealed the coexistence of Burkitt lymphoma and follicular thyroid adenoma, confirmed by immunohistochemical studies. The patient underwent hemityroidectomy and lymphadenectomy followed by chemotherapy for Burkitt lymphoma. Thyroid hormone replacement therapy was initiated postoperatively, and the patient remains under close endocrinological and oncological follow-up.
Discussion
This case underscores the importance of a multidisciplinary approach in managing pediatric thyroid nodules and lymphadenopathy, particularly when the presentation deviates from typical patterns. The coexistence of Burkitt lymphoma and follicular thyroid adenoma highlights the need for thorough diagnostic workup, including FNAB, imaging, and histopathological confirmation. Additionally, the potential link to familial cancer syndromes, such as *DICER1* mutation, warrants further investigation in this patient.
Conclusion
This rare case emphasizes the diagnostic and therapeutic challenges posed by concurrent thyroid and lymphoid pathology in children. Awareness of such presentations can aid in timely diagnosis and optimized care strategies.
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P499

JOINT3935

Overweight and obesity in survivors of pediatric brain tumor

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Introduction
Brain tumors are the most common solid tumor in children. These patients may have an increased risk of obesity due to the location of the tumor (hypothalamus) or by the oncological therapies.
Objectives
To characterize a population of brain tumor survivors in pediatric age using body mass index to assess risk factors of overweight/obesity.
Methods
Retrospective analysis of the medical records of patients diagnosed with a brain tumor in pediatric age, followed up in the Endocrinology Late-effects clinics of our center. The statistical analysis was performed using SPSS software.
Results
We obtained a sample of 181 patients, 103 (57%) of whom were male. The median age at the diagnosis of brain tumor was 5. 7 (0-17. 8) years. The most prevalent tumor types were astrocytomas (38. 7%) and medulloblastomas (24. 3%). The most common locations were the diencephalic sellar/suprasellar region (38. 9%) and the posterior fossa (36. 7%). Of the 181 patients, 74. 6% underwent surgery, 74% received chemotherapy and 53% received central nervous system radiation, with a median dose of 54Gy (17. 2-60). At least one endocrinopathy was present in 64. 6% of patients, with the most prevalent being GH deficiency (45. 3%), hypothyroidism (37%), and pubertal alterations (28. 2%). At the start of follow-up, 62. 9% of the patients were of normal weight/underweight, 13. 3% were overweight, and 23. 8% were obese. At last follow-up, 50. 2% were of normal weight/underweight, 27. 1% were overweight, and 22. 7% were obese. Regarding the patients who had already reached the adulthood in the last follow-up ($n = 101$), 19 (18. 81%) were obese – 14 (13. 86%) had class I obesity, 3 (2. 97%) had class II obesity, and 2 (1. 98%) had class III obesity. The median follow-up was 9 (0-29) years. The patients were divided into two groups (according to status in the last appointment): group A, with overweight/obesity, and group B, with normal weight/underweight. No statistically significant differences were identified between the groups regarding sex, age at diagnosis, and tumor location. Group A included significantly more patients who had undergone brain radiation ($P < 0.001$). This group also had a significantly higher number of patients with endocrinopathies ($P = 0.006$), with a notably greater number of patients having pubertal changes and hypothyroidism.
Conclusions
At the end of follow-up, 49. 8% of the patients had overweight or obesity. With this work we highlighted risk factors for weight gain in these patients. It's important to identify those at higher risk in order to adopt strategies of weight control in these patients.
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P500

JOINT3752

Treatment with GnRH analogues in paediatric and adolescent patients with cancer diagnosis undergoing chemotherapy

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Introduction
The use of GnRH analogues aims to protect ovarian function during chemotherapy. While its effectiveness remains controversial, it may help reduce the risk of premature ovarian failure. However, its long-term impact on spontaneous pregnancy rates is still uncertain.
Objective
To determine the ovarian function and follicular reserve in patients who received treatment with GnRH analogues (GnRHa) during chemotherapy.
Population and Methods
Patients with a history of oncological disease in the childhood-juvenile stage treated at the Professor Alejandro Posadas National Hospital were studied between 11/01/2020 and 10/31/2022 by determining AMH, antral follicle count and FSH levels. The participants were recruited during the follow-up of cancer treatment. Descriptive statistics were presented.
Results
Of 31 pubertal patients, 16 completed the analogue treatment, 9 did not complete the treatment, and 6 did not receive it. The median age at the start of oncological treatment was 13. 1 years (8. 1–17. 6), at the end 14. 9 years (10. 2–20. 3) and at evaluation 23. 1 years (14. 8–31. 9). The median follow-up period was 8. 4 years (5–20. 3). The diagnosis was: 15 ALL; 4 AML; 7 Hodgkin's Lymphoma; 3 Non-Hodgkin's Lymphoma; 2 Ovarian Dysgerminoma. 7 patients had FSH values $\geq$25 mIU/mL (3 completed GnRHa treatment, 2 had incomplete treatment, and 2 did not receive it). 3 evidenced ALL (20%); 3 AML (75%); 1 Hodgkin's Lymphoma (14. 3%). 10 patients had AMH values $<$1 ng/ml (3 completed GnRHa treatment, 3 incomplete treatment and 4 did not receive it). 4 evidenced ALL (26. 7%); 4 AML (100%); 1 Hodgkin lymphoma (14. 3%); 1 ovarian dysgerminoma (50%). AMH levels $<$1 ng/mL and/or FSH $\geq$25 mIU/mL were observed in 3 of 13 with chemotherapy (QMT) alone, 1 of 6 with QMT + radiotherapy (RT), 1 of 5 with QMT + surgery (CX), 1 with QMT + BMT (bone marrow transplant) + CX, and all 4 with QMT + RT + BMT The median AMH was 2. 1 ng/ml (0. 1-4. 8) for those with complete GnRHa treatment, 1. 9 ng/ml (0. 1-6. 5) for incomplete treatment, and 0. 7 ng/ml (0. 1-2. 5) for no treatment. The median FSH was 7. 7 mUI/ml (4. 9-200) with complete treatment, 28. 7 mUI/ml (5. 1-70) with incomplete treatment, and 14. 0 mUI/ml (7. 7-123. 3) without treatment.
Conclusion
There does not seem to be any differences in ovarian function or follicular reserve in these cases; however, Conclusions should be drawn based on a sufficient sample size. The impact on fertility would be closely related to the therapy received.

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P501

JOINT2331

Genomic view of poorly diffentiated thyroid cancer as a bridge between well differentiated and anaplastic thyroid cancer

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Introduction
Poorly differentiated thyroid cancer (PDC) is a relatively infrequent form of differentiated thyroid cancer with intermediate prognosis between well differentiated (WDTC) and anaplastic cancers (ATC). But, this finding is debatable in literature. Genomics is the one of definitive modalities to clarify this moot point. ATC tends to express P53 and KMT2D mutations frequently, while WDTC have no such mutations. Similar Indian studies are scanty in PDC. In this context, we set out study the prevalence of these somatic mutations in surgical tissue samples of PDC.
Material and Methods
This prospective study was conducted on surgically managed thyroid cancer patients. Institutional ethical committee approval was obtained. Diagnosis was based on biochemical confirmation, imaging, fine needle aspiration cytology and later confirmed by histopathology. We selected 15 PDC, 4 ATC and 40 WDTC cases. Tumour tissue samples were taken from ex-vivo thyroidectomy specimen within operation theatre. After appropriate processing of samples, DNA extraction, cDNA preparation, PCR amplification, application of 2 sets of Primers were performed as part of mutational analysis of P53 and KMT2D genes.
Results
Heterozygous mutations in KMT2D gene and missense mutation in P53 gene were found in 4/15 (26. 6 %) and 7/15 (45%) of PDC cases respectively. In ATC, KMT2D mutations were seen in 3/4 (75%) and 4/4 (100%) cases. None of these gene mutations were seen WDTC cases.
Conclusions
Our study shows a distinct correlational pattern of mutations in KMT2D and P53 genes suggesting a causative linkage between the gene function and cancer cell differentiation. Further, PDC appears to be intermediate in mutation frequency, with ATC on higher side of scale. Though our results are not robust, it provides a platform for larger multi-institutional studies to justify this observation in future.
Key words
Thyroid cancer; Poorly differentiated cancer; Anaplasia; Follicular cell)

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P502

JOINT1930

Menin expression in parathyroid tumors of patients with multiple endocrine neoplasia type 1 phenocopies

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Introduction
Patients with two or more tumors associated with multiple endocrine neoplasia type 1 (MEN1) harboring no *MEN1* mutations are designated as MEN1 phenocopies (phMEN1); most of them have a combination of pituitary adenomas and primary hyperparathyroidism (PHPT).
Aim
To evaluate menin expression in parathyroid tumors of patients with phMEN1 in comparison with parathyroid tumors of genetically confirmed MEN1 (gMEN1) and sporadic PHPT (sPHPT).
Material and methods
Immunohistochemical staining for menin (Abcam, ab2605, UK) was performed on FFPE parathyroid tumor samples from eight patients with phMEN1 (6–PHPT+ acromegaly, 1 – PHPT + Cushing's disease, 1 – PHPT + prolactinoma), nine patients with gMEN1 and 10 patients with sPHPT. Menin expression was evaluated as either nuclear or cytoplasmic or both (positive or negative, positive expression was scored as absent, weak, intermediate or strong).
Results
phMEN1 group included 2 males, 6 females (2 atypical parathyroid adenomas in males and parathyroid adenomas in all females). gMEN1 group included 2 males, 7 females (8 – parathyroid adenomas, 1 - hyperplasia). sPHPT included 2 males, 8 females, all had parathyroid adenomas. Groups did not differ in sex, calcium and parathyroid hormone levels. phMEN1 patients were older than gMEN1 (P = 0, 000056). Nuclear menin expression was positive in 6 phMEN1 (2 – weak, 3 – intermediate, 1 - strong), 0 gMEN1, 6 sPHPT (2 – intermediate, 4 - strong). Cytoplasmic menin expression was positive in 4 phMEN1 (1 – weak, 3 - intermediate), 1 gMEN1 (weak), 7 sPHPT (4 – weak, 3 - intermediate). phMEN1 and gMEN1 groups, and sPHPT and gMEN1 groups differed in nuclear menin expression (p=0, 0085 and p=0, 0050 respectively). gMEN1 and sPHPT groups differed in cytoplasmic menin expression (p=0, 0094). phMEN1 and gMEN1 groups, and sPHPT and gMEN1 groups differed in nuclear and/or cytoplasmic menin expression (p=0, 045 and p=0, 0094 respectively). Despite no statistically significant difference of menin expression between phMEN1 and sPHPT groups, it was noteworthy that menin expression was stronger in sPHPT and was weaker in phMEN1.

Conclusion
Menin expression is preserved in parathyroid tumors of phMEN1 in comparison with gMEN1, though it seems to be attenuated compared to sporadic parathyroid tumors. This may indicate that different mechanisms are involved in parathyroid tumorigenesis in phMEN1.

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P503

JOINT3947

Targeted management of recurrent paraganglioma with SDH-B mutation: a case report

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Paragangliomas are rare neuroendocrine tumors that can arise in various locations throughout the body. While typically benign, these tumors can exhibit aggressive behavior and malignant potential, particularly when associated with genetic mutations. They can secrete catecholamines, leading to a range of adrenergic symptoms which further complicates their diagnosis and management. One of the most clinically significant mutations linked to hereditary paragangliomas involves the succinate dehydrogenase subunit B (SDH-B) gene. Patients with these mutations are at higher risk for malignancy and tumor recurrence, presenting unique challenges. We report the case of a 41-year-old patient with an abdominal paraganglioma harboring an SDH-B mutation, initially treated in January 2022 with both biochemical and imaging evidence indicating complete response. In August 2024, the patient presented with adrenergic symptoms and biochemical evidence of recurrence and was started on phenoxybenzamine. A thoracoabdominal-pelvic CT scan showed no signs of disease, but a subsequent gallium PET scan revealed a focal area of intense abnormal uptake in the posterior region of the left acetabulum, suggestive of metastatic paraganglioma. The case was discussed in a multidisciplinary team meeting, with the option for a targeted approach, based on the most recent clinical guidelines. Surgical intervention by the orthopedic team was deemed unfeasible due to the difficulty in accurately locating the lesion intraoperatively, and the only remaining surgical option- a total hip replacement—was associated with significant morbidity. Similarly, image-guided intervention was ruled out due to the risk of sciatic nerve injury. Subsequently the case was referred to radiation oncology, where **stereotaxic radiotherapy** was selected as the preferred treatment modality. This case highlights the elevated risk of recurrence in patients with SDH-B mutations and underscores the complexities involved in managing them, particularly due to the size, location, and metastatic potential of the lesions. A multidisciplinary approach is critical, as decision-making often requires input from various specialties to determine the most appropriate treatment plan. In patients with solitary metastases and low tumor burden, local control is typically the first-line option. Furthermore, this case emphasizes the importance of considering stereotaxic radiotherapy in the treatment of paragangliomas, a modality that may be underutilized.

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P504

JOINT984

Thyroid core-needle biopsy. the first 569 results in Romania

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Background
There are two types of thyroid nodule biopsy: fine-needle aspiration (FNAB) and core-needle (CNB). Multiple studies mainly from Eastern Asia demonstrate safety and efficacy of CNB, however it is very rarely used in Europe.
Methods
Retrospective analysis of the first 569 thyroid nodule CNBs performed in Romania. All CNBs were performed using 18G semi-automatic biopsy instruments. We used the Korean Thyroid Association reporting system (KTA-CNB) for histology reports.
Results
Of 569 CNBs, there were only 5 non-diagnostic results (0. 9%), 34 category III results (6%) and 63 category IV results (11%). Among nodules which previously underwent FNAB, CNB offered a conclusive result (either benign or malignant, KTA II, V and VI categories) in 80% of Bethesda 1, 80% of Bethesda 3, 68. 4% of Bethesda 4 nodules. There were no non-diagnostic results in these nodules. We performed on average 2. 2 passes per lesion. There were no major complications (none of complications required hospitalisation), some minor adverse events were limited to bruising, perithyroidal hematoma and pain during or after procedure. Four patients had intrathyroidal hematoma, three patients developed transitory hoarseness which resolved spontaneously in 20-90 minutes.
Conclusion
The CNB is a safe and reliable diagnostic procedure for thyroid nodules. It offers very low chance of non-diagnostic results, lower chance of inconclusive results with a better stratification of risk between different subcategories (III a-d, IV a-c). CNB is a procedure which improves patient experience by reducing the number of procedures needed to make a clinical decision. It is a useful and cost-efficient tool, especially in the absence of molecular testing. CNB offers additional advantage of immunohistochemistry in cases suspected for medullary thyroid cancer, lymphoma or metastatic lesions.

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P505

JOINT1904

Periprostatic adipose tissue (PPATs) adipokine profile highlights lipocalin-2 as a potential key player in the pathophysiological association between PPAT, obesity and prostate cancer microenvironment

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Prostate cancer (PCa) is a hormone-dependent tumor and one of the most prevalent cancers in men worldwide. PCa progression is influenced by its interaction with the surrounding tumor-microenvironment, highlighting the role of periprostatic adipose tissue (PPAT), which is a mediator of PCa microenvironmental regulation through the secretion of bioactive molecules (e. g., adipokines). Yet, the nature/influence of this complex secretion derived from PPATs remains to be fully elucidated. Herein, we investigated the potential dysregulation of the expression and secretion profile of PPAT adipokines in PCa patients. Specifically, by integrating transcriptomic (on PPATs) as well as proteomic and metabolomic (in PPAT-secretome) approaches on a well-characterized cohort of PPAT-samples [75 PCa-patients vs 22 benign-prostate-hyperplasia (BPH) control-subjects], we identified a significant signature of dysregulated adipokines in PCa patients. Subsequent unsupervised clustering analyses allowed the identification of two distinct molecular phenotypes of PCa patients with a unique fingerprint of alterations in adipokines (T1 and T2) that presented distinctive clinical-metabolic alterations (i. e., BMI, diabetes, and dyslipidemia), being lipocalin-2 (LCN2) the only adipokine showing consistent differences at transcriptomic- and proteomic-levels. Functional approaches in different prostate cell models [normal-like (PNT2) and PCa (DU145, LnCaP and 22Rv1)] revealed that exogenous LCN2 treatment did not alter proliferation, apoptosis, or colony formation in any of the prostate cell models, but migration was significantly increased in PNT2 and decreased in DU145, wherein a differential expression profile of LCN2 receptors (especially SLC22A17), may directly contribute to this differential effects observed across cell models. Molecularly, LCN2 treatment was associated with alteration in critical oncogenic/metabolic-pathways, including neutrophil-degranulation, inflammation, and autophagy, suggesting a connection with the inflammasomes. Further analyses revealed a weight-dependent association pattern between LCN2 and individual inflammasome components. Additionally, arachidonic acid (prostaglandin precursor) in PPAT-secretome positively correlated with LCN2 levels specifically in the obese PCa-patients, suggesting a metabolic link to LCN2-mediated effects. Our findings highlight LCN2 as a potential key player in the interaction between PPAT, obesity and PCa-microenvironment, with a potential influence on inflammation and tumor cell behavior.

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P506

JOINT1018

Clinical, hormonal, and neuroradiological characteristics and therapeutic outcomes of prolactinomas in children and adolescents at a single center

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Aim
Prolactinoma, a prolactin (PRL)-secreting pituitary tumor, is the most common functioning pituitary adenoma, comprising 40–60% of cases. However, it is rare in childhood and adolescence, accounting for less than 3% of childhood supratentorial tumors. This study evaluates the clinical characteristics, treatment responses, and outcomes of Korean adolescents with prolactinoma at a single center.
Method
This retrospective study included patients diagnosed with prolactinoma at Samsung Medical Center from March 2005 to August 2024. Clinical data, PRL levels, and MRI findings at diagnosis and after treatment with dopamine agonists were analyzed. Outcomes of medical and surgical management were also assessed to determine factors influencing treatment success.
Result
A total of 28 patients (22 female, 6 male) with a median age of 16. 9 years (range: 10. 1–18. 5) were included. Females commonly presented with galactorrhea (50. 0%) and amenorrhea (40. 9%), whereas males had visual deficits (50. 0%) and headaches (50. 0%). Microadenomas ($\leq$ 10 mm) were found in 12 patients, and macroadenomas ($>$ 10 mm) in 16. PRL levels were significantly higher in macroadenomas than in microadenomas (2, 197. 7 vs. 141. 4 ng/mL, $p < 0.001$). Panhypopituitarism occurred in 81. 3% of macroadenoma cases vs 8. 3% in microadenomas ($P = 0.008$). Surgery was performed in 86% of macroadenoma cases compared to 18% of microadenomas ($p < 0.001$). Male gender, PRL levels, and tumor diameter were positively correlated with tumor size. Among 20 patients treated with dopamine agonists, 10 responded positively. Transsphenoidal surgery (TSA) was performed in 18 cases, achieving PRL normalization in 12. Three patients required Gamma Knife Surgery due to resistance, intolerance, or recurrence after TSA.
Conclusion
Adolescent females with prolactinoma are more common, but males more often present with macroprolactinomas and mass effect symptoms. Macroprolactinomas frequently cause panhypopituitarism, necessitating early intervention. Gender differences in prognosis suggest a need for more aggressive treatment in males. Early detection, individualized therapy, and timely hormone replacement are crucial for optimizing long-term outcomes.
Keywords
Prolactinoma, Trannssphenoidal approach, macroprolactinoma
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P507

JOINT937

Severe hypercalcemia in an infant caused by PTHrP secretion from renal malignancy

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Background
Severe hypercalcemia is a rare but serious condition in infants and children. It can present with symptoms such as hypotonia, poor feeding, vomiting, constipation, abdominal pain, lethargy, polyuria, dehydration, and seizures. The causes of hypercalcemia are categorized based on parathyroid hormone (PTH) levels. PTH-dependent hypercalcemia is characterized by elevated PTH, while PTH-independent hypercalcemia results from factors such as excessive production of parathyroid hormone-related protein (PTHrP) or 1, 25-dihydroxyvitamin D. PTHrP is a protein similar to PTH and can be secreted by certain tumors, including renal cell carcinoma, pheochromocytoma, and benign congenital mesoblastic nephroma. Hypercalcemia associated with PTHrP is rare, particularly in infants.
Case Presentation
A 5-month-old female, born at term with a normal pregnancy and delivery, presented to the emergency room with restlessness, constipation, and poor appetite. Routine lab tests revealed hypercalcemia (19 mg/dL), elevated ionized calcium (2. 43 mmol/l), and hypophosphatemia (3. 5 mg/dL). Further endocrine evaluation showed undetectable PTH levels, 25-hydroxyvitamin D at 37 ng/mL (normal range: 30-100), and low 1, 25-dihydroxyvitamin D at 27 pg/mL (normal range: 32-196). Urinalysis showed hypercalciuria (calcium/creatinine ratio of 2938 mg/gr). PTHrP testing was pending.
Management
Initial treatment included intravenous fluids, furosemide, calcitonin, and bisphosphonates, which normalized the calcium levels. Given the severity of hypercalcemia, hypophosphatemia, hypoparathyroidism, and low 1, 25-dihydroxyvitamin D3, malignancy was suspected as a cause of PTHrP secretion. Abdominal ultrasound demonstrated a renal mass. A subsequent CT scan of the chest, abdomen, and pelvis revealed a 53x51x69 mm lesion in the upper pole of the left kidney, along with five possible metastatic sites in the right lung. Left nephrectomy was performed, and biopsies of the renal lesion and lung metastasis confirmed the diagnosis of rhabdoid tumor of the kidney. Chemotherapy was initiated.
Conclusion
Although constipation and restlessness are often benign and common in infants, they can sometimes signal more serious underlying conditions, such as hypercalcemia. This case emphasizes the need to consider hypercalcemia in differential diagnoses and presents a rare cause—rhabdoid tumor of the kidney—as an underlying etiology.
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P508

JOINT1949

Premature pubarche in 20 month old girl as a first sign of Li-Fraumeni syndrome – case report

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Introduction
Li-Fraumeni syndrome is a rare autosomal dominant disorder that predisposes carriers to numerous tumors, including adrenocortical carcinoma.
Case report
A 20-month-old girl was referred to our clinic because of obesity and premature pubarche. The symptoms started 4 months before examination. She was born at full term, birth weight 3550 gr (P 50-75th), birth length 52 cm (P50). First physical examination was as follows: height 93. 5cm ($P > 99$, $+3.54$ SD), weight 18. 7 kg, BMI 21. 4 kg/m2 (P99, $+3.39$ SD), telarche Tanner 1, pubarche Tanner 2, discreetly enlarged clitoris. Initial laboratory findings were in reference range. Karyotype was 46, XX while the bone maturity corresponded to age. Testosterone levels and DHEAS levels were high (2. 32ng/ml and 4176. 9 mg/dl, respectively), FSH 0. 4 IU/l, LH 0. 2 IU/l, cortisole 480 nmol/l, estradiol 20. 4 pmol/l, progesterone 9. 28 nmol/l. Abdominal ultrasound showed solid oval tumor in the upper pole of the right kidney. Abdominal MRI confirmed limited expansive tumor of the right suprarenal gland, measuring 46x46x62mm (AP, LL, KK). The abdominal mass was completely removed. Histopathology findings showed that the mass was in fact adrenocortical carcinoma (ACC): CS I, pTNM$>$ T2, Nx, Mx. Follow-up and treatment was carried out according to COG ARAR 0332 protocol, so the first follow-up was one month after surgical treatment. The hormone levels, abdominal ultrasound and chest x-ray were normal. As the tumor was under 100gr, with normal post-operative hormone levels it was stratified as stage one. Since the ACC is rare, the genetic analysis was carried out and showed germline mutation in the TP53 tumor suppressor gene, so the patient was diagnosed with Li-Fraumeni syndrome. After the diagnosis, the patient is being monitored in accordance with "Toronto protocol": the hormone levels are checked every 6 months, abdominal ultrasound 3 every months and whole body and brain MRI once a year. Two and a half years after diagnosis the patient remains cancer free.
Conclusion
Adrenocortical carcinoma (ACC) is a rare malignant tumor that can cause precocious puberty. First and second stages have a good prognosis, while the third and fourth stages have a poor prognosis. Furthermore it can be a sign of a Li-Fraumeni syndrome that demands close monitoring of the patients due to higher probability of other malignant tumors.
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P509

JOINT3933

Challenges in the diagnosis of patients with mild and moderate hypercalcitoninemia and nontoxic multinodular goiter

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Background
correct diagnosis and management of patients with multinodular goiter and basal calcitonin between 10 and 100 pg/mL is challenging.
Patients and Methods
4 patients (2 M/2W), aged 55-68 years, residents in an iodine-sufficient area, showing mild and moderate basal hypercalcitoninemia and multinodular goiter were presented. Basal serum calcitonin was measured by chemiluminescence. Calcitonin was also measured from the fine needle aspiration (FNA) washout fluid in suspicious thyroid nodules. A FNA cytology exam was performed in all patients according to guidelines and histology confirmed diagnosis in operated ones.
Results
All patients showed multinodular goiters, with nodules' maximum diameters ranging from 1. 1-2. 9 cm. Serum basal calcitoninemia ranged from 1. 22 to 8. 14 $\times$ ULN. CEA was normal in all patients but one. Calcitonin measured from the fine needle aspiration washout fluid (FNA-Ctn) was normal ($<$ 0. 5 – 0. 68 pg/mL) in all patients but one with increased value (25116 pg/mL). This patient had a large non-suspicious thyroid nodule (20/12. 3/13. 8 mm, EU-TIRADS 2) and a small suspicious nodule (6/5 mm, EU-TIRADS 4) in whom fine needle aspiration and measurement of FNA washout fluid was performed. Cytology exam and histology confirmed medullary microcarcinoma. RET assessment is pending In the other 3 patients with normal FNA-Ctn, cytology revealed Bethesda II cytology of the dominant nodule ($n = 2$) and papillary thyroid carcinoma -Bethesda V citology of the suspicious nodule ($n = 1$); the suspicious nodules were not accessible for FNA in 2 patients. Because a C cells hyperplasia could not be ruled out in these 3 patients, total thyroidectomy was performed. Pathology exam was medullary microcarcinoma in one patient, C cells hyperplasia in 2 patients, one of them also associating a papillary thyroid carcinoma. Postoperative serum calcitonin levels were normal in all patients.
Conclusion
in patients with mild and moderate hypercalcitoninemia, cytology exam and calcitonin measurement in the fine needle aspiration washout fluid, especially in highly suspicious nodules, irrespective of theirs dimensions, is a useful diagnosis tool.

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P510

JOINT2492

Redifferentiation treatment in radioiodine refractory metastatic papillary thyroid cancer

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Thyroid cancer is the most common endocrine cancer. Differentiated thyroid cancer (DTC), is by far the most common. DTC has an excellent prognosis, with a survival rate of more than 90% at 10 years. However, a minority of patients with DTC ($<$10%) develop distant metastases. The first-line treatment for metastatic thyroid disease is radioiodine. However, more than half of these lesions lose their avidity for radioiodine, becoming radio-refractory and in these cases survival decreases drastically. In the last decades much has been learned about the molecular pathways affected in DTC and their importance in the prognosis of these tumors. In particular, the BRAF mutation is highly frequent in DTC and seems be related to a worse prognosis of the disease. It also appears to be related to the risk of dedifferentiation of the lesions. In this context, drugs aimed at blocking these molecular points have been developed with the aim of inducing cell redifferentiation. The purpose of this study is to evaluate the efficacy of a redifferentiating treatment based on Dabrafenib and/or Trametinib during a short period of time in patients with BRAF or RAS mutated radioiodine refractory metastatic papillary thyroid cancer (PTC).
Methods
retrospective study including 13 patients under follow-up in the Endocrinology and Oncology Departments of the Hospital Universitario de Getafe diagnosed with radiorefractory metastatic PTC and BRAF or RAS mutation carriers, previously treated or not with systemic therapy. The selected patients receive redifferentiating treatment with Dabrafenib and/or Trametinib (depending on the mutation) for 6 weeks. Then, we perform a WBS with 5mCi of I31 and in case of increased I131 uptake, we scheduled an admission for administration of a therapeutic dose of I131 after stimulation with rTSH. Subsequently, redifferentiating treatment is suspended. The primary objective was to determine the increase in I131 uptake of the metastatic lesions after the redifferentiation process and to determine the response (according to RECIST and PRECIST criteria) to the new dose of I131.
Results
After redifferentiation treatment, I131 uptake increased in 5 patients (40%) all of whom received a therapeutic dose of I131. A sixth patient receives the dose empirically. Of the six patients receiving treatment with I131, according to RECIST criteria, 2 achieve partial response, 3 achieve stable disease and 1 has disease progression. According to PERCIST criteria, 4 achieve partial metabolic response, 1 achieves stable metabolic disease and 1 has disease progression.

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P511

JOINT1536

The metastatic medullary thyroid carcinoma: a rare cause of ectopic ACTH-dependent cushing's syndrome

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Introduction
Ectopic Cushing's syndrome (ECS) accounts for 15% of all endogenous Cushing's syndromes and 10-20% of ACTH-dependent Cushing's syndromes. Medullary thyroid carcinoma (MTC) is a rare cause of ectopic ACTH secretion in patients with ACTH-dependent Cushing's syndrome, described in less than 1% of MTC cases.
Summary
We present the case of a 68-year-old patient with pronounced hypokalemia and weakness, initially attributed to hypercortisolemia due to Cushing's syndrome (previously diagnosed as an adrenal incidentaloma). Based on very high basal and suppressed ACTH levels and high basal calcitonin value of 2239. 00 pg/mL, ectopic secretion of ACTH was supposed and neck and chest imaging was performed. The imaging revealed a multinodular goiter with cervical lymphadenopathy and neoplastic change in the left lung. Additionally, a percutaneous lung biopsy of the detected lung tumor confirmed the suspicion of metastatic MTC. In preoperative treatment, severe hypokalemia was corrected with high doses of potassium administered both orally and parenterally until the introduction of ketoconazole (200 mg three times daily). Ketoconazole reduced cortisol levels, and hypokalemia was corrected without evidence of hepatotoxicity. A PET/CT scan using 18F-FDG showed moderately increased accumulation of 18F-FDG (SUV max 1. 7) in nodules in the right thyroid lobe (21 mm in diameter), with further intensification of 18F-FDG uptake (SUV max 2. 1) in the upper lobe of the left lung at the junction of S3 and S4. The patient underwent combined surgery, including a total thyroidectomy and atypical resection of the upper lobe of the left lung (OPIII U-VATS). Postoperatively, ketoconazole was discontinued, and cortisol levels remained normal. Serum potassium levels normalized without the need for potassium replacement therapy.
Conclusion
The expected therapeutic effect of the surgery was achieved in terms of the prompt resolution of ectopic ACTH secretion from the metastatic medullary carcinoma and the control of hypercortisolism effects, which were life-threatening for the patient. Postoperatively, ketoconazole was discontinued, while maintaining normal cortisol levels and serum potassium values without the need for potassium supplementation. Monitoring of calcitonin levels continues,

with an assessment for the potential use of targeted therapy with tyrosine kinase inhibitors.

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P512

JOINT2483

Management of ectopic cushing's syndrome: a retrospective analysis of therapeutic outcomes

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Background

Ectopic Cushing's syndrome (ECS) is a rare and severe endocrine disorder caused by excessive ACTH secretion from extra-pituitary tumors. Given its high morbidity and mortality, timely diagnosis and effective management are crucial. This study evaluates the outcomes of pharmacological and surgical interventions in patients with confirmed ECS.

Methods

We conducted a single-center retrospective study analyzing ECS treatment outcomes from 2012 to 2024 at the Division of Endocrinology, University Hospital Centre Zagreb. Patients received pharmacological therapy (metyrapone, etomidate, ketoconazole) and/or underwent bilateral adrenalectomy. Descriptive statistical methods were used for data analysis.

Results

The study included 12 patients (median age: 43. 5 years; range: 22-74), with a female predominance (83. 3%). Identified ACTH-secreting tumors included lung carcinoid ($n = 1$), small cell lung carcinoma ($n = 2$), pancreatic neuroendocrine tumor ($n = 3$), medullary thyroid carcinoma ($n = 1$), breast neuroendocrine carcinoma ($n = 1$), thymus neuroendocrine carcinoma ($n = 1$), mediastinal neuroendocrine carcinoma ($n = 1$), and two cases with unknown tumor origin. At diagnosis, metastases were present in nine patients (75%). Pharmacological therapy was administered to seven patients (58. 3%) using metyrapone alone ($n = 2$), ketoconazole alone ($n = 2$), an etomidate-metyrapone combination ($n = 1$), or a metyrapone-ketoconazole combination ($n = 2$). The median dose of metyrapone used was 1500 (1000-4000) mg and ketoconazole 400 (200-800) mg. ECS was successfully controlled in three of these patients, while the remaining four required subsequent bilateral adrenalectomy. In total, nine patients (75%) underwent bilateral adrenalectomy, including five for whom surgery was the primary treatment. One patient achieved remission through lung resection. At the time of analysis, seven patients had died due to disease progression, with a median time to death of 16 (1–51) months. The median overall survival was 20 (1–154) months.

Conclusion

The management of ECS requires a multimodal approach, incorporating both pharmacological and surgical interventions. While pharmacological therapy was effective in some patients, bilateral adrenalectomy was necessary in certain cases

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P513

JOINT2809

The impact of 12 months of aromatase inhibitors on body composition in postmenopausal women with early-stage breast cancer

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Background

Breast cancer is the most common cancer type for women in Denmark as well as globally. There's a large and growing group of non-metastatic breast cancer survivors, which draws more attention to long term side effects of the anti-estrogen adjuvant cancer therapy. The decrease in estrogen may thus change distribution of body fat with an increase in visceral fat. The aim of this observational study is to assess potential side effects of aromatase inhibitors on the body composition on postmenopausal women with early-stage breast cancer.

Methods

A cohort of postmenopausal women with early breast cancer (EBC) were examined post chemotherapy (baseline), and after 12 months of aromatase inhibitor treatment, and compared to an age- and postmenopausal status matched healthy control group (CON). The examination was done with dual energy X-ray absorptiometry (DXA) scans. We excluded patients with known prior malignancy, pre-existing endocrine diseases and pre-existing diseases that can affect cancer or the endocrine system.

Results

We included 15 EBC participants and 8 controls. The mean age was for EBC 59. 1 ($\pm$5. 1), and for CON 60. 8 ($\pm$3. 3). As expected, there was no difference in body composition between EBC and CON at baseline: visceral adipose tissue (VAT) EBC 396. 7g ($\pm$200), CON 334, 1g ($\pm$173) $p > 0.05$; fat mass (FM) EBC 29. 0kg ($\pm$9. 2), CON 26. 5kg ($\pm$7. 0) $p > 0.05$; fat% EBC 37. 4% ($\pm$5. 3), CON 36. 3% ($\pm$4. 9) $p > 0.05$; lean body mass (LBM) EBC 45. 5kg ($\pm$8. 5), CON 44. 1kg ($\pm$5. 9) $p > 0.05$). There were no changes in body composition from baseline to 12 months (mean change (95% CI)), VAT (EBC +47. 8g (-63. 5-159. 1), $p > 0.05$; CON +71. 6g (-42. 7-186. 0), $p > 0.05$), FM (EBC -0. 5kg (-2. 7-1. 7), $p > 0.05$; CON -1. 6kg (-4. 3-1. 1), $p > 0.05$), fat% (EBC +0. 8%-points (-0. 6-2. 3), $p > 0.05$; CON -1. 3%-points (-3. 0-0. 5), $p > 0.05$) and LBM (EBC -0. 8kg (-2. 0-0. 4), $p > 0.05$; CON -0. 1kg (-3. 0-2. 8), $p > 0.05$).

Conclusion

These preliminary results suggest no interaction between 12 months of aromatase inhibitor treatment post chemotherapy and body composition, where no changes was found between the two groups nor within the groups.

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P514

JOINT3910

Extraordinary cortisol and 11-deoxycorticosterone co-secretion from an ectopic peritoneal adrenocortical carcinoma

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Background

Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy that typically arises in the adrenal glands. Its occurrence in ectopic adrenal tissue is exceptionally rare, posing significant diagnostic and therapeutic challenges.

Case Presentation and Literature Review

We describe the case of a 71-year-old female presenting with severe Cushing's syndrome and extreme hypercortisolism (17, 000 nmol/l; normal range: 166-507 nmol/l). Imaging revealed normal adrenal glands but extensive peritoneal carcinomatosis with a peritoneal mass at the hepatic hilum. An FDG-PET scan revealed intensely hypermetabolic peritoneal foci diffusely distributed, including perihepatic regions (SUVmax 18. 5 in the posterior-superior area), Hormonal assays confirmed ACTH-independent cortisol hypersecretion (ACTH $<$0. 84 pmol/l; normal range: 1-10. 75 pmol/l), along with markedly elevated levels of 11-deoxycorticosterone (DOC) (14, 177 pmol/l; normal range: 30-400 pmol/l), other steroid hormone precursors, and androgens (Testosterone: 18. 23 nmol/l; normal range: 0. 16-1. 11). Peritoneal histopathological examination and immunohistochemistry, with positive expression of synaptophysin, SF1 and inhibin A, established the diagnosis of high-grade ectopic ACC. Despite optimal medical therapy with osilodrostat and metyrapone, cortisol secretion remained uncontrolled, and the patient's condition deteriorated rapidly, leading to fatal complications. We reviewed 16 previously reported cases and found our case to be unique due to its location and the extreme steroid levels.

Conclusion

This case underscores the exceptional presentation of a functional ACC arising in adrenal rest tissue in the peritoneum leading to a severe Cushing syndrome producing extremely high levels of cortisol, DOC, and androgens. Such an occurrence is unparalleled in the literature.

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P515

JOINT1992

Patient reported outcome measurements (PROM) for the evaluation of the psychosomatic status in patients with adrenocortical carcinoma

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Background
Several studies have shown that distress, depression and fear of progression (FoP) are common in cancer patients and negatively impact quality of life (HRQoL). However, no studies have explored these aspects in patients with adrenocortical carcinoma (ACC).
Objectives
This observational study investigates FoP, distress and depression in patients with ACC and their impact on HRQoL.
Methods
Adults (≥18 years) with ACC were included during regular hospital visits. Patients filled out questionnaires addressing FoP (FoP-questionnaire, short-form), HRQoL (EORTC-QLQ-C30), distress (National Comprehensive Cancer Network distress thermometer) and depression (patient health questionnaire, PHQ-9). Patients were distributed according to different clinical parameters to assess possible influencing factors. Multiple linear regression on HRQoL subscales ('total symptoms', 'total functioning') was performed in order to identify associated psychosomatic variables.
Results
Over a 12-months period, 105 patients were included (56. 2% female; median age = 49 years). Most patients demonstrated an elevated level of distress (62%) and a high level for FoP (59%). A major depression according to PHQ-9 was present in 41% of participants. The HRQoL questionnaire showed a higher level for functional problems (median = 62. 2) in comparison to symptoms (median = 33. 3). These results were neither influenced by tumour burden, hormone secretion nor by cancer treatment. In the multiple linear regression only depressive symptoms revealed a significant effect for HRQoL 'total symptoms' (B_{stand} = 0. 620, $P <$. 001) and for HRQoL 'total functioning' (B_{stand} = -0. 673, $P <$. 001). Most of our patients (80%) showed a need for psychosomatic counselling revealed by the questionnaires.
Conclusions
Patients with ACC show similar values for distress, FoP, depression and HRQoL independent of their clinical characteristics. The questionnaires revealed the need for psychosomatic intervention that should be offered to all patients with ACC.

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P516

JOINT3848

Endocrine toxicity constitutes an independent predictor of survival in patients with extensive stage small cell lung cancer

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Endocrine immune-related adverse events (e-irAEs) complicate the treatment of patients with lung cancer (LC) treated with immunotherapy. Although the incidence of e-irAEs as well as their impact on survival outcomes in LC cancer patients has been previously reported, evidence is limited for patients with extensive-stage small-cell lung cancer (ES SCLC). We retrospectively assessed patients with SCLC receiving chemoimmunotherapy in the first-line treatment setting at "Sotiria" General Hospital for Chest Diseases, Greece. Kaplan-Meier curves were used to calculate real-world survival outcomes and cox proportional hazards regression analysis was utilized to identify associations with e-irAEs. In total, 193 patients were included, 73 patients receiving atezolizumab plus platinum-etoposide (EP) and 120 patients receiving durvalumab plus EP. 31 patients (17. 1%) experienced an e-irAE. The reported e-irAEs included hypothyroidism in 21 patients (11. 6%), hyperthyroidism in 7 patients (3. 9%) and hypophysitis in 3 patients (1. 7%). e-irAEs were mild (grade 1-2) in almost all (96. 8%) patients. Discontinuation of immunotherapy was not required, although treatment was temporarily interrupted in 2 patients with hypophysitis. The incidence rate and type of e-irAEs were similar among patients receiving atezolizumab and durvalumab (18. 2% vs 16. 5%, P = 0. 936). Median overall survival was higher in patients with e-irAEs compared to patients without (17. 9 vs 9. 6 months, HR: 0. 42, 95% CI 0. 26 – 0. 70, p <0. 001). The difference in real-world overall survival remained statistically significant in multivariate analysis. Median progression-free survival was also higher (7. 5 vs 6. 3 months, HR: 0. 60, 95% CI: 0. 39 – 0. 93, P = 0. 02). In conclusion, the development of e-irAEs remained an independent predictor of survival outcomes in patients ES-SCLC receiving chemoimmunotherapy after extended recruitment and follow-up.

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P517

JOINT3281

Six unrelated italian kindreds with multiple endocrine neoplasia type 4 (MEN4) harboring variants of the CDKN1B gene

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Multiple endocrine neoplasia type 4 (MEN4), caused by heterozygous inactivating mutations of the *CDKN1B* gene, is a rare hereditary syndrome presenting a combination of multiple endocrine tumors. It is characterized by a great overlap with MEN1 syndrome, having primary hyperparathyroidism (PHPT) the highest penetrance. Other tumors including renal, gonadal, adrenal, and thyroid tumors may be present. Here we describe six new MEN4 kindreds. The germline DNA of all the probands underwent next generation sequencing using a panel of PHPT-related genes. The proband of family 1 was a 55-yr woman with PHPT and bilateral adrenal lesions. An inferior left parathyroid adenoma was removed leading to the remission of PHPT after 21 months follow-up. The proband and her two siblings, both having mild elevated PTH levels and normocalcemia, carried a *CDKN1B* variant (c. 482C>G, p. Ser161Cys). The proband of family 2 was a 29-yr woman with PHPT and uterine myoma. An inferior left parathyroid adenoma was excised, resulting in the remission of PHPT after 43 months of follow-up. The proband and her mother affected by PHPT carried the *CDKN1B* variant c. 356T>C, p. Ile119Thr. The proband of family 3 was a 42-yr woman with PHPT, pancreatic neuroendocrine tumor (PNET) and single adrenal lesion. Inferior and superior right parathyroid adenomas were removed, leading to the remission of PHPT after 45 months of follow-up. The proband's mother was also affected by PHPT and is under surveillance. Both carried the *CDKN1B* variant c. 358G>A, p. Gly120Arg. The proband of family 4 was a 60-yr woman with PHPT, a non-functioning PNET, uterine myoma, bilateral adrenal hyperplasia, and melanoma. An inferior right parathyroid adenoma was removed leading to the remission of PHPT after 9 months of follow-up. She carried the *CDKN1B* variant c. 230A>C, p. Gln77Pro. The proband's sister, affected by PHPT, and the healthy nephew carried the same variant. The proband of family 5 was a 30-yr woman with PHPT. A superior left parathyroid adenoma was removed leading to the remission of PHPT after 66 months of follow-up. The proband and the healthy mother carried the *CDKN1B* variant c. 470C>T, pThr157Ile. The proband of family 6 was a 59-yr woman with recurrent PHPT due to right inferior, and left superior and inferior parathyroid adenoma. She carried the *CDKN1B* variant c. 274C>T, p. Pro92Ser. The *CDKN1B* variants segregate with the disease in all kindreds although they were classified as variants of unknown significance. Their functional consequences remain to be established.

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P518

JOINT517

Whole exome sequencing of gastroeneteropancreatic neuroendocrine tumors reveals specific SNV associated with epithelial-mesenchymal transition

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Background
Endogenous hyperinsulinemic hypoglycemia is a rare condition which can be caused either by an insulinoma or, less frequently in adults, by nesidioblastosis. A possible origin theory of these is based on a correlation between genetic alterations and metabolic pathways, which could result in an inadequate cell differentiation. This theory has been endorsed by evidence suggesting that dediferenciation has a relation with the pathogenesis of diabetes. Epithelial-mesenchymal-transition (EMT) is a widely explored process in oncology and could be a crucial step relating genetic variants with gastroenteropancreatic neuroendocrine tumors.
Objective
To evaluate genetic variants that could relate EMT with endogenous hyperinsulinism.
Material and methods
Pancreatic tissue from 7 patients was analyzed by means of whole exome sequencing (WES). The pathology diagnosis was nesidioblastosis in five, insulinoma in one, and insulinoma with nesidioblastosis in one.
Results
After searching for single nucleotide variants (SNV) present in more than 50% of the patients, we found the following: *FN1* c. A2449C:p. T817P, c. G6688A:p. V2230I (nonsynonymous) and c. G4725A:p. E1575E (synonymous) in 85%; *FN1* c. A5691T:p. G1897G and c. T2442A:p. P814P (synonymous) in 71%. *CDH1* c. C2253T:p. N751N (synonymous) in 71%. *CDH2* c. C2448T:p. A816A and c. C1431G:p. P477P in 85%. *MMP2* c. C1806T:p. F602F, c. G1380A:p. T460T in 57%. *SNAI1* c. G531A:p. T177T, c. T279C:p. D93D (synonymous) and c. T353C:p. V118A (nonsynonymous) 57%.
Conclusion
Genetic variants for EMT related genes could help to make an association between EMT and endogenous hyperinsulinemia. C*DH1, CDH2 MMP2 and FN1* have been previously described in B-Cell dedifferentiation, thus highlighting the importance to understand the molecular mechanisms involved in the pathogenesis of these diseases.

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P519

JOINT1871

Persistent severe hypokalemia as a critical marker of diagnosis and response to treatment in ectopic cushing's syndrome (ECS) caused by small-cell lung cancer (SCLC)

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Introduction
ECS is a rare condition caused by excessive ACTH secretion from various tumors, with SCLC being the most common cause (20-30%). While ECS is reported in 1-6% of SCLC cases, recent data suggest it may be underestimated, reaching up to 25%. Patients with ECS at the course of SCLC are often not referred to endocrinologists. Severe hypercortisolemia in ECS leads to complications such as hypokalemia, worsening the prognosis.
Aim
This study reviews the clinical presentation, diagnostic methods, and treatment of ECS caused by SCLC, focusing on identifying a marker to aid diagnosis in non-endocrinology departments.
Materials and Methods
A retrospective analysis of 39 ECS cases (2000-2025) was performed, with 7 cases (18%) associated with SCLC. Diagnosis was based on clinical features, biochemical tests, imaging, and in some cases, ACTH detection in tumor samples.
Results
Seven patients (5 male, 2 female), aged 55-74 years (mean 65. 4), were analyzed. Initial symptoms included edema (4/7), muscle weakness (4/7), and resistant hypertension (1/7). All had significant weight loss (4-11 kg, mean 6. 6 kg). Muscle weakness was noted in 6/7, and bacterial infections in 5/7 (sepsis in 2). Typical Cushing's symptoms were infrequent: central obesity (3/7), plethora (3/7), and striae (1/7), with no weight gain observed. Laboratory tests revealed hypokalemia in all patients, with potassium levels between 1. 14 and 2. 97 mEq/l (mean 2. 1), requiring high supplementation (up to 200 mEq/day) and spironolactone (6/7; 50-400 mg/d). The average time from first symptoms to ECS diagnosis was 1. 4 months. All patients were diagnosed in the metastatic stage. Serum cortisol levels ranged from 22. 7 to 192 µg/dL (mean 91. 7 µg/dL). Metyrapone (4 patients) reduced cortisol by 44% and modestly decreased potassium supplementation (mean 12. 2%). Osilodrostat (5 patients) reduced cortisol by 63. 4% and potassium supplementation needs by over 50% (mean 50. 1%). 5 patients died (mean survival 2. 5 months). In one case, cortisol therapy enabled chemoimmunotherapy, leading to survival over two years.
Discussion
The proportion of SCLC cases among ECS patients (18%) in our study was lower than in the literature, likely due to limited referrals to endocrinologists. Weight loss, common in cancer, and severe, refractory hypokalemia were the only symptoms, which occur in all patients. Early hypercortisolism treatment, particularly with osilodrostat, caused a significant reduction in potassium supplementation needs, highlighting its benefit. Persistent hypokalemia may serve as a key marker for ECS diagnosis in SCLC patients, who often do not present classic Cushing's symptoms, especially in non-endocrinology wards.

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P520

JOINT943

Liver transplantation in a patient with small-intestine neuroendocrine tumor (NET) and carcinoid syndrome

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Background/Aims
Liver metastasis (LM) constitute a major prognostic factor in patients with neuroendocrine tumors (NET). Symptoms of carcinoid syndrome (CS) occur when serotonin and other substances (tachykinins, prostaglandin and histamine) are secreted directly into the systemic circulation, generally associated to small-intestine NET with LM. In case of stage IV disease, resection of the primary tumor can be considered, followed by liver-directed therapies or, in very exceptionally selected cases, liver transplantation (LT).
Results
31-year-old male, ECOG PS 0, with irrelevant medical history, referred for right-upper quadrant abdominal pain, diarrhea and flushing; initial abdominal imaging revealed multiple hepatic lesions. Laboratory evaluation documented elevated chromogranin A (CgA) (176. 0 ng/mL; reference range $<$102. 0) and slightly raised urinary 5-hydroxyindoleacetic acid (u5-HIAA) (37. 8 mg/24h; reference range $<$15). Patient underwent ileoncolonoscopy, with inconclusive findings due to inadequate preparation, and a [^{68}Ga]Ga-DOTANOC PET-CT, compatible with probable primary NET of the terminal ileum, with mesentery lymph nodes metastasis and extensive LM. After multidisciplinary evaluation, the patient initiated monthly lanreotide therapy and liver biopsy was performed soon after, revealing hepatic involvement by NET G2 (Ki67 5%). Cardiology assessment excluded carcinoid heart disease. He was then submitted to segmental ileal enterectomy and cholecystectomy; pathological examination confirmed ileal NET G1 with lymph node metastasis (Ki67 $<$ 1%; pT2N1). Subsequent imaging and evaluations demonstrated stable exclusive liver disease and normalization of CgA and u5-HIAA levels. Nevertheless, exuberant CS symptoms persisted subsequently, despite optimized lanreotide therapy (120 mg 3/3 weeks). Concerning patient age, good performance-status and stable exclusive but symptomatic liver disease, LT was considered over additional local or systemic therapies on a multidisciplinary setting. After further experts' opinion, the patient was considered a suitable candidate. The procedure was recently carried out at an experienced reference center after patient's consent, approximately three years

after the initial diagnosis. The patient is currently CS-related symptoms' free and [^{68}Ga]Ga-DOTANOC PET-CT re-evaluation is being planned.
Discussion
In this case, the patient remained symptomatic despite normal u5-HIAA levels; symptoms' resolution shortly after LT highlights the role of unmeasured substances in CS. The case also reflects the complexity of managing patients with metastatic NET and the importance of a multidisciplinary approach, moreover in the presence of hormonal secretion. Quality-evidence on LT in this setting is still scarce; therefore, patients should be judiciously selected.
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P521

JOINT3966
Thyroid nodule progression prediction using convolutional neural networks and ultrasound images
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Thyroid cancer incidence has been increasing worldwide over the last decade. Early detection of nodules from volumetric imaging tests such as CT or MRI due to other medical problems account for a fraction of new cases, however, ultrasound imaging is the most commonly used detection tool. Confirmed nodules are scored for risk of malignancy based on the American College of Radiology (ACR) Thyroid Imaging Reporting & Data System (TI-RADS). TI-RADS scores are based on five features: composition, echogenicity, shape, margin and echogenic foci. Composition is scored from 0 to 2 points, while echogenicity, shape, margin and echogenic foci can receive up to 3 points. The sum of points and size of nodule are used to determine the need for a fine-needle aspiration (FNA) procedure to confirm malignancy. Automated scoring of ultrasound images based on convolutional neural networks (CNNs) have been proposed and can provide useful pointers to a radiologist, but remain essentially "black-box" models, failing to provide novel insights about the output they produce. In this work, we propose a CNN-based automated scoring tool trained on TI-RADS that learns a non-linear mapping from ultrasound image to a Euclidean space, which we refer to as the "disease space". Inspired by Mihail *et al*., (Mihail, 2015) we impose the following constraints during the learning phase of the transformation to the new space: 1) L2 norm = TI-RADS score and 2) distance between similar images is minimized. Cluster analysis in this space reveals specific disease modes. Critically, this allows for nodule progression prediction by interpolating along the L2 norm vector. While the CNN component of our tool acts as a black-box, the disease space's L2 norm one-to-one correspondence with TI-RADS score allows us to gain novel insights into malignancy prediction, given enough data points and ground truth from FNA. In our evaluation, we use 2 datasets: 347 thyroid ultrasound images of thyroid nodules from the DDTI (Digital Database Thyroid Image) and 13 thyroid ultrasound images of thyroid nodules from a private hospital in Romania. These patients signed an informed consent form committing to the use of their data only for scientific research.
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P522

JOINT85
Bilateral phaeochromocytomas in a young patient with a pathogenic MAX gene variant
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Background
Phaeochromocytomas are catecholamine-secreting tumours originating from chromaffin cells in the adrenal medulla and can be symptomatic or asymptomatic. They may arise sporadically or in the context of hereditary syndromes such as MEN2, VHL, and hereditary paraganglioma-phaeochromocytoma (PGL-PCC) syndrome. Germline MAX gene mutations are a rare but known cause of hereditary PGL-PCC syndrome, manifesting as phaeochromocytomas/paragangliomas in affected patients.
Methods
This is a case report of a young patient with a pathogenic MAX gene variant who developed metachronous bilateral phaeochromocytomas.
Case Presentation
A 31-year-old lady with known hypertension presented with significant weight loss over one year, associated with increasing lethargy and episodes of diaphoresis. Her urine catecholamines and metanephrines were significantly elevated (adrenaline 2x above ULN and noradrenaline 37 × above ULN), and magnetic resonance imaging of her abdomen revealed a large 9cm left suprarenal mass. Right adrenal gland was normal. She was clinically diagnosed with a left phaeochromocytoma and underwent left adrenalectomy. Her young age at presentation prompted suspicion of hereditary syndromes – further genetic testing identified a pathogenic MAX gene variant associated with autosomal dominant hereditary PGL-PCC syndrome. Predictive testing was offered to at-risk family members. Subsequently, the patient was monitored for recurrence with annual urine catecholamine/metanephrine levels, and a full body MRI was performed every two to three years for the detection of paragangliomas. Despite the patient being asymptomatic, post-operative surveillance detected a right adrenal nodule two years later, followed by steadily rising urine catecholamine/metanephrine levels five years later. She was initially reluctant for surgery as she was asymptomatic but eventually opted for right adrenalectomy nine years later. Post-operatively, the patient was prescribed lifelong glucocorticoid and mineralocorticoid replacement therapy. She is currently well and remains under close follow-up and surveillance.
Conclusion
This case demonstrates the importance of genetic testing in young patients diagnosed with phaeochromocytoma. Predictive testing should be offered to at-risk family members. Close surveillance with biochemical screening and imaging is paramount to detect recurrence and/or new disease, even in the absence of symptoms. In patients with pathogenic MAX gene variants, a full body MRI extending from the base of skull to the coccyx is recommended.
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P523

JOINT2177
Cribriform morular carcinoma (CMC), a heterogeneous neoplasm of the thyroid gland. Report of four cases
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In the 2022 WHO classification, CMC was removed from the group of papillary carcinomas and included as a thyroid tumour of uncertain histogenesis. This neoplasm accounts for 0. 1-0. 2% of all TCs and was first described in 1994. Almost all CMC have genetic alterations in the Wnt/beta-catenin pathway, with APC mutations being the most common, associated with familial adenomatous polyposis (FAP) or as a sporadic form. We present four women with different clinical presentations. Case 1. Cerebellar medulloblastoma at 11 and colectomy by colectomy at 28 with positive genetics. Sonographic screening showed multinodular goiter with CNB suggestive of PTC. Surgery (2010) at 43 years showed four unencapsulated CMC foci 1. 5-4 mm in diameter, intrathyroidal with IHQ positive for TTF-1 and negative for HBME-1. Treated with I131 and without recurrence after 14 years of F-U. Case 2. Self-detected nodule with CNB suggestive of PTC. Surgery (2012) at 31 showed unifocal, unencapsulated, well-defined 38mm neoplasm with vascular invasion. IHQ positive for TTF-1 and negative for thyroglobulin and HBME-1 except in morules. Negative for mutation in APC and normal colonoscopy. Excellent therapeutic response 12 years after treatment with I131. Case 3. Positive genetic study for APC three years earlier (maternal carrier, c. 1548+1G>T) with subtotal colectomy and immature ovarian teratoma. Self-detected nodule with CNB suggestive of CMC. Surgery (2019) at 32y showed two foci of 20 and 3mm, unencapsulated, without vascular invasion and negative sentinel node (0/7). IHQ positive for TTF-1, beta-catenin and Ck19, negative for thyroglobulin and HBME-1. Treatment with I131 and excellent response five years later. Mesenteric desmoid tumour from 2021. Case 4. Positive genetics for APC (maternal carrier, c. 637C>T) and resected colon polyps seven years earlier. Self-detected nodule with CNB suggesting CMC. Surgery at age 21 (November 2024) revealed seven foci of CMC (12-44 mm). The largest had extensive vascular invasion (nine vessels) and focal extrathyroidal

extension. Two of nine LNs with tumour foci in the central compartment. IHQ positive for TTF-1, nuclear and cytoplasmic beta-catenin and Ck19 and negative for thyroglobulin and HBME-1 except in morules, Ki-67: 8% with negative study for mutations in TERT promoter. Defined as an independent entity in the recent WHO classification, CMC shows a wide clinical variability at presentation. Sporadic cases tend to be solitary tumours, whereas CMCs associated with germline APC mutations tend to be multifocal. This neoplasm may present an aggressive histological picture even in young patients, especially in larger tumours.

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P524

JOINT1273

Identifying vulnerable pituitary tumor patient subgroups after endoscopic transsphenoidal surgery: a prospective study on psychological well-being and self-perceived health

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Introduction

Transsphenoidal surgery (TSS) is the first-line treatment for most patients with pituitary tumors. The tumor, its treatment and comorbidities may significantly affect psychological well-being (PGWB) and self-perceived health. The aim of this study was to identify vulnerable subgroups among patients with pituitary tumors after TSS.

Methods

This prospective study included consecutive patients before TSS (baseline) and 12 months after surgery using the PGWB index and EuroQol Visual Analogue Scale (EQ-VAS) as described in the study protocol[1]. We investigated care type (personalized vs standard), clinical characteristics and adrenal insufficiency (AI) at 12-month as determinants of PGWB and EQ-VAS changes post-TSS.

Results

Totally, 148 patients (63 females, 43%), with a median age of 62 years (Q1-Q3 48. 3-69. 8) were included, of whom 118 (80%) had a non-functioning pituitary adenoma (NFPA). Before TSS, young age, female sex, living alone and having a secreting pituitary adenoma were associated with lower baseline PGWB. A subgroup analysis confirmed these findings in patients with NFPA, likewise all variables except sex remained significant in patients with functioning tumors. Similar patterns were seen for self-reported overall health, where young age, female sex and having a secreting tumor were related with lower baseline scores. However, in patients with NFPA, only age remained significant, and no variable correlated with baseline EQ-VAS in the functioning group. In the multivariate regression analysis on the full cohort, a functioning pituitary adenoma was associated with lower improvement in PGWB scores (β -0. 159, $P = 0.036$). Similarly, being born outside of Sweden was a negative determinant of EQ-VAS score improvement (β -0. 173, $P = 0.017$). Multivariate regression analysis on patients with NFPA showed that male sex and AI at 12-months contributed to less improvements in PGWB score (male sex β -0. 212, $P = 0.025$, AI β -0. 225, $P = 0.015$). In patients with functioning adenomas also including remission status at 12 months, only being born outside of Sweden (β -0, 331 $P = 0.045$) was correlated with less improvement EQ-VAS.

Conclusion

This study suggests that having a functioning pituitary adenoma and being foreign-born are vulnerable subgroups of pituitary tumor patients. The presence of AI among NFPA is also a negative predictor of outcome. These patients may need additional support during the post-operatory period to improve their psychological and overall health.

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P525

JOINT3647

Comparative evaluation of postoperative pathology in patients with fine needle aspiration biopsy cytology of bethesda category IV

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Objective

This study aims to evaluate the postoperative pathology results of thyroid nodules with Bethesda Category IV cytology. The study also seeks to determine the malignancy rate, tumor subtypes, and the surgical approach of these patients.

Methods

A retrospective analysis was conducted on patients who underwent fine needle aspiration biopsy (FNAB) at Ankara Bilkent City Hospital and were classified under Bethesda Category IV. Demographic data, preoperative thyroid function tests, ultrasound characteristics, and surgical interventions were reviewed. Postoperative pathology results were analyzed to determine malignancy rates and tumor characteristics.

Results

104 patients with FNAB result of Bethesda Category 4 were examined. 70 patients whose postoperative pathology was available were included in the study. In the classification of patients according to gender, 56 (53. 8%) patients were female and 14 (13. 5%) patients were male. The mean age was 46. 68 ± 13.99. FNAB cytology subtypes were follicular neoplasm suspicious (74. 3%), follicular neoplasm (%4. 3) and Hurthle cell neoplasm (21. 4%). Bilateral total thyroidectomy was performed in 62 patients (% 88. 6), right lobectomy in 5 patients (% 7. 1), and left lobectomy in 3 patients (%4. 3). Of the 70 patients, 26 (37. 2%) had malignant tumors, with papillary thyroid carcinoma being the most common malignancy (84. 6%). Pathology of 11 patients (%15. 7) was papillary carcinoma follicular variant, and pathology of 1 patient (%1. 4) was papillary carcinoma oncocytic variant. Other malignancies included follicular carcinoma (%2. 9) and Hurthle cell carcinoma (%2. 9).

Conclusion

The overall malignancy rate in patients with Bethesda Category IV cytology was 37. 2%, with papillary thyroid carcinoma being the most commonly diagnosed malignancy. Our malignancy rate in Bethesda category 4 is consistent with the literature; however, the final histopathological diagnoses of the lesions in this category were more commonly reported as classical papillary thyroid carcinoma (PTC) rather than follicular variant PTC or follicular cancer. This suggests that pathologists should review and reassess their reports for Bethesda category 4 lesions.

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P526

JOINT1180

Unravelling thermotolerance in adrenocortical carcinoma: implications for hyperthermia-based therapies

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Introduction

Adrenocortical carcinoma (ACC) is a rare, aggressive cancer with limited treatment options and frequent resistance to chemotherapy, highlighting the need for improved therapies. Hyperthermia is used to treat ACC metastases primarily through radiofrequency ablation to control disease burden. Incomplete tumour

ablation risks exposure to sub-lethal hyperthermia in the transitional zone of heating with the potential for development of thermotolerance. Few studies have examined the biological effects of hyperthermia on ACC cell survival and function. This study explored the thermotolerance in ACC, where cells resist subsequent thermal stress after initial sublethal heat exposure. We hypothesise that sublethal hyperthermia induces thermotolerance to subsequent exposure at 48°C or 50°C, compared to "naïve" (non-hyperthermia exposed) cells, mediated by the heat shock response and TMEM16F, a calcium-dependent scramblase involved in cellular repair.

Methods

ACC primary cell lines, H295R and HAC15, and the metastatic cell line MUC-1, were pre-treated at 45°C using heat-controlled water baths. Cells were rechallenged at 48°C or 50°C after 24 hours or 7 days and compared to naïve cells. Cell death was assessed via Sytox Blue staining via flow cytometry, and protein expression of HSP70, HSP90, P-HSP27, and TMEM16F was analysed using Western Blot.

Results

Surviving ACC cells previously exposed to hyperthermia demonstrated evidence of heat stress following hyperthermia but did not develop thermotolerance. There was no difference in viability between naïve and pre-treated cells at 48°C or 50°C, though MUC-1 showed higher resistance at higher temperatures ($\geq$48°C) compared to H295R and HAC15. While heat stress was evident in all cells following hyperthermia, there was no significant difference in HSP70 or HSP90 expression post-rechallenge between naïve and pre-exposed cells. A marked reduction in P-HSP27, was observed in both naïve and rechallenged cells at 50°C and this reappeared 24 hours post-rechallenge. Additionally, TMEM16F expression was lost immediately at both 48°C and 50°C but reappeared 24 hours post-rechallenge at 48°C only.

Conclusion

Hyperthermia of 45°C did not confer thermotolerance in H295R and HAC15 cells. The marked reduction in P-HSP27 and transient loss of TMEM16F suggest a diminished heat shock response at higher temperatures. Their reappearance 24 hours later indicates a delayed role in recovery but this is insufficient to confer protection against subsequent thermal stress. These findings emphasise the complexity of ACC cell responses to hyperthermia but are reassuring clinically, indicating that thermotolerance may not develop in transitional zones of cancers incompletely ablated whereby they remain sensitive to further ablation challenges.

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P527

JOINT1787

Diagnostic and therapeutic specificity of thyroid nodules in children

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Goals

To study the epidemiological, clinical, and therapeutic particularities of children operated on for thyroid nodules.

Patients and Methods

Retrospective study of 40 patients aged 18 or less who underwent surgery for thyroid nodules over a period of 15 and a half years [01/2010-06/2024].

Results

Forty children were operated on for thyroid nodules. The mean age was 15 years 8 months. The sex ratio (M/F) was 1/8. The mean duration of evolution was 4 months. The pathological history was noted to be Graves' disease in 4 cases (10%), congenital hypothyroidism in 3 cases (7. 5%) and papillary thyroid carcinoma in the family in 1 case (2. 5%). The mode of discovery was a basicervical swelling in the majority of cases. Cervical ultrasound was systematically requested in all our patients with a chest CT scan in 2 cases and a thyroid scintigraphy in 4 cases. Fine needle aspiration cytology was performed in 3 cases (7. 5%). Surgery consisted of total thyroidectomy in 23 cases (57. 5%), loboishmectomy in 17 patients (42. 5%), accompanied by mediastinal-recurrent lymph node dissection in 12 cases (30%) and functional in 2 cases (5%). Definitive histology concluded with papillary carcinoma in 11 cases (27. 5%), encapsulated vesicular with limited angioinvasion in 1 case (2. 5%). The evolution was favorable in all patients with a mean follow-up of 6 months.

Conclusion

Thyroid nodules are rare in children. They are more aggressive than in adults. A malignant lesion must be suspected in time and treated promptly.

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P528

JOINT2070

Intracranial germ cell tumors presenting with precocious puberty and diabetes insipidus in female patients: three case reports

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Intracranial germ cell tumors (ICGCTs) in children are one of the factors leading to peripheral precocious puberty. Beta-human chorionic gonadotropin (β-HCG) exhibits luteinizing hormone (LH)-like functions. Intracranial germ cell tumors secrete β-HCG, which binds to LH receptors in the testes, triggering gonadotropin-releasing hormone (GnRH)-independent testosterone secretion, thereby causing precocious puberty. However, ovarian activation in females requires the simultaneous action of LH and follicle-stimulating hormone (FSH), and β-HCG has a low FSH-like activity, meaning that peripheral precocious puberty caused by intracranial germ cell tumors is more commonly seen in males. Female cases are rare. This clinical study summarizes the clinical features and pathogenesis of three cases of β-HCG-secreting non-gonadal germ cell tumors of the brain, presenting as peripheral precocious puberty and central diabetes insipidus. One case progressed to rapidly advancing central precocious puberty. The three patients all presented with central diabetes insipidus and peripheral precocious puberty, with two cases also complicating central adrenal insufficiency and central hypothyroidism. The β-HCG levels in peripheral blood were 5010 mIU/ml, 314. 3 mIU/ml, and 202. 8 mIU/ml, respectively. After treatment with radiotherapy and chemotherapy, β-HCG levels normalized, and the Tanner stage regressed to stage I. One case progressed to rapidly advancing central precocious puberty. Analysis suggests that this is related to prolactin (PRL), tumor-derived aromatase, and FSH-like function. Therefore, for female patients with precocious puberty, regular testing for β-HCG and alpha-fetoprotein (AFP) is necessary, especially for those with central nervous system symptoms. A thorough evaluation with pituitary region MRI (plain and contrast-enhanced) is crucial to exclude organic diseases such as tumors. Furthermore, in younger female patients with precocious puberty, vigilance for organic lesions should not be relaxed.

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P529

JOINT2183

Adrenocortical carcinoma in a 9-year-old girl with li-fraumeni syndrome: a case report

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Introduction

Adrenocortical carcinoma (ACC) is an extremely rare and aggressive malignancy in children, with an incidence of 0. 1–0. 3 cases per million. Pediatric ACC is often linked to germline TP53 mutations, particularly in Li-Fraumeni syndrome (LFS). We present a case of a 9-year-old girl with ACC, highlighting its aggressive course, treatment challenges, and the role of genetic predisposition.

Case Presentation

A previously healthy 9-year-old girl developed progressive weight gain, facial acne, hirsutism, and fatigue over several months. While on vacation, she experienced seizures, altered consciousness, and hypertension (150/90 mmHg), requiring emergency intubation. Imaging revealed a 10 cm right adrenal mass, and laboratory tests showed significantly elevated cortisol (1626 nmol/l; normal 177–578), testosterone (20. 16 nmol/l; normal 0. 31–1. 94), and DHEA-S levels.

MRI suggested a malignant adrenal tumor. She underwent an adrenalectomy, which confirmed an adrenocortical carcinoma (pT2N0). Postoperatively, she required hydrocortisone replacement, and further genetic testing identified a pathogenic TP53 variant, confirming LFS. Adjuvant therapy with mitotane was initiated, but two months post-surgery, abdominal MRI revealed peritoneal metastases. A second surgery removed multiple metastatic lesions, followed by chemotherapy (mitotane, temozolomide, cyclophosphamide). Despite treatment, the disease progressed, with new hepatic and peritoneal metastases. Given limited therapeutic options, pembrolizumab was introduced alongside metyrapone for hypercortisolism control. However, the patient's condition deteriorated, with persistent tumor progression. At 13 months post-diagnosis, she succumbed to the disease.

Discussion

ACC in children is often diagnosed late due to nonspecific symptoms. In this case, signs of Cushing's syndrome and virilization were present but not initially recognized. The association with LFS underscores the importance of genetic screening in pediatric ACC cases, as TP53 mutations significantly impact prognosis and treatment strategies. Despite aggressive surgical and systemic therapy, prognosis remains poor, particularly in metastatic disease. Mitotane remains the cornerstone of treatment, but novel approaches, including immunotherapy, are being explored. This case highlights the urgent need for better therapeutic strategies for pediatric ACC, particularly in genetically predisposed patients.

Conclusion

This case illustrates the aggressive nature of ACC in a child with LFS and the challenges in managing this rare malignancy. Early recognition, genetic testing, and novel treatment strategies are crucial for improving outcomes in pediatric ACC.

Keywords

Adrenocortical carcinoma, Li-Fraumeni syndrome, pediatric cancer, TP53 mutation, mitotane, immunotherapy.

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P530

JOINT2952

Association of hemizygous MAMLD1 gene mutation and testiculer germ cell neoplasia *in situ*: a case report

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Introduction

MAMLD1(Mastermind like domain containing1,)on the Xq28 found specific expression in fetal sertoli and leydig cells. It was identified as critical for the development of male genitalia and predicted to enhance the expression of several Leydig cell-specific genes via Hes3-related Notch signaling pathway. Its hemizygous pathogenic variants cause 46, XY differences/disorders of sex development (DSD), hypomasculinized external genitalia at birth and are possibly associated with age-dependent deterioration of testicular function. It may play an important role in the testicular function including testosterone production during the fetal period and after birth.

Case

Here we describe a patient (46, XY) manifested penoscrotal hypospadias with micropenis and bilateral cryptorchidism. The male proband is the first child of his healthy, nonconsanguineous parents. He was born at 30 wk, with a weight of 2, 800 g (3, 8SD) and a length of 42. 0 cm(0, 57 SD). Cryptorchidism, penoscrotal hypospadias with micropenis, bifid scrotum was detected and he had bilateral orchiopexy at 6 months of age. A stimulation test with hCG (10 months) showed significant increase in testosterone concentrations(stimulated testesteron 302ng/dl, stimulated DHT 18ng/dl, stimulated androstenodion 6ng/dl) at 10 months of age, stimulated T/DHT ratio was >12 initially lead to the suspicion of 5α-reductase deficiency. However, mutation analysis of the SRD5A2 and AR gene was not detected. Bilateral testiculer microlithiaisis was detected at ten years old. Calcific density showed significant increased in US throughout the follow-up period. At the age of 14, according to the Tanner, right and left testis volumes were 12 and 15 cc, LH, FSH and total testesteron, AMH values were 11, 4mU/mL, 12, 5 mU/mL, 560 ng/dl, 4, 54 ng/ml respectively. Serum β-hCG and AFPlevels were within normal limits. Because of risk factor for testicular tumor, our patient underwent whole exome sequencing with CNV, MAMLD1 gene deletion on exon 3-5 was identified. Surgical right testis biopsy was applied, multifocal germ cell neoplasia *in situ* was detected. The focal immature seminiferous tubules with leyding cell hyperplasia were observed.

Discussion

Patients with 46, XYDSD harbouring MAMLD1variants manifest a broad spectrum of phenotypes and mostly present with hypospadias. Although both testes were descended into the scrotum within the first year of life and Sertoli/leydig cells produced sufficient hormones during pubertyin our patient, a testicular tumor developed. This is the first reported Mamld1 gene deletion a possible association with the causation of testicular tumor. We would like to emphasize that Patients with MAMLD1 mutation should be closely screened through physical examination and imaging techniques.

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Environmental Endocrinology

P13

JOINT1775

The effect of iodine- and selenium-fortified eggs on urinary excretion: findings from a randomized controlled study

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Background

Iodine and selenium are essential micronutrients for thyroid function, metabolism, and neurodevelopment. Deficiencies remain a global public health concern, particularly in regions with low soil iodine and selenium content, including Lithuania. While salt iodization programs have helped mitigate iodine deficiency, complementary strategies such as biofortified foods are needed to improve dietary intake. Eggs, widely consumed across populations, can serve as an effective vehicle for iodine and selenium delivery when hens' feed is fortified. This study assessed the short-term impact of consuming iodine- and selenium-fortified eggs on urinary iodine (UIC) and selenium (USeC) excretion in adults following a low-iodine and low-selenium diet.

Methods

A randomized, double-blind, controlled trial was conducted at Vilnius University, Lithuania, enrolling 130 healthy adults aged 18–45. Participants were randomly assigned to consume either one iodine- and selenium-fortified egg (intervention group) or one standard egg (control group) per day for five days while adhering to a diet low in iodine and selenium. Spot urine samples were collected at baseline (day 0), day 3, and day 5. Urinary iodine/creatinine (UI/Cr) and selenium/creatinine (USe/Cr) were calculated for urine dilution. Daily urinary iodine excretion (UIE) and selenium excretion (USeE) were estimated using the Kawasaki formula. Iodine deficiency was defined as UI/Cr $<$ 100 μg/gCr and selenium deficiency was defined as USe/Cr $<$25 μg/gCr. Participants were included in the analysis if their urinary creatinine level was ≧20 mg/dL (iodine and selenium analysis) and if their CKD-EPI albuminuria category was A1 (selenium analysis). Statistical analyses included Student's t-tests and paired t-tests.

Results

At baseline, 74.8% of participants were iodine deficient (UI/Cr: 80.73 ± 34.74 μg/gCr), and 93.3% were selenium deficient (USe/Cr: 17.16 ± 4.91 μg/gCr). By day 5, UI/Cr was significantly higher in the intervention group compared to the control group by 17.06 μg/gCr (93.41 ± 44.43 μg/gCr vs. 76.35 ± 36.74 μg/gCr, $P = 0.036$), and UIE was higher by 31.83 μg/24h (161.85 ± 84.60 μg/24h vs. 130.02 ± 61.09 μg/24h, $P = 0.031$). For selenium, USe/Cr increased by 1.09 μg/gCr in the intervention group ($P = 0.077$) and by 1.41 μg/gCr in controls ($P = 0.075$) compared to baseline. USeE increased significantly in the intervention group by 2.13 μg/24h (from 30.01 ± 8.64 μg/24h to 32.14 ± 11.04 μg/24h, $P = 0.047$), but no significant changes were observed in the control group.

Conclusion

Consumption of iodine- and selenium-fortified eggs significantly increased urinary iodine excretion, while selenium changes were modest. These findings support fortified eggs as a promising approach to improving iodine and selenium status. Further research is needed to assess long-term effects and scalability.

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P14

JOINT2939

Impact of early-life exposure to phthalates on anogenital distances in a cohort of healthy children and their mothers, from birth to three years of age

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Background
Ano-genital distances (AGDs) are androgen-dependent body characteristics influenced by the intra- and extra-uterine-hormonal environment. Phthalates are ubiquitous environmental contaminants and endocrine disrupting chemicals (EDCs) with reproductive toxicity and anti-androgenic effects. The aim of this study is to assess phthalates exposure during the first 3 years of life in a cohort of healthy term infants and their mothers and the possible association with AGDs.
Methods:
Single-center, prospective birth-cohort study, assessing phthalates exposure in single urine samples collected at birth(T0), 3(T3), 6 (T6), and 36 (T36) months in children, and at T0 and T36 in mothers. After solid-phase extraction, samples were analyzed for 8 major phthalate metabolites (MMP, MEP, MnBP, MBzP, MEHP, MEHHP, MEOHP, MCOP) by triple Quad LC/MS Mass Spectrometry. Then we evaluated Hazard Indices based on EFSA' tolerable daily intake (HI-TDI) and on reference doses for anti-androgenicity (HI-RfD-AA), to estimate the potential synergic effect of different phthalates on development reproduction. Ano-penile distance (AGD-AP), ano-scrotal distance (AGD-AS) and penile length (PL) for male, ano-fourchette distance (AGD-AF) and ano-clitoris distance (AGD-AC) for female, were measured by a Vernier caliper at each timepoint. Spearman correlation coefficient between HIs and AGDs were calculated.
Results
A total of 188 mother–infant pairs were enrolled. The table summaries AGDs values (means ± S.D.) in males and females. In males AGD-AP at T36 showed a significant strong negative correlation with HI-TDI and HI-RfD-AA in mothers at T0 (r: −0.569 P<0.001and r: −0.500 P<0.001, respectively). Moreover, negative associations were detected for PL and mothers' HI-TDI and HI-RfD-AA at T36 (r: −0.299 P:0.057 and r: −0.342 P:0.029, respectively). At T36 in females moderate-strong negative correlations was detected between AGD-AF and HI-TDI and HI-RfD-AA at T3 and at T6 (r: −0.436 P:0.026, r: −0.403 P:0.041; and r: −396 P:0.045, r: −0.446 P:0.022; respectively); and between AGD-AC and HI-TDI and HI-RfD-AA at T3 and T36 (r: −0.478 P:0.013, r: −0.523 P:0.006; and r: −0.533 P:0.002, r: −0.465 P:0.01; respectively).
Conclusions
The development of AGDs during the first three years of life appears to be influenced by environmental factors that may also affect the child's later sexual development.

Sex (M/F)	AGDs (cm)	T0 (104/80)	T3 (70/52)	T6 (54/39)	T36 (47/31)
Males	AGD-AP	4.89 ± 0.59	6.85 ± 0.90	7.36 ± 1.14	8.89 ± 0.11
	AGD-AS	1.95 ± 0.66	3.59 ± 0.88	3.98 ± 1.12	4.57 ± 0.87
	PL	2.42 ± 0.59	2.79 ± 0.62	2.84 ± 0.69	3.77 ± 0.82
Females	AGD-AC	3.85 ± 0.69	4.65 ± 0.81	5.23 ± 0.97	6.80 ± 1.31
	AGD-AF	1.20 ± 0.42	1.71 ± 0.56	2.04 ± 0.63	2.31 ± 1.12

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P531

JOINT1564

Plasma phthalate metabolites correlate with genetic alterations in PCOS patients with metabolic dysfunction

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Background
The incidence of polycystic ovarian syndrome (PCOS) has been rising in India, affecting one in five women. While the aetiology of PCOS is multifactorial, growing evidence suggests that metabolic dysfunction and environmental contaminants, particularly phthalate exposure, may play a role. This study investigates the association between plasma phthalate metabolite concentrations and metabolic dysfunction in PCOS patients. Additionally, it explores the role of phthalates in modulating gene expression related to glucose and lipid metabolism, potentially linking phthalate exposure to metabolic dysfunction.
Methodology
Age-matched PCOS patients (n = 177) and healthy controls were recruited in the study after obtaining ethical clearance (IECPG-294/07. 06. 2023). PCOS patients were diagnosed according to the evidence-based Rotterdam diagnostic criteria (2023), and female individuals with no history of irregular menses, thyroid-related issues and metabolic dysfunction were recruited as healthy controls. Their plasma, serum and buffy coat samples were collected. Participants were screened for basic biochemical parameters, including fasting plasma glucose and lipid profile. The PCOS group was further stratified into high (hiTyG) and low (loTyG) triglyceride-glucose index (TyG) subgroups, using a cut-off value of 8. 5 based on studies conducted in Asian population. Plasma phthalate metabolite levels were quantified using LC-MS/MS, and gene expression analysis was conducted using qPCR.
Results
The PCOS group exhibited significantly higher fasting triglyceride levels (P<0. 001), with nearly 65% of them showing an elevated TyG index (P < 0. 01) indicative of metabolic dysfunction. The PCOS-hiTyG group had significantly higher phthalate metabolite concentrations compared to controls (P < 0. 01). Moreover, a strong correlation was observed between elevated plasma phthalate metabolite levels and increased TyG index ($r_{Pearson}$=0. 7610, P < 0. 05), with altered expression of key metabolic genes, including *pparγ, cd36, glut4*, and *pten*. These gene alterations negatively correlated with both the TyG index and phthalate metabolite levels (P < 0. 05), suggesting that phthalates may actively contribute to metabolic dysfunction in PCOS.
Conclusion
This study establishes a novel, significant link between phthalate exposure and genetic alterations in PCOS, highlighting phthalates as potential exacerbators of metabolic dysfunction. These findings underscore the need to monitor phthalate exposure in vulnerable populations and further investigate environmental contributors to endocrine disorders. Additionally, the study emphasizes the importance of early metabolic dysfunction screening in PCOS patients, advocating for the inclusion of indices such as the TyG index in early diagnosis.
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P532

JOINT1591

Longitudinal exposure to benzophenones, parabens, and simple phenolic substances in children and adolescents and effects on puberty

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Introduction
Puberty timing is influenced by exposures to different groups of endocrine disrupting chemicals (EDCs) with different properties. However, our recent systematic review and meta-analysis failed to make firm Conclusions on the impact of EDCs on pubertal development as the majority of the existing studies are cross-sectional using varying statistical approaches.
Aim
The aim of the present study was to investigate the impact of prepubertal concentrations of non-persistent EDCs (i. e. benzophenones, parabens and simple

phenolic substances) in relation to pubertal onset in a longitudinal cohort based on data from the Copenhagen Puberty Study.
Methods
In total, 215 healthy children and adolescents (50. 7% girls) were examined every six months for 7 years contributing with a total of 1, 527 examinations, with the median number of examinations per child being 7 (range: 2-14). All children underwent a clinical examination including pubertal staging and had a blood sample drawn for the measurement of reproductive hormone concentrations. Furthermore, the children provided a first morning urine sample at each visit from which urinary concentrations of 9 benzophenones, 7 parabens and 8 phenolic substances were determined using LC-MS/MS.
Results
Several chemicals were detectable in more than 90% of the urine samples, including benzophenone-3 (BP-3), methyl paraben (MeP), and bisphenol A (BPA). In general, chemical concentrations were positively correlated indicating co-exposure from several sources. There was a tendency towards prepubertal urinary BPA concentrations being associated with higher age at pubertal onset in boys (lowest vs. highest BPA tertile: mean age at onset 11. 4 vs. 11. 8 yrs, p-trend = 0. 12) and lower age in girls (10. 9 vs. 10. 1 yrs, p-trend = 0. 08). There were no clear associations for prepubertal concentrations of MeP and BP3 in relation to pubertal onset.
Conclusion
All participants were exposed simultaneously to a cocktail of several non-persistent chemicals. There was a strong tendency towards prepubertal BPA levels influencing timing of normal sexual maturation. Detailed statistical analyses of cocktail effects of chemicals on reproductive hormones and timing of puberty are needed and will be further analysed in the project.

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P533

JOINT1322

Higher pfas exposure associated with lower 24h urine aldosterone in pregnant women. the odense child cohort

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Background
Aldosterone is an independent predictor of higher placenta weight and birth weight. Accordingly, mice studies demonstrated aldosterone to have essential trophic effects on fetoplacental growth. Perfluoroalkyl substances (PFAS) are synthetic endocrine disrupting chemicals of high persistency. PFAS have been suggested as an inducer of aldosterone secretion in adrenocortical cells. However, there is no available *in vivo* data on PFAS exposure and 24-hour (h) urine (U-) aldosterone levels.
Objective
To investigate associations between first trimester PFAS concentrations and levels of 24-h U-aldosterone in third trimester.
Methods
In Odense Child Cohort (OCC), serum (S-) concentrations of five PFAS: perfluorohexane sulfonic acid (PFHxS), perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA) were assessed in 1, 611 eligible women at median gestational week (GW) 12 (25^{th}, 75^{th} percentile: 10, 15). Among these, 24-h U-aldosterone was available in 469 women at median GW 29 (25^{th}, 75^{th} percentile: 28, 29). Multiple linear regression models were performed to estimate associations between S-PFAS concentrations (both as continuous and categorized data) and 24h U-aldosterone levels in pregnancy.
Results
Included women had a mean age of 30. 1 ($\pm$ 4. 5 SD) years, were predominantly nulliparous (58. 5%) with a median pre-pregnancy BMI of 24. 9 (5^{th}, 95^{th} percentiles: 19. 6, 36. 1) kg/m^2. In adjusted analyses, a doubling in S-concentrations of PFOS, PFOA, and PFNA were associated with a decrease in 24h U-aldosterone levels by -4. 8 % (95% CI: -8. 4%, -1. 0%), -5. 9% (95% CI: -9. 1%, -2. 7%), and -6. 2% (95% CI: -9. 9%, -2. 4%), respectively. Compared to the first tertile, exposure of PFOS and PFOA in third tertile, and PFNA in the second and third tertile statistically significantly decreased concentrations of 24-h U-aldosterone. A statistically significant dose-response relationship was observed across exposure tertiles for PFOS, PFOA, and PFNA (P-value for linear trend $<$ 0. 01) in the association with 24-h U-aldosterone.
Conclusion and Perspectives
Higher exposure concentrations of PFOS, PFOA, and PFNA in first trimester were associated with lower concentrations of 24-h U-aldosterone in third trimester. Aldosterone is an essential trophic factor for fetoplacental development. PFAS concentrations during pregnancy have been associated with negative pregnancy outcomes, including pregnancy loss and low birth weight. Hence, our observed inverse association between PFAS and aldosterone may be an important mechanistic link for the potential implications of PFAS on fetal growth.

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P534

JOINT3984

Circadian temperatures in relation to thyroid function and cold exposure among subsistence hunters in east greenland

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Background
Habitual cold exposure is mandatory to hunters living in East Greenland. Hunters in Greenland depend on the ability to produce heat. Brown Adipose Tissue has the capacity to produce heat by activation of Uncoupling Protein-1 (UCP1). Upregulation of UCP1 for activating BAT depends on triiodothyronine (T3) in concert with sympathetic stimulation. Hence, these hunters provide a unique model for intervention on the effect of blocking the sympathetic system during cold exposure.
Aim
We aimed to explore body temperature and thyroid hormones while blocking sympathetic activity in Greenlanders with habitual cold exposure.
Methods
We studied Greenlandic hunters (n = 7; healthy men) in East Greenland for 10 days during winter (February). The intervention comprised of a non-selective beta-blocker (Propranolol; 160 mg) taken daily for seven consecutive days. Blood samples were drawn daily for measurement of thyrotropin (TSH) and thyroid hormone levels, and body temperature was measured morning (AM) and evening (PM). Hunters reported the daily number of hours spent outdoor. Body temperature, TSH, fT3, and fT4 were compared prior to, and following intervention.
Results
Hunters spent an average of 5. 2 hours outdoor, and the body temperature was 35. 8 ^{o}C AM and 36. 2^{o}C PM. Body temperature decreased with intervention for PM measurements (36. 66^{o}C; 35. 76^{o}C), while not for AM measurements (35. 84^{o}C; 35. 99^{o}C). The circadian difference was lower with intervention (0. 82^{o}C; 0. 26^{o}C). Both PM temperature and circadian difference associated with the number of hours spent outdoors, with the latter explaining 18% of the circadian difference in body temperature. Average TSH was 2. 31 before and 3. 53 mIU/l with intervention, and fT3 was 3. 14 without and 2. 91 pmol/l with intervention. The pre-to-post intervention difference of 0. 61^{o}C for PM temperature was seen in parallel with a decrease of 0. 23 pmol/l in fT3 and rise of 1. 22 mIU/l in TSH.
Conclusion
Body temperature was stable with more than 5 hours spent outdoor in the Arctic winter. Intervention with a beta-blocker was followed by changes in body temperature in the evening while not in the morning. Changes in thyroid hormone levels were in keeping with the anticipated role of adrenergic stimulation of the thyroid gland. The rise in pituitary stimulation of the thyroid may be a response to decreased adrenergic drive on the thyroid. The results illustrate the complex interaction by thyroid hormones and adrenergic system to uphold body temperature.

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P535

JOINT2142

Endocrine disruption by phthalates and substitute substances: a hidden link to hypertension via adrenal steroidogenesis?

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Phthalates, widely used as plasticizers, are well-documented endocrine disruptors associated with adverse effects on reproductive, developmental, and cardiovascular health. Despite being increasingly replaced by substitutes like adipates, terephthalates, and cyclohexane derivatives, these substitutes are produced in large quantities and frequently detected in human samples. While they exhibit lower migration rates from primary applications such as food packaging and medical devices, the effects of long-term exposure on endocrine systems - specifically on adrenal steroidogenesis - remain poorly understood. To evaluate the influence of three established phthalates, adrenal NCI-H295R cells were treated with diethylhexylphthalate (DEHP), diisobutylphthalate (DiBP), and diisononylphthalate DiNP), three non-phthalate alternatives, namely diethylhexyladipate (DEHA), diethylhexylterephthalate (DEHT), and 1, 2-cyclohexanedicarboxylic acid diisononyl-ester (DINCH), alongside an equimolar mixture of all six substances combined, for 72 hours in triplicate. Cell viability and the secretion of 15 steroids were assessed via LC-MS/MS. While concentrations $>$ 100μM were cytotoxic, lower doses of DEHP, DiNP, DEHT, DINCH and the mixture mainly stimulated the mineralocorticoid pathway. Aldosterone levels rose by 2. 30$\pm$0. 55-, 2. 76$\pm$1. 08-, and 2. 51$\pm$1. 49-fold at 10μM of DINCH, DiNP and mixture respectively. Its precursor corticosterone increased by 2. 68$\pm$1. 31-, and 2. 79$\pm$1. 46-fold at 1μM of mixture and DEHP. Also elevated cortisol levels were detected, e. g. 2. 00$\pm$0. 84- or 2. 15$\pm$0. 87-fold at 10μM of DINCH and mixture, accompanied by reduced cortisone levels. Notably, 21-deoxycortisol was strongly elevated (e. g. 2. 72$\pm$0. 99-fold at 1μM DiNP). While androgens were mildly affected, estradiol was increased. Further, DEHA and DiBP treatment resulted in less altered steroid levels. However, previously described inhibition of androgen levels by phthalates, were not detected following treatment with substitutes (DEHA, DEHT, DINCH). Importantly, all substances induced significant disruption of adrenal steroidogenesis when combined, indicating additive effects of phthalates and non-phthalate substitutes. The observed dysregulation of mineralocorticoids may affect blood pressure and fluid homeostasis. This aligns with evidence linking phthalate exposure to hypertensive phenotypes, particularly in highly exposed neonatal intensive care unit patients. Interestingly, most components are known for altering the renin-angiotensin-aldosterone-system. Alteration of adrenal steroidogenesis could therefore provide a mechanistic explanation for phthalate- or substitute-induced hypertension. Moreover, chronic activation of the hypothalamic-pituitary-adrenal, potentially associated with phthalate exposure, may influence adrenal glucocorticoid synthesis. Although this remains speculative in the context of the current findings, it aligns with previous research highlighting the vulnerability of mineralo- and glucocorticoid synthesis both *In vitro* and epidemiological studies, to phthalates and their emerging alternatives. This highlights the need for further research on their potential as risk factors for cardiovascular and endocrine health.

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P536

JOINT2740

The impact of phthalates on adrenal steroidogenesis in HAC15 cells

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Background
Phthalates entail as endocrine disrupting chemicals and have been shown to be associated with a range of endocrine and metabolic disorders. Dibutylphthalate (DBP) and Diethylhexylphthalate (DEHP) account as one of the most common used phthalates and are found in everyday products, toys and medical equipment. In humans they are quickly metabolized to monobutylphthalate (MBP) and monoethylhexylphthalate (MEHP). We investigated the influence of those two metabolites on cultured adrenocortical cells *In vitro*.

Methods
We exposed cultured HAC15 cells to five different concentrations (ranging from 1nM to 10μM) of MBP, MEHP and the mixture of both, and assessed cell viability, expression levels of key enzymes of steroidogenesis and levels of reactive oxygen species (ROS).

Results
Cell viability was significantly decreased upon exposure of high concentrations of MBP (10μM), while it was increased upon exposure of medium concentrations (100nM) of MEHP. qRT-PCR analysis revealed a significant decrease of mRNA expression of *CYP11B2* upon exposure of even low MBP concentrations ($P = 0.0002$) while MEHP disrupted *CYP11B2* expression in a non-monotonic manner ($P < 0.0001$). Expression levels of *CYP11B1* and *CYP21A2* were decreased upon exposure of high concentrations of both chemicals. The results of co-exposure of both phthalates demonstrated an additive effect on *CYP11B2* and *CYP11B1* expression, while expression of *CYP21A2* was increased. There was an increase of ROS by 20% upon exposure of phthalate mixture ($P < 0.05$).

Conclusion
The data suggest that even low concentrations of MBP and MEHP can cause serious disruption of adrenal corticosteroid synthesis, which is even intensified upon co-exposure of both and potentially mediated by increased ROS. Further studies are required to study the influence upon co-exposure with angiotensin II and ACTH as well as the underlying mechanism.

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P537

JOINT2867

Early-life exposure to phthalates and risk assessment in a cohort of healthy mother-infant dyads: a 3-year follow-up study

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Background
Phthalates (PAEs) are ubiquitous environmental contaminants and recognized endocrine disruptors. PAEs are classified as reproductive toxicants; the extent of their early-life exposure remains limited and not extensively studied. The present study aims to assess perinatal and postnatal PAEs exposure in children (from birth to 36 months) and their mothers (at delivery and after 36 months).

Methods
Single-center, prospective birth-cohort study, assessing PAEs exposure in urine samples at birth (T0), 3(T3), 6(T6), 15(T15), 36(T36) months in children, and at delivery and T36 in mothers. After solid-phase extraction, 8 major PAEs metabolites (MMP, MEP, MnBP, MBzP, MEHP, MEHHP, MEOHP, MCOP) were analyzed by triple Quad LC/MS Mass Spectrometry. We described exposure patterns and estimate daily intake (DI). A risk assessment was performed by calculating risk quotients (RQ) based on EFSA' Tolerable Daily Intake (TDI) and reference doses for anti-androgenicity (RfD-AA). Hazard Indices (HI) were estimated by applying both the commonly used threshold of 1 and the the recently proposed 0. 1 limit to account for the overall risk of other toxicants co-exposure.

Results
188 mother-child pairs involved. PAE metabolites were widespread and detected in most urine samples at any time and showed a U-Shaped trend with lowest values at T3 and a progressive increase at the following observation times. The same trend was observed for DI, which in more than 25% of cases exceeded the EFSA threshold, excluding most DIs at T3. When calculating RQ, both RQ-TDI and RQ-RfD-AA showed median values below 1 at each timepoint for every PAE; and mothers presented the lowest quotients at T0. However, different subjects showed valued above the limit as reported in the table.

		T0		T3	T6	T15	T36	
		Mothers (n=186)	Newborns (n=164)	Infants (n=115)	Infants (n=101)	Toddlers (n=78)	Children (n=97)	Mothers (n=98)
HI-TDI	>1	0. 5%	2%	0	0	3%	2%	1%
	>0.1	6%	61%	15%	28%	63%	56%	20%
HI-RfD-AA	>1	1%	10%	1%	4%	21%	26%	1%
	>0.1	31. 6%	90%	46%	69%	82%	86%	67%

Conclusion
Exposure to PAEs appears broad and extensive in early years of life, even for the most toxic compounds banned by the EU in children's products. Our results showed that, despite European strict legislation, most children and their mothers exceed the newer most conservative risk threshold for antiandrogenic effects. Preventive public health measures to protect vulnerable groups are needed.

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P538

JOINT1275

Exposure to per- and polyfluoroalkyl substances during fetal development and risk of testicular germ cell cancer in adult life

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Background
Testicular germ cell cancer (TGCC) originates in fetal life, and exposure to environmental chemicals during fetal development may play a role. However, reliable epidemiological data are lacking due to the long latency between fetal exposure and disease onset, and challenges in accurate exposure assessment. Per- and polyfluoroalkyl substances (PFAS) can act as endocrine disruptors during fetal life with potential effects on reproductive health. We investigated the association between exposure to PFAS during fetal development and risk of TGCC in adult life.
Methods
We conducted a nested case-control study of 549 mother-son pairs (103 TGCC cases, 446 matched controls) using prospectively collected data. The sample population included more than 100, 000 pregnant women with biobanked serum samples collected between 1985-1995, a period before PFAS restrictions and thus of high exposure potential. Sons of these women diagnosed with TGCC were identified from the Danish Cancer Registry until 2023. Concentrations of eight PFAS were quantified in maternal serum by liquid chromatography tandem mass spectrometry. Associations of individual PFAS and their mixtures with risk of TGCC were estimated through stratified Cox regression and quantile g-computation models.
Results
In main analyses, no strong or statistically significant associations were observed between individual PFAS and TGCC risk. However, hazard ratios (HR) for sulfonic acids (e. g., PFOS, PFHxS, PFHpS) generally suggested higher TGCC risks, whereas carboxylic acids tended to be associated with lower risks. Mixture analyses supported this opposing pattern, showing slightly higher TGCC risk for the JOINT effect of sulfonic acids (HR 1. 13, 95% CI: 0. 89; 1. 44) and lower risk for carboxylic acids (HR 0. 72, 95% CI: 0. 51; 1. 02). Stratified analyses by TGCC histological subtype demonstrated consistent differences, with generally positive associations for seminomas, in contrast to generally inverse associations for nonseminomas. For PFOS, a quartile increase in concentrations was associated with a higher seminoma risk (HR 1. 31, 95% CI: 0. 98; 1. 76).
Conclusions
Our study, using biobanked maternal serum collected decades prior to diagnosis, provides no robust evidence linking PFAS exposure during fetal development to TGCC risk in adult life. However, indications that sulfonic acids may have an adverse effect compared to carboxylic acids were observed. The generally weak associations may reflect the limited sample size or the complexity in identifying specific chemicals during fetal development as risk factors for TGCC in epidemiological studies. Further research is needed to clarify whether other environmental chemicals, possibly as mixtures, may contribute to the development of TGCC.

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P539

JOINT2160

From sea to sample: tracing iodine nutrition in the faroe islands

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Background
Thyroid health depends on sufficient iodine nutrition, which conversely relies on dietary habits. Dairy products, tap water, and marine foods are potential sources of iodine and may contribute to the iodine intake. In the Faroe Islands, dietary habits shift from the traditional diet dominated by iodine-rich marine foods. We investigated potential sources of iodine and their relation to iodine nutrition among populations in the Faroe Islands.
Methods
We collected a variety of Faroese foods and tap water and conducted three cross-sectional studies between 2000 and 2020 to include adolescents, adults, and pregnant women. Participants were randomly selected to ensure a representative sample of the Faroe Islands. Participants filled in a questionnaire on demographic and iodine-related determinants. A spot urine sample was collected for iodine determination using the Sandell-Kolthoff reaction modified according to Wilson and van Zyl.
Results
Marine foods and seabirds had iodine contents ranging from 300 µg/kg. Lamb meat iodine content varied by 100%, depending on whether it was herded on an island with beaches (105 µg/kg) or cliffs (53 µg/kg) facing the ocean. Tap water iodine content was <2 µg/l. We estimated the iodine intake from four scenarios of Faroese meals, and it varied from 50 µg to just over 200 µg with diets rich in marine foods. The three studies covered the age span from 14 through 74 years without overlapping. The study of adolescents included 129 participants, and the median urinary iodine concentration (UIC) in this group was 166 µg/l. The study of pregnant women included 647 participants with an average age of 30 years and a median UIC of 110 µg/l when assessed in median pregnancy week 18. In the study of adults aged 40 through 74, the 491 participants had a median UIC of 101 µg/l. Diet impacted UIC with a dependency on fish and whale meals, while dairy products were not a source of iodine among Faroese.
Conclusion
Faroese marine foods were iodine-rich, and the populations included reported the intake of these foods. UIC in sub-populations in the Faroe Islands showed a dependency on marine meals, while dairy products had little influence on UIC.

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P540

JOINT2734

Menopause related psychological symptoms influence work and careers more than vasomotor symptoms: findings from a cross-sectional study among 1562 women in diverse occupations

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Introduction
Women over 40 are the fastest-growing demographic workforce worldwide. Women aged 40–65 constitute up to 50 – 60 % of the active female workforce. During this career stage, women are usually at the peak of their proficiency and experience but often face challenges related to menopausal transition (perimenopause/menopause period), with symptoms that negatively impact their work work and career development.
Aim
We aimed to investigate the relationship between menopausal symptoms and work and career development.
Methods
This was a cross-sectional study with snowball sample of 1562 women, aged 40-65 (Mean = 49; SD = 5. 45), working full time in private (52%), public (46. 1%) and non-governmental organisation (NGO) (1. 9%) sectors. Menopausal symptoms were assessed using the Menopause Rating Scale (MRS), while work ability was measured via the Work Ability Index (WAI). Additional measures included perceptions of symptom-related work problems (SWP), menopause hormone treatment (MHT) use, and menopause as career risk (MCR), measured with three questions: intent to leave the job, skipped promotion due to menopausal symptoms and whether menopause was viewed as non-threatening for their professional goals.
Results
There was a moderate negative correlation between WAI and MRS ($r(1561) = -.56$; $p < .001$), WAI and SWP ($r(1561) = -.60$; $p < .001$) and a weak positive correlation between MRS and MCR ($r(1481) = .34$; $p < .001$). Hierarchical linear regression showed that menopausal symptoms had the strongest effect on work ability, when controlled for age and MHT. Age and MHT were entered in the first block, and MRS subscales and SWP as predictors. The first model was found to be significant $F(2, 1560) = 14.32$, $P < .001$, $R^2 = .02$ showing that younger age and MHT had a protective effect against diminished work ability ($\beta = -.11$; $p < .001$, $\beta = -.08$; $p < .001$ respectively). Furthermore, the second model ($F(6, 1556) = 185.31$, $P < .001$, $R^2 = .42$) showed that psychological symptoms and SWP were the only significant predictors ($\beta = -.27$; $P < .001$ and $\beta = -.38$; $P < .001$) of work ability, whereas vasomotor and urogenital symptoms did not affect work ability.
Conclusion
The results of our study show that women's work and careers are negatively impacted by menopause with psychological symptoms having the most profound detrimental effect, stressing the need to understand menopause and its consequences beyond vasomotor symptoms. Thus, these findings highlight the need for interdisciplinary collaboration, mental health support and increased workplace awareness.

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P541

JOINT2693

Awareness of endocrine disrupting chemicals among medical students and physicians: is it time for urgent curriculum and training reform?

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Endocrine-disrupting chemicals(EDCs) have diverse sources of exposure in everyday life. Some may have transgenerational effects, and they are associated with endocrine cancers, metabolic diseases, and fertility problems. Raising public awareness is crucial considering the undeniable role of individual choices in EDC exposure. As physicians are one of the most trusted sources of information, the EDC awareness of physicians is essential for public education. There are no published studies about EDC awareness of medical students. In this study, we aimed to determine the EDC awareness of Turkish medical students and physicians using a validated scale in the Turkish language.
Methods
EDC awareness scale, a 24-question item, was used to determine EDC awareness. The participants were reached via message or e-mail.
Results
We reached a total of 617 participants. 381 were medical students (60. 8 % female, 39. 2 % Male), and 236 were physicians (62% female, 38% male). The median EDC general awareness score was significantly higher in physicians compared to students (2. 12(1. 5) vs 2. 87 (1. 63) $P < 0.001$). Mean EDC awareness total score was also higher in physicians (3.4 ± 0.54 for students, 3.63 ± 0.6 for physicians ($P < 0.001$). Female physicians' awareness was significantly higher than their male counterparts (3(1. 38) vs 2. 75(1. 56) $P = 0.027$). Age and healthy life awareness scores significantly correlated with EDC awareness scores. In particular, endocrinologists' scores were significantly higher than other subspecialties (General awareness score 2. 75(1. 5) vs. 3. 56(1. 63) $P < 0.001$; EDC awareness total score 3.59 ± 0.58 vs. 3.96 ± 0.56 $P = 0.003$)
Discussion
Despite the large number of public EDC awareness studies, the number of EDC awareness studies in physicians is scarce. For the first time in the literature, we have demonstrated that the medical students' EDC awareness is generally low. The physician's awareness is significantly higher than that of students, suggesting a post-graduate training process. Female gender, increasing age, and healthy life awareness are the major determinants of EDC awareness. Medical schools in Turkey do not include EDCs as a part of the curriculum. To raise the younger generations' awareness, curriculum reform may be necessary.

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P542

JOINT3717

Phthalates: an endocrine disrupting hazard from birth to adulthood

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Introduction
Endocrine disruptors represent a growing threat due to increased presence of these substances in the environment as a part of commonly used items. Among these compounds, phthalates are of particular concern because of their ubiquity and association with disruptions of steroidogenesis, gametogenesis, and tissue differentiation.
Objective
This article aims to elaborate a comprehensive analysis of the impact of phthalate exposure on puberty, growth, and reproductive system function, while elucidating the mechanisms by which they affect the endocrine system.
Methods
A review of scientific literature from the last 5 years from online data-bases such as NCBI, HINARI and Scopus regarding phthalate effects on the endocrine system and development during puberty was conducted.
Results
Exposure to phthalates was identified as a prominent cause of precocious puberty, including an earlier onset of menarche. In males, phthalates also exhibited an interference with testosterone metabolism. Suppression of thyroid function, as well as a decrease in sperm quality and motility in males and impaired ovarian function in females were also associated with exposure to phthalates. Phthalate-exposed individuals showed reduced height growth during childhood and delayed bone mineralization.
Conclusions
Phthalate exposure significantly affected the endocrine system, resulting in long-term consequences for pubertal development, reproductive health, and physical growth. The widespread occurrence of these findings in multiple studies substantiates the necessity for regulations concerning the use of endocrine-disrupting compounds, including phthalates.

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P543

JOINT859

Final adult height in male patients with central precocious puberty after GnRH agonist treatment

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Objective
Central precocious puberty(CPP) is on the rise around the world. Premature puberty and acceleration of bone maturation can cause a decrease in the final adult height(FAH) by rapid bone fusion, so it is beneficial to FAH by inhibiting excessive sex hormone secretion and bone maturation through Gonadotropin-releasing hormone agonist(GnRHa) treatment. This study was conducted on a large scale compared to previous studies to see how FAH of patients with CPP treated with GnRHa was beneficial compared to the target height(TH) what factors were associated.
Methods
This study involved a total of 92 patients who were treated with GnRHa and reached FAH of total 668 male patients diagnosed with CPP at the department of pediatrics of Severance children's hospital between January 2000 and June 2024. FAH was defined as the bone age(BA) of 16 years or older, and the yearly growth rate(YGR) was less than 1 cm/yr, the difference between FAH and TH(FAH-TH) was evaluated for growth benefits after GnRHa treatment. We compared the difference between BA and chronological age(CA) at the beginning and end of treatment. In addition, we analyzed the correlation with factors such as Tanner stage, age at start and end of treatment, treatment period, height, weight, body mass index(BMI), predicted adult height(PAH), standard deviation score(SDS), BA at beginning and end of treatment, laboratory test results (LH, FSH, peak LH, Testosterone) with FAH via univariate linear regression followed by multivariate linear regression.
Results
TH was 172. 39±3. 36cm, initial PAH was 169. 04±4. 34cm, FAH was 173. 62±6. 42cm, FAH showed a statistically significant increase of 1. 23±5. 86cmcompared to TH ($P = 0.047$), and 4. 58±4. 11cmcompared to initial PAH ($P < 0.001$). The difference between BA and CA was 1. 69±0. 64 years before treatment and 0. 57±1. 00 years after treatment. 1. 12±0. 91 years of delay in bone maturation at the end of treatment was significantly observed ($P < 0.001$). The difference between the FAH and TH was positively associated with height and PAH before treatment (β=0. 434, 0. 359, respectively, all $P < 0.05$), negatively associated with initial testosterone and peak LH (β=-0. 240, 0. 221, respectively, all $P < 0.05$). The difference between the FAH and initial PAH was positively associated with height before treatment (β=0. 473, $P < 0.05$), negatively associated with age, weight before treatment and peak LH (β=-0. 349, 0. 301, -0. 382, respectively, all $P < 0.05$).
Conclusion
GnRHa benefits FAH and inhibits bone maturation in male CPP patients. Taller height, PAH, younger, less weight, low testosterone and peak LH level at treatment is better for FAH.

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P544

JOINT1693

Association between urinary 3-phenoxybenzoic acid and thyroid function among 6-year-old children according to iodine status

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Background
3-phenoxybenzoic acid (3PBA), a metabolite of pyrethroid insecticides, has been linked to alterations in thyroid hormone levels in adults and pregnant women. However, research on 3PBA exposure in children and its interaction with iodine status remains limited. This study examines the relationship between early life 3PBA exposure and childhood thyroid function according to iodine status.
Methods
A total of 439 children aged 6 (231 boys and 208 girls) were included from the Environment and Development of Children cohort. Thyroid function was assessed through serum levels of thyrotropin (TSH), triiodothyronine (T3), and free thyroxine. Urine 3PBA concentrations were measured using morning spot urine samples. Iodine status was categorized based on urinary iodine concentration (UIC) as follows: iodine deficient (< 100 μg/l, $n = 19$, 4. 3%), adequate (100–199 μg/l, $n = 42$, 9. 6%), more than adequate (200–299 μg/l, $n = 54$, 12. 3%), mild excessive (300–999 μg/l, $n = 170$, 38. 7%), and severe excessive (≥ 1000 μg/l, $n = 154$, 35. 1%) groups. The association between urinary 3PBA levels and thyroid function was analyzed.
Results
The geographic mean creatinine-adjusted urinary 3PBA concentration was 1. 1 ± 2. 4 mg/g. Higher urinary 3PBA levels were significantly associated with increased serum T3 levels (β=2. 191, SE=1. 096, P-value=0. 046), after adjusting by age, gender, family history of thyroid disease, gestational age, birth weight and second-hand tobacco smoking. UIC group was significant effect modifier on relationship between serum TSH and urinary 3-PBA levels. In iodine-deficient group, urinary 3-PBA levels was positively associated with serum TSH levels (β=0. 51, SE=0. 212, P-value=0. 039). In iodine-excess group, urinary 3-PBA levels was positively associated with serum T3 levels (β=3. 66, SE=1. 831, P-value=0. 047)
Conclusion
Urinary 3PBA concentration was related to thyroid function in 6-year-old children, with iodine status acting as an effect modifier. These findings suggest that both iodine deficiency and excess influence the relationship between pyrethroid exposure and thyroid function in early childhood. Further research is needed to understand the long-term health implications of these interactions.

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P545

JOINT758

The LIFE-MILCH project: exposure to endocrine-disrupting chemicals in breast milk samples from the risk assessment model

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Introduction
The LIFE-MILCH project (www. lifemilch. eu) investigates exposure to endocrine-disrupting chemicals(EDCs) in mother-infant dyads during the first year of life. By analyzing EDC levels in breast milk(BM) and in mothers and infant urine samples, the study explores associations with neurodevelopment, growth, adiposity, pubertal stages, and genital features in infants. The first goal was to develop a risk assessment model to guide safety guidelines to optimize breastfeeding benefits while protecting long-term health. Here, we present data on exposure to EDCs in BM during the first 6 months of life.
Methods
We report data on 264/654 BM samples from the risk assessment model, enrolled in Parma, Reggio Emilia, and Cagliari in Italy. Healthy mothers with uncomplicated pregnancies were enrolled at 36-41 weeks of gestation. BM was collected at 1(T1), 3(T2), and 6 months(T3) after delivery. In all BM samples EDCs were measured by UPLC-MS/MS. Values were normalized to the blank; data > LOQ were further normalized for dilution. The analysis followed EFSA 2010 indications. Overall, Bisphenols (4congeners), Phthalates (PHTs) (14congeners), Polycyclic aromatic hydrocarbons (PAHs) (11congeners), Parabens (7congeners), Pesticides (3congeners), and two pyrethroids have been assayed.
Results
The most relevant and persistent bisphenol was BPA, detected in 60. 0% of samples at T1 and in 51. 0% at T3. BPS was detected in 14. 2% of samples at T1 and in 18. 8% at T3. In all samples, PTHs were ubiquitously high:DBP was detected in 88. 1% of BM samples at T1, in 95. 8% at T2, and in 86. 1% at T3; DEP and MEP were detectable in 46. 9% and 31. 5% of samples at T1, and in 55. 9% and 24. 5% at T3; BBP increased from 19. 2% at T1 to 33. 9% at T3. DMP, MnOP, MBP, and MEHP were detectable in over 28% of samples at all time points. In contrast, MEOHP, MBzP, MMP, and MEHHP halved at T3 compared to T1. DEHP, DnOP, and PAHs, except the indenopyrene, were subtly detectable. Parabens were variably detected, with MePB and EtPB increasing from 47. 3% and 34. 6% at T1 to 55. 9% and 51. 8% at T3. Pesticides and pyrethroids were scarcely detected. Preliminary data showed no associations of EDCs with length, weight, head, and abdominal circumferences during the first 6 months of life.

Conclusion
Preliminary exposure data confirmed that BM contains numerous EDCs from the environment. Further research is warranted to understand the effects on health. This project will follow children over time to evaluate the influence of real-life exposure to multiple EDCs on health outcomes.

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P546

JOINT981

An investigation of basic biochemical and endocrinological parameters in 34, 595 patients with occupational heavy metal exposure: a Turkey cohort

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Purpose
This study aimed to investigate the relationship between heavy metal levels and various endocrinological parameters in individuals from heavy metal exposure.
Methods
The basic biochemical and endocrinological laboratory parameters and heavy metal levels (arsenic, lead, mercury, manganese, cadmium, zinc, chromium, antimony, nickel, cobalt, selenium, copper, lithium, molybdenum, thallium, and selenium) of 34, 595 individuals whose heavy metal levels were measured were reviewed in this study.
Results
The average age of the participants was 42 years, and 54. 4% of them were male. The rates of thyroid dysfunction, diabetes mellitus, and prediabetes in individuals involved in occupations associated with a high risk of heavy metal exposure were 14. 3%, 12. 8%, and 21. 4% respectively. The results indicated higher fasting blood glucose levels in individuals with toxic arsenic levels, lower high-density lipoprotein (HDL) levels in those with toxic cadmium levels, lower HDL and low-density lipoprotein levels in those with toxic manganese levels, and higher liver enzyme and triglyceride levels in those with toxic zinc levels.
Conclusions
An increased prevalence of thyroid dysfunction was observed in younger individuals involved in occupations associated with a high risk of heavy metal exposure, even when the heavy metal levels were not toxic. Furthermore, there were indications of potential heavy metal toxicity-related liver pathologies as well as glucose and lipid metabolism disorders in younger individuals. The most rational approach to prevent and reduce these adverse effects is to limit the duration and amount of heavy metal exposure across the entire population, starting from the occupational groups at risk.
Keywords
Endocrine disruptors, heavy metals, heavy metal exposure, occupational diseases
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P547

JOINT59

Triptorelin stimulated gonadotropin concentrations for precocious puberty

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Background
Gonadotropin-releasing hormone (GnRH) stimulation test is the gold standard to identify central precocious puberty (CPP). However, intravenous GnRH for testing is commercially limited.
The aim of the present study was to evaluate the diagnostic accuracy of triptorelin-stimulated luteinizing hormone (LH) concentrations in the diagnosis of CPP among girls presenting with premature thelarche (PT) compared to the gold standard GnRH test.
Methods
A retrospective study of 186 girls with sexual precocity was undertaken. All girls underwent subcutaneous triptorelin injection. Blood samples before and 30, 60, 90 and 120 min after the injection were analyzed for LH and follicle-stimulating hormone (FSH) levels. Girls with peak triptorelin-stimulated LH concentrations $\geq$5. 0 IU/l were classified as having CPP.
Results
Eighty-eight patients (47. 3%) were classified as CPP and the rest (98 out of 186, 52. 7%) as PT. The peak LH was achieved at 60 minutes after triptorelin-stimulation in CPP groups, but 120 minutes in PT groups. On cross-sectional frequency, ninety-three percent of CPP group patients were diagnosed CPP with LH levels of $\geq$5 IU/l at 90 min and 120 min, each. The cumulative frequency of LH $\geq$5 IU/l was 90. 9% at 60 minutes, 95. 5% at 90 minutes, and 100% at 120 minutes.
Conclusions
Subcutaneous triptorelin can be used as an alternative to confirm the diagnosis of CPP. We tried to propose shorter duration of subcutaneous triptorelin-stimulation test for diagnosing CPP. The peak LH showed at 60 minutes after injection in CPP group, but the cumulative frequency of LH $\geq$5 IU/l was 100% at 120 minutes. Not to miss one single CPP patient, it is necessary for 120 minutes full examination.

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P548

JOINT1610

Sex-specific associations between maternal and postnatal exposure to bisphenol a (BPA) and children's body mass index: a prospective cohort study

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Background
Exposure to bisphenol A (BPA) may affect the weight of exposed individuals and/or offspring, while the influence of BPA on obesity by sex remains controversial.
Aim
To investigate sex-specific associations between maternal and postnatal exposure to BPA and children's body mass index (BMI) in a prospective cohort study of 592 mother-child pairs.
Methods
We used data from the Environment and Development of Children study, a prospective birth cohort study in South Korea. We assessed BPA concentration levels in mid-term pregnant women and their children, aged 2 to 10 years, to evaluate the age- and sex-specific associations with children's BMI and BMI Z-scores (BMI-Z) in linear regression models and sex-specific associations across years in mixed models after adjusting for potential confounders.
Results
We observed an increased BMI or BMI-Z in boys but decreases in girls associated with maternal exposure to BPA. While the difference in BMI was pronounced at age 10, standardized BMI-Z showed consistently significant sex differences at all ages. Postnatal exposure to BPA was negatively associated with BMI and BMI-Z at ages 2 and 10, but we did find significant differences by sex.
Conclusion
Findings from this prospective study support the assertion that maternal BPA levels have sex-dimorphic effects on childhood BMI.

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Fetal and Neonatal Endocrinology

P15

JOINT1191

Differential expression and protein abundance of key regulators of the IGF, adiponectin and PPAR signalling pathways in placentas from small, adequate and large for gestational age newborns

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Background/Objective
Foetal growth involves a complex interplay of molecular systems, including the insulin/insulin-like growth factor (IGF) system, adiponectin, and peroxisome proliferator-activated receptors (PPARs) signalling pathways. This study aimed to investigate the expression and abundance of a subset of genes and proteins associated with these pathways in placental tissue and cord blood collected from small-for-gestational-age (SGA), appropriate-for-gestational-age (AGA), and large-for-gestational-age (LGA) infants, as well as associated first-trimester maternal serum.
Methods
A total of 55 LGA-, 61 SGA-, and 109 AGA-born infants were included in the study. RT-qPCR was employed to analyse placental tissue samples collected at term, focusing on differential expression of 22 key genes, including IGF1, IGF2, IGF1R, IGF2R, INSR, IGFBP1-7, PPARA, PPARB, PPARG, RXRA, RXRB, ADIPOQ, ADIPOR1, ADIPOR2, APPL1, and APPL2. A blinded assessor evaluated a subset of placental samples ($n=78$) using semi-quantitative IHC analysis to validate differential gene expression at the protein level. ELISA was utilised to measure the abundance of chosen proteins (IGF1, IGF2, sIGF2R, IGFBP2, PAPP-A) in first-trimester maternal serum samples, as well as four proteins (IGF1, IGF2, sIGF2R, IGFBP2) in cord blood samples collected at term.
Results
The expression of placental genes IGF1, IGF2, IGF2R, IGFBP2, and PPARA varied among the three groups, with significant findings for IGF1, IGF2, and PPARA after multiple testing corrections. No meaningful expression of ADIPOQ was observed. With IHC analysis, strong expression of IGF1, IGF2, IGF2R was observed in the LGA group compared to the SGA and AGA groups. Strong expression of PPARA was observed in the LGA group compared to the SGA group. Weak expression of IGFBP2 was observed in both the LGA and AGA groups compared to the SGA group, with weaker expression in the LGA group compared to the AGA group. A strong positive correlation was found between cord blood IGF1 and infant birth weight (rs $=0.73$, $P<0.001$), and a strong negative correlation with IGFBP2 (rs $=-0.56$, $P<0.001$). A modest positive correlation was observed for IGF2 (rs $=0.42$, $P<0.001$). No associations were found between maternal serum protein levels and infant phenotype.
Conclusion
This study shows for the first time in humans an association between PPARA and foetal birth weight and confirms the association between the IGF signalling pathway and birth weight.

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P16

JOINT279

The pharmaceutical-grade oral Glyburide = Glibenclamide suspension, AMGLIDIA, is safe and efficacious in French patients with neonatal diabetes mellitus

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Context
Neonatal diabetes mellitus (NDM), a rare form of diabetes, is often linked to mutations in the K-ATP, *KCNJ11* and *ABCC8* genes or a genetic anomaly in chromosome 6q24. Management with pharmaceutical grade pediatric-adapted oral glyburide suspension (OGS), AMGLIDIA® has proven effective in restoring insulin secretion and stopping insulin injection.
Objective
This study aimed to evaluate its efficacy, effectiveness and safety.
Methods
Observational nation-wide retrospective study. A cohort of 27 patients affected by NDM in France was collected and analyzed annually over a median follow-up period of 2.7 years and up to 9 years of treatment.
Results
At baseline, the median HbA1c was 6,5% [5,8; 7,9]; 6,5% for *KCNJ11* mutated patients, 6,4% for *ABCC8* mutated patients, and 8.9% for the patient with chromosome 6 anomaly. All groups showed a non-significant *(P=0,382)* reduction in HbA1c levels with time to 6,27% in the KCNJ11 cases, 5,93% in the ABCC8 mutated cases and 7.4% in the 6q24 anomaly patient. At baseline, the overall median dose of the OGS was 0,15 mg/kg/day ranging from 0,1 to 0,185. Serious adverse events were minimal, with hypoglycemia reported in only 2 patients and diarrhea in 1.
Conclusion
A very good HbA1c was maintained, with a non-significant decrease in dose requirements over time, up to 9 years and the overall safety profile was favourable. Long-term use of AMGLIDIA® allowed an excellent metabolic control and a reassuring and manageable safety profile, making it a viable first line and long-term treatment in neonatal diabetes mellitus.

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P549

JOINT2785

Hypospadias and fetal growth restriction: a shared genetic origin?

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Background
Placental dysfunction is suspected to be linked to hypospadias since placental HCG stimulates fetal testis and subsequently support urethral development in the male fetus. Preterm births and intra-uterine growth restriction are thus associated with an increased risk of hypospadias but a shared molecular mechanism has not been elucidated yet. We aim to identify a JOINT genetic basis for hypospadias, preterm birth and fetal growth restriction using next generation sequencing (NGS).
Method
Prospective comparative multicenter study including 276 children with hypospadias. Phenotype ranged from glandular to penoscrotal hypospadias, without abnormal karyotype or pathogenic variants of candidate genes for XY-DSD. Genes included in the NGS panel were genes implicated in hypospadias or gonadal/genital development and that are expressed in the placenta. Frequency of variants was compared between preterm vs full-term patients, and between small for gestation age (SGA) vs normal growth patients. Univariate analysis and multivariate logistic regression analysis with stepwise backward selection were used.

Results
57 Hypospadiac boys were preterm (20. 6% of cases). Among these children, the variant *rs4986873* on *CYP11A1* (a gene implicated in testicular steroidogenesis and trophoblastic development) was more frequently found than in full-term babies (8. 8% vs 1. 8%, OR = 5. 239, $P = 0.015$). 44 hypospadiac boys were SGA (15. 9% of cases). Among these children, 4 variants in *RSPO1*, *ARID1A*, *CITED2 and CUL7* were more frequent than in hypospadiac patients without growth restriction. The identified variants are rs45577433 in *RSPO1* (OR = 7. 35, $P < 0.01$), rs35428899 in *ARID1A* (OR = 4. 14, $P = 0.01$), rs1131400 in *CITED2* (OR = 6. 73, $P < 0.01$) and rs9394939 in *CUL7* (OR = 4. 1, $P = 0.02$). This group of SGA patients had more severe hypospadias (40. 9% vs 24. 5% of mid-penile or posterior hypospadias, $P < 0.01$), more frequent chordee (53. 5 vs 35. 5%, $P = 0.03$), more frequent undescended testis (11. 9% vs 3. 15%, $P = 0.03$) and more frequent bifid scrotum (9. 3% vs 1. 3%, $P = 0.01$) than hypospadiac boys with normal growth.
Conclusions
We identified 5 variants that are more frequent in hypospadiac patients with prematurity (in *CYP11A1)* or SGA (in *RSPO1*, *ARID1A*, *CITED2* and *CUL7)* than in full-term hypospadiac boys with normal growth. These findings are in accordance with previous findings since besides being implicated in gonadal function and genitalia differentiation, CYP11A1 regulates trophoblastic proliferation and RSPO1, ARID1A, CITED2 and CUL7 regulate placental angiogenesis and have been associated with fetal growth retardation. These 5 genes may be at the crossroads of sex development and placental function. This finding makes a little further the connection between hypospadias and placental insufficiency at the molecular level.

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P551

JOINT3850

Deciphering the physiological downregulation of mineralocorticoid receptor expression at birth: implications of mir-409-3p and mir-431-5p

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Aldosterone regulates sodium homeostasis by binding to the Mineralocorticoid Receptor (MR). We have previously identified a critical temporal window during renal development with a down regulation of MR expression at birth, explaining the physiological sodium losses observed in newborns. However, the molecular mechanisms governing MR expression remain unclear. Here, we report the involvement of two microRNAs (miRNAs), miR-409-3p and miR-431-5p, in regulating MR expression during early renal development. Using miRNA sequencing, we identified these miRNAs as upregulated on mouse postnatal day 0 (D0) compared to day 8 (D8). RT-qPCR validated their differential expression, while luciferase reporter assays confirmed their functional interaction with MR transcripts. Functional studies using miRNA mimics and inhibitors revealed that miR-409-3p and miR-431-5p modulate MR expression and signaling in primary renal cell cultures. Specifically, their increased expression at D0 destabilizes MR transcripts and decreases MR expression and signaling, while their decreased expression at D8 leads to MR stabilization and enhanced mineralocorticoid signaling. Notably, digital droplet PCR (ddPCR) analysis of neonatal urine samples from the PREMALDO cohort demonstrated that these miRNAs are highly expressed at birth in humans but decrease gradually postnatally. Our findings identify miR-409-3p and miR-431-5p as key regulators of MR expression and mineralocorticoid signaling during renal development. These miRNAs could serve as potential predictive and non-invasive biomarkers of renal maturity and mineralocorticoid signaling efficiency notably in premature infants that have exacerbated sodium losses due to mineralocorticoid signaling defect in the neonatal period.

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P552

JOINT1773

Testing a continuous glucose monitoring assessment tool for congenital hyperinsulinism

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Congenital hyperinsulinism (HI) is a rare condition where excessive insulin secretion leads to persistent hypoglycemia. Uncontrolled hypoglycemia can cause neurological damage, but prompt detection minimizes this risk. Continuous glucose monitors (CGM) are not approved for use in HI, however, they are increasingly used off-label to monitor glucose levels. In the HI Global Registry, 51% of participants reported using CGM ($n = 255$). Early studies in HI suggest CGMs can support euglycemic control, enable timely interventions during hypoglycemia, and reduce the frequency of severe hypoglycemia, mirroring successes in diabetes. Importantly, CGMs may improve independence and quality of life for HI families by decreasing frequent glucose checks, alleviating anxiety around unrecognized hypoglycemia, and enabling safer participation in daily activities. There are no formal measures to assess the potential benefits of CGM use for people with HI. The Congenital Hyperinsulinism International Collaborative Research Network (CRN) is a patient-led, multi-disciplinary group comprised of clinicians, researchers, caregivers, industry partners, and people affected by HI. One CRN workgroup focuses on the importance of accurate and available glucose monitoring tools. The CRN developed a mutual decision-making tool for physicians and families to evaluate nine factors of life with HI— fasting duration before hypoglycemia, continuous feeding, injectable medications/pumps, glucometer use, hypoglycemia frequency, hypoglycemia unawareness, need for external decision-making, independence, and pancreatectomy status. The tool generates a score to facilitate conversations about the value of adding CGM to glucometer use. Six HI Centers of Excellence used the suggested scoring system to retrospectively assess up to 20 HI patients at each center. Individuals received a distinct CGM benefit score. Comparing the tool's assessment with real-world decisions physicians had made previously for that individual resulted in 87/99 (88%) agreements, including instances where both the tool and the physician agreed the patient would and would not benefit from CGM. Most disagreements occurred when the tool suggested benefit, but the physician had not recommended CGM. Of those scored as "may confer benefit" by the tool, 5/13 (38%) received a CGM. Five tool questions were significantly associated with CGM benefit using chi-square statistics. The success of the tool's pilot testing exemplifies the benefit of utilizing the CHI CRN to ensure that all stakeholder perspectives are considered and reflected in the creation of the tool. This tool provides a structured framework for facilitating clinician-family discussions about CGM use, with the potential to improve HI management and enhance quality of life for people with HI and their families.

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P553

JOINT1370

MEN2B syndrome, the impossible clinical challenge and how genomic newborn screening will improve morbidity and mortality

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Background
MEN2B syndrome, due to pathogenic M918T variant in the *RET* proto-oncogene, carries very high morbidity and mortality with >20% of patients deceased by 25 years of age. Larger cohort studies have demonstrated that thyroidectomy performed <1 year of age drastically changes morbidity and likely mortality. However, identifying these children is clinically extremely difficult due to the constellation of non-specific gastrointestinal, musculoskeletal and endocrine symptoms, which results in the mean age of diagnosis ~13 years of age by which time medullary thyroid carcinoma has metastasised.
Aims
We advocate that including the M918T variant in *RET* gene in universal newborn screening programs and careful exclusion of intestinal ganglioneuromatosis on histopathology is the only way to enable earlier identification of affected children, which will improve clinical outcomes and provide an opportunity for thyroidectomy within the first year of life.
Results
We present a 5-patient case series with excellent clinical photography and histopathology images, including subglottic mucosal ganglioneuromatosis which has not previously been described.
Conclusion
We highlight that there are unique clinical features identifiable in the first 12 months of life of severe, persistent chronic constipation and alacrima (tearless crying) but often their significance is not recognised. There are also identifiable histopathological features of intestinal ganglioneuromatosis on gastrointestinal biopsies with adequate submucosa when the reviewing pathologist maintains a broad differential diagnosis mindset and isn't blinkered by only excluding Hirschsprung disease.

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P554

JOINT2268

Altered neuronal function and impaired cognition among healthy people with different cortisol levels based on resting-state fMRI analysis

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Background
Higher levels of cortisol have been observed in persons with cognitive decline and dementia. However, studies investigating cognitive function among healthy people with different cortisol levels are scarce.
Objective and methods
To evaluate neurocognitive function among healthy people with different cortisol levels, 241 healthy people with a morning serum cortisol level <300 umol/l were recruited. Based on serum cortisol level tertiles, voluteers were divided into three groups. All volunteers underwent a battery of validated neuropsychological tests and rest-state function MRI (rs-fMRI).
Results
Adults in high tertiles of serum cortisol displayed a significantly decreased score on MoCA, compared to those in the middle and low tertiles($P < 0.05$). Performance on delayed recall and visuospatial and executive functions domains gradually deteriorated with increases in serum cortisol levels(All $P < 0.05$). Among rs-fMRI parameters, no significant difference was observed in voxel-based morphometry (VBM). And meanwhile, mean amplitude of low-frequency fluctuations (mALFF) significantly decreased in the middle occipital gyrus, inferior occipital gyrus, angular gyrus and superior parietal gyrus among adults in high tertiles of serum cortisol, compared to the other two groups.
Conclusion
We suggest that cortisol level might be associated with cognition function among healthy people.

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P555

JOINT2539

Which algorithm for antenatal management of disorders/differences of sex development? PECAN-VDG retrospective study of lyon multi-disciplinary prenatal diagnosis center experience

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Context
Detection of Differences of Sex Development (DSD) in the prenatal period is increasingly frequent, thanks to improved ultrasound techniques. As no consensus exists regarding prenatal management, we report our practice for suspected isolated DSD referred to our three Multidisciplinary Centers for Prenatal Diagnosis (MCPD) over a period of 10 years.
Material and methods
All women referred for isolated ultra-sonographic suspicion of DSD to our MCPD between January 2013 and December 2022 were included; the data collected were pregnancy course, prenatal ultrasounds, prenatal hormonal and genetic investigations and neonatal outcome. We considered DSD isolated if there is no other suspected malformation at the time of referral to the MCPD, except for minor cardiopathy, renal pyelic dilatation, or intrauterine growth restriction (IUGR). Statistics are descriptive with percentages and medians (Interquartile range, IQR).
Results
71 patients were referred to the MCPD for a suspected isolated DSD, of which 57 were confirmed and followed by the experts. There were 13 pregnancies achieved by assisted reproductive technology (22. 8%) and 10 multiple pregnancies (17. 5%). For each multiple pregnancy, only one foetus was concerned by DSD. We performed SRY testing on maternal blood and prenatal invasive explorations on 10 (17. 5%) and 34 (59. 6%) mothers, respectively. Twenty-six (76. 5%) hormonal analyses, 22 (64. 7%) biochemical analyses and 34 (100%) genetic tests were performed on amniotic fluid. The genetic analyses encompassed karyotype (100%), CGH array (67. 6%), DSD panel sequencing (14. 7%) and targeted gene analysis (35. 3%). Among our 57 suspected DSD, 42 were confirmed at birth and 2 after medical termination of pregnancy (for X-linked mental retardation or extreme IUGR), 3 were invalidated before birth, 2 were epispadias, 6 false positives, and 2 false negatives. At birth, 23 newborns (52. 3%) had intrauterine growth retardation (IUGR), and 23 (52. 3%) were preterm, including 14 IUGR and 2 induced premature births by amniocentesis. Genetic diagnosis was made in 13 cases, including 5 prenatally, out of them 3 diagnosis involving impaired intellectual prognosis.
Conclusion
Prenatal management of suspected DSD seems to be relevant and requires expert counselling to prepare the birth of DSD-newborns. Out of 57 patients, three exhibited a pathological condition with an altered neurological prognosis. Further prospective multicenter studies are necessary to confirm our Results and formulate recommendations for the prenatal management of DSD.

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P556

JOINT1735

Impact of in utero exposure to sesamol on the folliculogenesis and metabolism in F1 female offspring rats

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During last decades, diets rich in vegetables and seeds have grown in popularity. However, these so-called healthy diets can contain phytoestrogens which are potential endocrine disruptors. As hormonal fluctuations play a crucial role in genital tract differentiation, the fetal development represents a major period of vulnerability to endocrine disruptors. Sesamol, a phytoestrogen derived from sesame seeds, has a similar chemical structure to natural estrogen, enabling it to bind to estrogen receptors. By crossing the placental barrier, sesamol could disturb the hormonal balance of the foetus and interfere with the metabolism and the development of reproductive organs. The aim of this study is to investigate the effects of prenatal exposure to sesamol on the folliculogenesis and metabolism in F1 female offspring rats. From the 14th to the 19th day of gestation, pregnant female Sprague-Dawley rats were force-fed with different doses of sesamol (30 or 100 mg/kg/day). On the 4th day of post-natal life, female offspring rats were sacrificed to study reproductive (ovaries) and metabolic (liver, pancreas and kidneys) organs by histological analysis. Morphometric analysis of ovaries revealed that in utero exposure to sesamol enhanced the rate of apoptosis in oocytes present in primordial follicles, resulting in a 2-fold increase in the number of atretic follicles. However, the treatment does not affect the relative

proportion of primordial, primary and secondary follicles, and has no impact on the proliferation rate of follicular and thecal cells assessed by BrdU labeling. Concerning the study of metabolism, no major morphological alteration was observed in the kidneys of animals exposed to sesamol. However, the morphometric assessment of cell proliferation rate by anti-BrdU immunohistochemistry showed a significant decrease in the number of S-phase cells in the renal inner medulla. Moreover, a significant decrease in body weight was observed in animals exposed in utero to sesamol. Further analysis of the pancreas (anti-insulin and anti-glucagon IHC) and liver (anti-BrdU IHC, lipids accumulation) are in progress to fully understand this decrease in body weight. In conclusion, the present results indicate that sesamol seems to have a negative impact on the development of female gonads, which could lead to fertility dysfunctions in adulthood. We plan to study in greater detail the mechanisms by which sesamol increases follicular atresia and its impact on general metabolism.

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P557

JOINT767

Hypoglycemia to hyperglycemia: the clinical spectrum of ABCC8 gene variants

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Introduction
Genetic variants in the *ABCC8* gene, which encodes the sulfonylurea receptor 1 (SUR1) subunit of the ATP-sensitive potassium channel in pancreatic β-cells, have been associated with various clinical presentations, including hyperinsulinemic hypoglycemia (HH), transient or permanent neonatal diabetes mellitus (NDM), and maturity-onset diabetes of the young (MODY). The present study aims to evaluate the relationship between clinical presentations and the different variants detected in the *ABCC8* gene.
Methods
The clinical, biochemical, and molecular data of patients diagnosed with HH, NDM, MODY, or insulin-dependent diabetes and managed at our pediatric endocrinology clinic between 1990 and 2024 were retrospectively reviewed. Only patients with identified *ABCC8* gene variants were included in the analysis.
Results
The study analyzed 18 cases, comprising 12 with HH (Cases 1–12), 4 with permanent NDM (Cases 13–16), and 2 with MODY (Cases 17–18). Among the HH cases, 16. 6% ($n = 2$; Cases 1 and 2) had a histological diagnosis consistent with focal HH. Case 1, harboring a heterozygous c. 4114C>T(p. Gln1372Ter) variant, achieved remission following lesion resection. Case 2, with a heterozygous c. 2041-25G>A variant classified as a variant of uncertain significance (VUS), underwent subtotal pancreatectomy and achieved complete recovery. Autosomal recessive diffuse HH was identified in 33. 3% ($n = 4$; Cases 3–6), with variants including c. 3512del(p. Leu1171fs), c. 3643C>T(p. Arg1215Trp), c. 96C>A(p. Asn32Lys), and c. 2041-21G>A. Autosomal dominant diffuse HH accounted for 33. 3% ($n = 4$; Cases 7–10), associated with variants c. 3418G>T(p. Glu1140Ter), c. 4135G>A(p. Gly1379Ser), c. 1792C>T(p. Arg598Ter), and c. 4612-2A>G. Compound heterozygous variants were detected in 16. 6% ($n = 2$; Cases 11 and 12). Post-pancreatectomy diabetes developed in 25% of HH cases ($n = 3$; Cases 5, 6, and 7). Among the NDM cases, the identified variants included c. 2476C>T(p. Arg826Trp) (Case 13), c. 1144G>A(p. Glu382Lys) (Cases 14, 15), and compound heterozygous c. 1670T>G(p. Ile557Arg)/c. 3431G>T(p. Arg1145Leu) (Case 16). In the MODY group, Case 17 had a heterozygous c. 1616A>G(p. Tyr539Cys) variant, while Case 18 had a heterozygous c. 946G>A(p. Gly316Arg) variant.
Conclusion
Variants in the *ABCC8* gene result in diverse clinical presentations, ranging from severe hypoglycemia to diabetes. In HH cases, modulating genetic and environmental factors may influence disease progression, with the potential for hyperglycemia in the long term due to β-cell dysfunction or surgical interventions. Early identification through molecular analysis is critical for disease progression, preventing complications, and personalized treatment approaches.

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P558

JOINT1036

Dasiglucagon treatment consistently reduces hypoglycemia assessed by continuous glucose monitoring in children with congenital hyperinsulinism across subgroups

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Background/Objectives
Congenital hyperinsulinism(CHI) is the most common cause of severe recurrent hypoglycemia in children. Early treatment is necessary to limit the risk of neurologic/developmental sequelae. Dasiglucagon is a glucagon analog suitable for continuous subcutaneous infusion shown to raise blood-glucose in a dose dependent manner. A 2-part phase 3 trial evaluated the efficacy/safety of dasiglucagon as add-on to standard-of-care(SoC) in children with CHI ages ≥3 months-<12 years with persistent hypoglycemia comparing dasiglucagon+SoC vs SoC only. The trial reported lower rates of SMPG-detected hypoglycemia in both groups compared to baseline, w/o statistically significant difference, but clinically meaningful reductions in all CGM-recorded measures of hypoglycemia for dasiglucagon+SoC (post-hoc analyses). Dasiglucagon was well tolerated with a safety profile in line with class effects of glucagon. Evaluation of effect on CGM percent time in hypoglycemia<70 mg/dL for consistency across different subgroups is presented here.
Methods
Evaluation of CGM percent time in hypoglycemia<70 mg/dL across subgroups was performed for the controlled part of the trial comparing dasiglucagon+SoC vs SoC. The statistical analysis model was the same as that applied in the original trial, a generalized linear regression model with normal distribution and log link function with the addition of the categorical subgroup variable and an interaction term between treatment group and the specific subgroup variable.
Results
Table displays treatment ratios for CGM percent time in hypoglycemia<70 mg/dL by subgroup. Overall effects were consistently in favor of dasiglucagon based on point-estimates for all subgroups, except for the age group of 6-12years, where there was only 1 patient in this group on dasiglucagon. Interaction *P*-values were low for some subgroups.
Conclusions
Dasiglucagon treatment in children with CHI has reported clinically meaningful reductions in CGM-recorded measures of hypoglycemia. Subgroup analysis for CGM-percent-time in hypoglycemia<70mg/dL supports consistent efficacy across subgroups. Due to the small size of the subgroups, results should be interpreted with caution. These data support the efficacy and safety of dasiglucagon as a potential novel therapy for CHI.

Subgroup_at_baseline		N(Dasiglucagon+SoC:SoC_Only)	TreatmentRatio[95%CI] Dasiglucagon+SoC/SoC_Only
All subjects		15:16	0. 53[0. 36-0. 79]
Sex	Female	5:10	0. 50[0. 29-0. 87]
	Male	10:6	0. 74[0. 41-1. 32]
Age_Group	1-<24months	6:3	0. 21[0. 09-0. 46]
	2-<6years	8:9	0. 78[0. 54-1. 13]
	6-12years	1:4	1. 91[1. 08-3. 39]
Race	White	12:9	0. 62[0. 43-0. 90]
	Black/African_American	2:1	0. 26[0. 03-1. 95]
	Asian	1:2	0. 16[0. 00-44. 47]
Baseline_weight	5-<10kg	3:1	0. 13[0. 03-0. 61]
	10-<20kg	7:7	0. 67[0. 43-1. 05]
	>=20kg	5:8	0. 64[0. 36-1. 15]
Baseline_diazoxide_use	Yes	6:4	0. 89[0. 64-1. 24]
	No	9:12	0. 31[0. 17-0. 57]
Baseline_somatostatin_use	Yes	8:11	0. 35[0. 17-0. 69]
	No	7:5	0. 79[0. 50-1. 23]
Any_pancreatectomy_at_baseline	Yes	4:7	0. 94[0. 55-1. 61]
	No	11:9	0. 39[0. 23-0. 66]
Baseline_CGM% time>70mg/dL	3. 8%-<14%	3:5	0. 42[0. 08-2. 23]
	14%-<17%	4:3	0. 67[0. 35-1. 29]
	17%-<30%	4:4	0. 55[0. 24-1. 23]
	30%-<48%	4:4	0. 39[0. 20-0. 75]

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P559

JOINT2699

Update on genetic etiology in vietnamese children with congenital hyperinsulinism during 15 years (2010-2024) at tertiary pediatric center

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Introduction

Congenital Hyperinsulinism (CHI) is the most common cause of hypoglycemia related to inappropriate insulin secretion. More than 30 genes have been identified as contributors to persistent hyperinsulinism, with mutations in the K-ATP channel genes (*ABCC8* and *KCNJ11*) being the most frequently observed in children with severe and persistent forms of the disease.

Aims

To elucidate the genetics of all probands with suspected CHI in Vietnam registered over the past 15 years.

Methods

We included 176 probands with CHI from Vietnam. All probands were screened for variants in the *ABCC8* and *KCNJ11* genes. Almost patients without mutations in the K-ATP channel genes, next-generation sequencing employing a panel of 28 CHI-related genes was used for analysis, including *ABCC8, AKT2, CACNA1C, CACNA1D, CREBBP, DNTTIP1, EP300, FOCAD, FOXA2, GCK, GLUD1, GPC3, HADH, HNF1A, HNF4A, INSR, KCNJ11, KDM6A, KMT2D, MAFA, AGEL2, NSD1, PHOX2B, PMM2, RNF10, SLC16A1* and *TRMT10A* genes and non-coding regulatory region of *HK1*. Genetic analysis was performed at the UK University of Exeter Clinical Laboratory.

Results

The genetic cause was identified in 120 out of the 176 CHI patients (68. 1%): 111 had mutations in the K-ATP channel genes (92. 5%), four in *GLUD1*, three in *HNF4A*, one in *GCK*, and one in *KMT2D* (associated with Kabuki syndrome). As a result, our findings confirm the predominant role of ATP-sensitive potassium channels in the pathogenesis of CHI in Vietnamese patients, with the remaining cases likely attributable to other factors. Furthermore, the *ABCC8* gene was found to have the most common pathogenic variants in the K-ATP channel (*ABCC8* ($n = 103$) and *KCNJ11* ($n = 8$)). We also discovered that 55 out of the 111 patients with mutations in the K-ATP channel were either homozygous or compound heterozygous, accounting for half of the cases. We identified 33 distinct variants, with c. 3403-1G > A and c. 2057T > C being the more common mutations in the K-ATP channel genes. One proband had a compound heterozygous pathogenic ABCC8 variant, with one variant inherited from the father (c. 3403-1G > A) and the other (c. 1543G > T) a mutation not identified in the mother. This suggests two possibilities: de novo mutation or germline mosaicism in the mother.

Conclusion

Genetic analysis revealed mutations in over 68 % of the CHI patients. *ABCC8* mutations are the most frequent cause of CHI in Vietnam. Half of the patients with mutations in the K-ATP channel were either homozygous or compound heterozygous, which means the variant can come from the mother, father, or be de novo.

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P560

JOINT3151 Collaborative global advocacy to improve the lives of children and families with congenital hyperinsulinism

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Background

Hyperinsulinism (HI) is a rare, life-threatening condition affecting 1 in 28, 000 babies each year. HI results in the over secretion of insulin from pancreatic beta cells, leading to persistent severe hypoglycemia. Hypoglycemia can lead to seizures, developmental delay, visual impairment and death. Limited treatment options exist. Congenital Hyperinsulinism International (CHI) is an international non-profit organization committed to improving the lives of children and families with HI. CHI's Collaborative Research Network (CRN) consists of 62 members and advisors from 17 countries, rare disease advocates, health care providers and researchers united around the common goal of improving the lives of people impacted by HI. Through research and advocacy, the CRN is focused on the attainment of timely and accurate diagnoses, supporting new evidence-based treatments and cures, standardizing clinical guidelines, and facilitating improved access to care.

Objective

The need for an advocacy statement arose from discussions with > 600 parents, young people, and health care providers from around the world. Discussions and interactions with families uncovered basic aspects of care not generally available in many regions and countries. Through the CHI CRN an advocacy working group was formed with the mission of creating a universal advocacy statement for persons affected by HI.

Methods

Through several meetings, both in-person and virtually, CHI CRN members representing 5 countries met to produce an advocacy statement that could be utilized to assure optimal outcomes for people impacted by HI. The statement was approved by the entire CHI CRN.

Results

The finalized advocacy statement will be utilized to convey the medical and developmental needs of children with HI, urgency of timely diagnosis, access to medications and blood glucose testing supplies. There is also a focus on access to radiologic and surgical expertise, which in some cases can lead to a cure. Consultation with one of the world's eight CHI Centers of Excellence (COEs) is emphasized. The need for transitional care for young adults is highlighted. The CHI CRN Advocacy Statement and List of Essential Medical Care, Medication, Supplies and Services is available on the CHI website to be used by Healthcare advocates, embassies, insurers, family members and health care providers as they navigate and advocate for people living with hyperinsulinism. This approach to advocacy can be a template for others working with rare diseases.

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P561

JOINT2941

Lower FT4 levels are associated with increased risk of C-section or assisted delivery

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Background and Objective

Thyroid function tests (TFT) during pregnancy differ from extra-gestational levels, particularly during the first trimester. It is unknown if there is an association between thyroid hormone levels during the three trimesters of pregnancy and mode of delivery. We compared thyroid hormone levels with the relative prevalence of Caesarian section or assisted vaginal delivery (CSA) vs normal vaginal delivery (NVD).

Methods

Delivery and newborn data from the database of Hadassah Medical Center, Jerusalem, were combined with thyroid function tests taken from the same women during pregnancy in the Clalit HMO, Jerusalem district. TSH, FT3 and FT4 z-scores were calculated according to biweekly reference levels from the same population. The risk of having FT3 or FT4 lower than 1. 5 z-score and the median TSH was calculated for the CSA vs NVD groups.

Results

There were 17, 512 mother–child pairs, 13030 were NVD and 4512 were CSA. There was a higher prevalence of FT4 z-scores below -1. 5 in the CSA groups throughout all trimesters: first trimester: 7% vs. 3. 3% ($P = 0. 001$), second: 7. 3% vs. 2. 9% ($P = 0. 001$), third: 5. 9% vs. 2. 3 ($P = 0. 039$). For median TSH z-scores there was also a significant difference by mode of delivery, for CSA vs. NVD the median TSH were, by trimesters, respectively as follows: first: 1. 54miu/l vs. 1. 59 ($P = 0. 07$), second: -1. 74 vs. 1. 76 ($P = 0. 001$) and third: 1. 98 Vs. 2. 11 ($P = 0. 04$)

Conclusion

There is an association between gestational thyroid hormone levels and mode of delivery. We speculate that lower FT4 levels during pregnancy may be associated with lower smooth-muscle tone causing poorer uterine contractions. Further research is needed to better understand the clinical significance of this.

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P562

JOINT2032

Prevalence and predictors of small for gestational age neonates and endocrinological follow-up: a retrospective analysis of 2018 birth cohort

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Background
SGA status is an important indicator of neonatal health, with potential long-term implications for growth and development. The aim of this study is to analyze the prevalence and predictors of Small for Gestational Age (SGA) neonates by weight (SGAW) and length (SGAL) in a cohort of newborns in 2018 and their endocrinological follow-up.
Methods
A total of 1505 newborns were included in this retrospective study, with complete data obtained for 1440 neonates. SGA was determined as weight and/or length <-2 SDS according to neonatal Italian Charts. Multivariate linear regression was used to analyze factors influencing neonatal weight and length, while logistic regression was performed to identify predictors of SGA status.
Results
The prevalence of SGAW was 1. 9% (28/1504), while SGAL was 3. 0% (43/1440). A total of 15 neonates (14 term, 1 preterm) were SGA for both weight and length, 13 neonates (11 term, 2 preterm) were SGA for weight only, and 28 neonates (23 term, 5 preterm) were SGA for length only. Logistic regression identified gestational age ($\beta = 0.73$; $p < 0.001$), neonatal length ($\beta = -0.65$; $p < 0.001$), placental weight ($\beta = -0.01$; $p < 0.001$), and male sex ($\beta = 1.62$; $p < 0.001$) as the main predictors of SGAW. When removing neonatal length from the model, placental weight ($\beta = -0.02$; $p < 0.001$) and twin status ($\beta = 4.83$; $P = 0.010$) were the only predictors of SGAW. Logistic regression identified gestational age ($\beta = 0.83$; $p < 0.001$), neonatal weight ($\beta = -0.055$; $p < 0.001$), and number of previous deliveries ($\beta = 0.57$; $P = 0.018$) as the main predictors of SGAL. When removing neonatal weight from the model, placental weight ($\beta = -0.01$; $p < 0.001$), twin status ($\beta = 4.79$; $P = 0.001$), and type of delivery ($\beta = 1.06$; $P = 0.027$) were the only predictors of SGAL. Only 9% of SGA neonates underwent an endocrinological follow-up, and 2% qualified for growth hormone therapy.
Conclusions
This study confirms the importance of gestational age, placental weight, and twin status as key determinants of neonatal growth. The findings highlight the higher risk of SGAW and SGAL in twin pregnancies and in cases of lower placental weight. Additionally, the low percentage of SGA neonates undergoing endocrinological follow-up underscores the need for improved postnatal monitoring. The small proportion of SGA neonates qualifying for growth hormone therapy aligns with previous findings.

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Growth Axis and Syndromes

P17

JOINT139

Early life growth is important for pubertal growth and adult height

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Background
The early growth period, spanning from conception to approximately two years of age, is known to play a critical role in determining long-term health outcomes. We hypothesized that growth during early life could explain variations in pubertal growth, pubertal timing, and adult height.
Methods
The study was conducted on growth data from the population-based Swedish longitudinal $GrowUp_{1974\&1990}$ Gothenburg cohorts. A subgroup of 4,700 individuals (50% male, *Associations between birth characteristics, pubertal timing and adult height. Skogastierna et al Act.Ped 2024*), including participants across all gestational ages and birth sizes, was analyzed. Growth patterns were assessed using *QEPS* variables (*Modelling individual longitudinal human growth from fetal to adult life – QEPS I. Nierop et al J Theor Biol 2016*), which were examined in both univariate and multivariate linear regression models, stratified by sex; *Q*-function throughout all growth periods, and specific *E*- and *P*-functions, for early life growth and pubertal growth (*Insight into human pubertal growth by applying the QEPS growth model. Holmgren et al BMC Pediatr. 2017*), respectively.
Results
Multivariate analysis showed that early life growth accounted for 37–38% of the variation in specific pubertal growth but had a small influence on pubertal timing. Adult height variability was primarily explained by birth size (57–62%), early life growth (66–67%), and childhood growth (65–69%), with mid-parental height contributing to a lesser extent (35–39%). Additionally, height changes during puberty accounted for 8–9% of the variation in adult height.
Conclusion
These findings suggest that early life growth has a significant impact on pubertal growth and adult height but is less associated with the timing of pubertal growth.

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P18

JOINT2816

Genetic etiology of persistent short stature in chinese children born small for gestational Age

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Objective
Approximately 10%–15% of small for gestational age (SGA) infants fail to achieve catch-up growth by age 2 years, resulting in persistent short stature (SGA-SS). The genetic mechanisms of this condition remain poorly understood. This study aimed to systematically delineate the genetic landscape of Chinese SGA-SS children through integrated clinical phenotypes and multi-omics data, and to assess the diagnostic utility of a tiered genetic testing strategy.
Methods
A cohort of 97 SGA-SS children (birth length/weight < 10th percentile, height standard deviation score [Ht-SDS] < -2 s.d./3rd percentile at 2 years) underwent a stratified genetic evaluation. Subjects with a Netchine-Harbison Clinical Scoring System (NH-CSS) $\geqq 4$ or strong clinical suspicion of Silver-Russell syndrome (SRS) underwent first-line methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA). Those with NH-CSS ≤ 3 underwent whole-exome sequencing (WES). Undiagnosed cases were further investigated via cross-validation (reciprocal MS-MLPA and WES testing). All variants were classified according to ACMG guidelines and confirmed via Sanger sequencing. A cohort of 57 pediatric patients receiving 12-month growth hormone (GH) therapy was stratified by genetic testing results into two subgroups: a genetically positive cohort ($n=22$) and a genetically negative cohort ($n=35$).
Results
Genetic etiologies were identified in 41.2% (40/97) of patients. The pathogenic spectrum comprised:
1. Intracellular signaling pathways/cellular processes defects (14/40, 35%), involving 12 genes (*PTPN11, KMT2D, MAP2K1, SRCAP, CHD7, BPTF, RAD21, KDM5C, NSD2, DYRK1A, ACTB, FAM111A*).
2. Imprinting disorders 25% (10/40, 25%), including 9 SRS (11p15 hypomethylation/UPD7) and 1 Temple syndrome (UPD14).
3. 6 cases harbored variants in Paracrine factors/extracellular matrix-related gene variants (6/40,15%): *ACAN, ROR2, NPR2, FGFR3*.
4. Copy number variants (CNVs) (6/40, 15%).
5. Chromosomal abnormalities (4/40, 10%)
Notably, three novel pathogenic variants (*ROR2* c.1384C>T, *ACTB* c.1104delC, and *DYRK1A* c.1702_1705del) were identified. The genetically diagnosed group exhibited more severe postnatal growth retardation (baseline Ht-SDS: -3.49 ± 1.18 vs. -2.63 ± 0.692, $P < 0.01$), though GH therapy response (ΔHt-SDS) showed no intergroup difference ($P=0.694$).
Conclusion
This multi-omics investigation achieved a 41.2% diagnostic yield in Chinese SGA-SS, revealing intracellular signaling/cellular process and imprinting disorders as predominant mechanisms. Our tiered diagnostic approach (methylation analysis combined with WES) optimized detection efficacy, while three novel variants expanded the mutational spectrum. Despite genotype-specific growth patterns, GH responsiveness appears independent of specific genetic etiology, though larger validation studies are needed.

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P563

JOINT1473

One year treatment with anastrozole increases predicted adult height in peri-pubertal boys with aggrecan deficiency

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Background
Aggrecan is the primary proteoglycan of the cartilage growth plate and is encoded by the ACAN gene. Patients with heterozygous pathogenic variants in ACAN often present advanced skeletal maturation and premature epiphyseal fusion leading to short stature. Recently, mutations in the ACAN gene have been recognized as a major cause of idiopathic short stature. Aromatase inhibitors (AI) have been shown to delay skeletal maturation and improve height in patients with idiopathic short stature.
Objective
with the aim of preventing inappropriate skeletal maturation, we evaluated the effect of short-term treatment with an AI on growth, bone age and pubertal maturation in a group of peripubertal boys with ACAN mutations.
Patients and Methods
7 boys aged 9. 5-13. 1 years and confirmed mutation in the ACAN gene were included in the study. Their mean (±SD) height SDS was -1. 58±0. 79 (range from -2. 83 to -0. 45), bone age 10. 9-13. 6 years, and mean target height -1. 25± 0. 76 (range from -1. 71 to 009). Their testicular volume ranged from 2 to 12 ml. All patients were treated with anastrozole at the dose of 1 mg/daily for one year. BA and predicted adult age (PAH) were evaluated using the Bailey&Pinneau method. Informed consent was obtained from all parents or the legal guardians.
Results
After 1 year height SDS increased in 4/7 children (from -0. 21 to -0. 92, from -2. 83 to -1. 92, from -1. 01 to -0. 33 and from -0. 45 to -0. 17) did not change in 2 (from -1. 56 to -1. 54 and from -2. 27 to -2. 20) and worsened in 1(from -1. 77 to -2. 04). Bone age did not progress inappropriately in any of the subjects (range 11. 6-13. 9 years). PAH significantly increased in all subjects from a mean (±SD) of -2. 47±1. 22 to -1. 760±. 82 SDS ($P < 0.005$). Puberty progressed in 6/7 children with mean testicular volume increasing from 7. 8±3. 2 to 13. 3±6. 1 ml ($P < 0.01$) and remained unchanged in 1 (2 ml). Treatment was well tolerated and did not induce noticeable side effects in any of the subjects
Conclusions
Our preliminary results indicate that treatment with AI prevents excessive bone maturation in boys with Aggrecan deficiency in the peripubertal period. This translates in sustained growth and increase in PAH. Long-term follow-up is needed to verify the effect of AI on adult height in these patients.

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P564

JOINT2829

Macimorelin test: a safer and reliable alternative to the gold standard insulin tolerance test

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Introduction
The insulin tolerance test (ITT) remains the 'gold standard' test for assessing growth hormone (GH) deficiency (GHD) in adults. However, this test is labour and resource intensive. Furthermore, ITT causes unpleasant symptoms resulting from the hypoglycaemia which is required to stimulate growth hormone secretion. Due to safety concerns, the use of ITT in the UK has been limited to a few endocrine centres with expertise and confidence in performing this test. Consequently, some patients who likely have GHD are not being offered appropriate and timely assessment and treatment. Macimorelin, a novel orally administered GH-releasing peptide is a safe alternative with diagnostic accuracy comparable to ITT.
Aim
The aim of this audit is to compare the real-life experience of performing ITT compared with macimorelin test (MT) in terms of resource requirements, cost and adverse events reported by each patient who have undergone these tests.
Methodology
This is a retrospective review of 12 ITTs, from January to December 2019, and 12 MTs, from March 2023 to February 2024, performed in a tertiary endocrine centre in Birmingham, UK.
Findings
The average time for completing an ITT was 199 minutes (range= 189-320) compared with 134 minutes (range= 100-165) for MT. All 12 patients who had an ITT experienced adverse effects such as dizziness, feeling unwell and clammy whilst only 1 patient who underwent MT experienced the adverse effect of dizziness. ITT required significant human and material resources including supervision from a medical practitioner, at least 2 experienced nursing staff, cardiac monitoring and hypoglycaemia rescue equipment which were not all required for MT. The overall cost of an ITT was around 700 Euros compared with 420 Euros for MT.
Discussions
ITT, whilst considered the gold-standard test for diagnosing GHD, requires substantial human and material resources and is associated with significant adverse effects which prevents its widespread utilisation in clinical practice. Additionally, the overall cost of performing an ITT, taking into account the time and resources required, is considerably more compared with MT.
Conclusion
The availability of a safer, quicker and more-tolerable GH stimulation test like MT, should no longer prevent the provision of appropriate and timely diagnosis and treatment of patients with GHD. Considering both the financial and personal burden of performing an ITT, MT should be considered as a reliable alternative as it is easy and quick to perform, associated with minimal adverse effects and has a diagnostic accuracy comparable with ITT.

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P565

JOINT1993

Treatment with anastrozole alone or with GH increases final height in pubertal boys with short predicted adult height- real-world data

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Context
Short-statured mid-pubertal boys with predicted adult height (PAHt) below the third percentile present a significant therapeutic challenge. Aromatase inhibitors (AI) delay estrogen-driven epiphyseal fusion and possibly enhance adult height (AHt).
Objective
To assess the efficacy of AI treatment on AHt in mid-pubertal boys with a short PAHt due to advanced bone age (BA) or idiopathic short stature (ISS).
Design
Retrospective study.
Setting
Tertiary pediatric endocrine referral center.
Patients and methods
Two groups of mid-pubertal boys treated with AI were studied: 27 boys with fast puberty compared to matched untreated controls and 16 boys with ISS treated with GH and AI compared to those treated with GH only. Anthropometric measurements, BA and PAHt, were tracked. AHt was compared across groups.
Main outcome measures
Achieved AHt in AI-treated boys vs controls and the PAHt.
Results
Median AI treatment duration was 2. 8 for AI only and 2 years for the GH+AI groups. Throughout treatment, AI-treated groups showed similar height gain compared to their controls, a decrease in BASDS (AI only: $P = 0.009$; GH+AI: $P = 0.029$), and increased PAHt (AI only: $P = 0.003$; GH+AI: $P = 0.037$). AI-treated groups achieved taller AHt than their controls (AI only:166. 6±3. 1 vs. 163. 4±1. 3cm, $P = 0.003$; GH+AI:167. 3±6. 1 vs. 164. 9±3. 5cm, $P = 0.194$), and a more significant difference between AHt and PAHt groups (AI only: $P = 0.001$; GH+AI: $P = 0.050$).

Conclusions
AI treatment extends the growth period, resulting in an AHt surpassing initial predictions. Our findings underscore the potential of AI treatment in mid-pubertal boys with a short PAHt due to advanced BA or those with ISS treated with GH.

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P566

JOINT1462

Effect of a short-term course of transdermal testosterone on growth, puberty and adult height in boys with constitutional delay of growth and puberty (CDGP)

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Background
CDGP is one of the commonest reasons for referral to a pediatric endocrinologist. Boys with CDGP are shorter than their peers and pubertal onset is delayed. The differential diagnosis between CDGP and hypogonadotropic hypogonadism can be challenging. Although it is considered a self-limiting condition, boys with CDGP may present psychosocial burden and need treatment with testosterone to induce puberty, accelerate growth and improve quality of life. Transdermal administration of testosterone (TT) has been shown to be effective, but little is known on the long-term effects of in boys with CDGP.
Study design
Retrospective study in a single tertiary center of pediatric endocrinology.
Patients and Methods
The clinical records of 40 patients with CDGP who completed a long-term clinical evaluation were retrospectively analyzed. At the start of treatment, their mean (SD) age was 14 (0, 8) y, mean bone age was 12. 3 (0. 6) y, mean height standard deviation score (HSDS) was -1. 93 (0. 7), mean height velocity SDS (HVSDS) was -3. 26 (1. 78), mean BMI SDS was -0. 8 (1. 1), mean target height SDS (THSDS) was -0. 5 (0. 6), mean testicular volume (TV) was 4. 6 (1. 0) ml, and mean T concentration was 65. 2 (36. 6) ng/dl. All known causes of delayed growth and puberty had been excluded. Informed consent was obtained from the patients and from their legal guardians. All subjects were treated with TT gel (2%) at the dose of 10 mg/day for 3 months. They were re-evaluated after 6 months and 1 year from the start of treatment and at the attainment of adult height (HV $<$ 2 cm/y).
Results
After 6 months mean HSDS was -1. 76 (0. 91), and mean TV was 7. 4 (3. 2 ml). After 1 y mean HSDS was -1. 55 (0. 78), TV was 11, 5 (3. 7 ml), and mean T concentration was 281 (103) ng/dl. Mean adult HSDS was -0. 5 (0. 8) at a mean age of 18. 9 (1. 1) y, with a mean TV of 11. 4 (3. 7) ml, mean T concentration of 433 (90) ng/dl, and mean BMI SDS was -0. 39 (0. 9). The mean increase in HSDS between treatment start and adult height was 1. 3 (0. 65). All subjects reached their genetic TH. Treatment was well tolerated and did not induce noticeable side effects.
Conclusions
This study shows that a 3 months course of TT accelerates growth and pubertal progression and has no detrimental effects on adult height.

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P567

JOINT1079

Genetic insights into short stature: an evaluation of clinical, hormonal, and genetic parameters in a real world paediatric cohort

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Aim
To assess the identification of genetic causes in children with short stature (SS) and to identify diagnostic patterns and inheritance in the real world.
Methods
A real world cohort referred for SS (n = 150; 91 males, height $<$-2 SD or short for parents) was grouped as: atypical Growth Hormone deficiency (GHD, n = 8), no genetic diagnosis (non-SGA, n = 49; SGA, n = 33), genetic diagnoses (GH-axis-related, n = 4; bone-related, n = 20; non-GH/bone-related, n = 14; possibly SS-related/VUS (variant-of-unknown-significance), n = 10), and pre-referral genetic diagnosis (n = 12). Typical GHD, Turner syndrome, and Constitutional Delay of Growth and Puberty were excluded.
Results
Boys' mean referral age was 6. 13 $\pm$ 4. 34 years and girls' 7. 10 $\pm$ 4. 2 years. Boys' mean referral height was -3. 03 $\pm$ 1. 29 SD and girls' -3. 19 $\pm$ 1. 37 SD. Genetic diagnosis was made in 33% of patients, plus 7% showed VUS. Missense variants prevailed in GH-axis- and bone-related gene variants, and copy-number-variations (CNVs) in the VUS-group. Predominant pathogenic gene variants were *CUL7* (4x, 2 siblings), *NPR2* (3x, 2 siblings), chromosome 14 hypomethylation (3x, 2 siblings), *SMAD4* (3x), *ATM* (2x, siblings), *DYRK1A* (2x), *CDC45* (2x, siblings), *H19* hypomethylation (2x). GH-axis-related genes included *PTPN11*, *BRAF*, *SOS1* and *IGF1R* variants. VUS included *SHOX* (3x), *ACAN*, *KMT2A*, *FGFR1*, *FGFR2*, *MNX*, 21q22. 2 duplication, 10q22. 2-23-3 duplication. Inherited variants prevailed in bone-related gene variants, de novo in non-GH/bone variants. Eleven boys and one girl had pre-referral diagnoses. Excluding those, gender did not affect genetic diagnosis likelihood ($p > 0.05$), nor did being SGA or having microcephaly (HC $<$-2SD). Genetic diagnosis likelihood was higher if height $\leq$-2. 5 SD vs height $>$-2. 5 SD (30% vs 23%). Patients with bone-related genetic variants had most severe SS (height SDS -3. 89 $\pm$ 2. 15 vs others -2. 97 $\pm$ 1. 11; P = 0. 0035), and higher BMI SDS (0. 27 $\pm$ 2. 03). Patients with GH-axis-related variants had the lowest BMI SDS (-2. 45 $\pm$ 0. 36; ANOVA P = 0. 035). Dividing IGF1 into quintiles, elevated IGF1 prevailed in GH-axis (25%) and bone-related (29%) diagnoses, while atypical GHD had most frequent low IGF1 (38%). Non-GH/bone diagnoses were more prevalent in those with microcephaly (17% of genetic diagnoses if HC $\leq$ 2 SDS), while bone-related diagnoses were more frequent if HC $>$ 2 SDS (20% of the genetic diagnoses).
Conclusions
Genetic testing is crucial for SS, including for mild SS (-2 to -2. 5 SD), enabling personalised care and potentially improving clinical outcomes. Bone-related gene variants are the leading cause for short stature, and affected patients are shorter, often with high IGF1, which requires further research.

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P568

JOINT318

Evaluation of the pharmacokinetics (PK), pharmacodynamics (PD), and safety of the new capsule formulation of LUM-201, an oral growth hormone secretagogue

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Objectives
The primary objectives were to evaluate the relative bioavailability (BA) between the tablet and capsule formulations, to assess the food effect (FE) on the BA of the capsule formulation, and to evaluate the safety and tolerability of the capsule formulation. Secondary objectives included evaluating the PK of the major metabolite of LUM-201 (M8) and the PD response (serum GH) to the new formulation.
Methods
Part 1 was a 4-sequence, 4-treatment, 4-period crossover study to determine the relative bioavailability of the tablet and the new capsule formulation. Part 2 was a 2-sequence, 2-treatment, 2-period crossover study to evaluate the food effect on the capsule formulation. Comparisons are reported as Dose-Normalized $AUC_{0\text{-inf}}$ ($DNAUC_{0\text{-inf}}$) and Dose-Normalized C_{max} (DNC_{max}).
Results
The new capsule formulation showed bioequivalence to the tablet formulation in terms of $DNAUC_{0\text{-last}}$ and $DNAUC_{0\text{-inf}}$. Compared with the 90 mg tablet dose, significant decreases in DNC_{max} were observed with 85. 3mg whole capsule (14. 1% lower), with 85. 3mg capsule contents in a dosing cup (20. 4% lower), or 85. 3mg capsule contents in banana puree (14. 4% lower). Food increased the C_{max} of LUM-201 by 64. 4% and $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ by 17. 8%. There was no significant effect of food on the PK parameters of the metabolite M8; the geometric least squares (GLS) mean ratio% (90% CI) for M8 C_{max} was 106. 30% (74. 20, 152. 20), and for $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$, the ratios were 96. 40% (82. 40, 112. 80) and 96. 50% (82. 70, 112. 50), respectively. Serum GH concentrations increased similarly across all dose formulation treatment groups. Regarding food

effect with LUM-201, the fed state reached C_{max} 30 min later than the fasted state (C_{max} of fed = 14. 10 ng/mL; C_{max} of fasted = 22. 18 ng/mL). Importantly, serum GH reached similar C_{max} values by 1. 5 h after dose regardless of fed state. Serum IGF-1 concentrations remained stable over time in both parts of the study. Safety and tolerability of LUM-201 were consistent with the established safety profile; no SAEs were reported.
Conclusions
Overall, the study demonstrated that the new capsule formulation of LUM-201 has a favorable investigational safety profile, is well-tolerated, and exhibits comparable bioavailability to the tablet formulation, with consistent PK parameters for the metabolite M8 and encouraging PD responses. The new LUM-201 capsule formulation filled with mini-tablets produces similar PK and PD results compared with the current tablet formulation and offers children & their caretakers a more flexible and user-friendly oral capsule formulation.

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P569

JOINT2599

The need for early reassessment in children with growth hormone deficiency

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Introduction
Diagnosing childhood-onset growth hormone deficiency (GHD) requires biochemical testing through provocative measures. Retesting in late adolescence or early adulthood is crucial to determine the need for continued recombinant human growth hormone (rhGH) treatment. Early retesting can prevent potential over-treatment of this condition.
Aim
We aimed to define the predictive criteria for children with GHD who may benefit from the reevaluation of GH status early in the course of rhGH treatment.
Methode
Seventy-five children with growth hormone deficiency were retested at least after one year of GH treatment. The initial clinical, laboratory characteristics and treatment response of those with a normal (GH $\geq$6. 7 ng/ml) and those with a subnormal response were compared.
Results
After retesting, 31 (41. 3%) patients had a GH response of $\geq$6. 7 ng/ml. The mean age at revaluation was 12. 1$\pm$3. 8 years and the mean duration of GH treatment was 4. 13$\pm$2. 4 years. Children with permanent GHD are significantly smaller at diagnosis (-3. 28 vs -2. 65 SDS), have a higher height gain (1. 99 vs 1. 33 SDS) and more MRI abnormalities ($P < 0.0001$). Biochemical parameters: IGF1 SDS at diagnosis, IGF1 at re-evaluation SDS, initial GH peak, re-evaluation GH peak, were all significantly lower in the permanent GHD group ($P < 0.0001$).
Dicussion
The present findings are in agreement with those previously reported by other groups, which demonstrated that the GH response to stimulation was found to be normalised in a number of patients diagnosed with GHD. The results of the present study carry significant clinical implications, in terms of both the accuracy of diagnosis and the efficacy of therapeutic decisions, with the objective of avoiding the cost and burden of long-term growth hormone (GH) treatment, the efficacy of which is uncertain.
Conclusion
Early retesting is recommended for paediatric patients with suspected growth hormone (GH) deficiency to ensure accurate diagnosis.

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P570

JOINT3638

Long-acting pegylated growth hormone in prepubertal children with turner syndrome: a 3-year multicenter study in China

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Background
Short stature is a major feature of Turner syndrome (TS) and requires long-term growth hormone (GH) treatment. We report the results of the 3-year trial evaluating the efficacy and safety of pegylated recombinant human growth hormone (PEG-rhGH) in the treatment of children with TS.
Methods
Eleven hospitals in China conducted this 3-year multicenter, open-label, randomized, negative-controlled, phase 2 and 3 clinical trial. First-year patients were randomized to 0. 1 mg/kg/week (LD), 0. 2 mg/kg/week (HD), and an untreated control group. In the second year, the control group was directly given 0. 2 mg/kg/week of PEG-rhGH, and the other children were adjusted according to the annual growth rate of each visit and IGF-1 SDS, and the maximum single dose should not exceed 0. 4 mg/kg/week. The study reported changes in the height standard deviation score (Δ HT-SDS), while observing drug-related side effects over time. The trial has been registered with ClinicalTrials. gov, number NCT03189160.
Findings
A total of 180 patients aged 2. 9 to 16. 2 years were randomly assigned to each study group. 144 patients completed 3-year-treatment. The average ΔHT-SDS from baseline after 3-year-treatment was 0. 92, 1. 32, 0. 77, respectively in the LD, HD and control group. There were statistically significant differences between any two of the three groups ($P < 0.0001$ for all). There were statistically significant differences in change in IGF-1SDS and IGF-1/IGFBP-3 from baseline after 3-year-treatment between any two of the three groups ($P < 0.0001$). Injection site atrophy occurred in 3 cases (1. 67%) and injection site sclerosis occurred in 1 case (0. 56%). No serious treatment-related adverse events There were no adverse events that resulted in discontinuation, dose reduction, or death. Laboratory test indicators at each visit after treatment did not show any special safety issues.
Conclusion
The study is the first a clinical trial for registration of long-acting rhGH for the treatment of short-statured children with TS. PEG-rhGH injection 0. 2 mg/kg/w can significantly improve HT-SDS of Turner syndrome, and had a good safety and tolerability.

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P571

JOINT1760

Gastrointestinal and nutritional challenges in silver-russell syndrome: changes in management and outcomes since 2015

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Background
Silver-Russell syndrome (SRS) is a rare (epi)genetic disorder characterized by severe intrauterine and postnatal growth retardation, relative macrocephaly at birth, prominent forehead, body asymmetry and early feeding difficulties. Primary molecular causes are loss of methylation within the 11p15. 5 imprinting control region (*H19/IGF2*) [11p15 LOM] and maternal uniparental disomy of chromosome 7, [upd(7)mat]. While feeding difficulties are a key feature of SRS, gastrointestinal manifestations were first described in 2014 by Marsaud *et al*. In 2015, the first international consensus on SRS was published, providing standardized recommendations. It remains unclear whether these recommendations have influenced management and subsequently the nutritional status and of patients born after this publication.

Objective
To assess the evolution of gastrointestinal and nutritional manifestations in SRS patients born after the 2015 international consensus and compare findings to previous data published in 2014 for patients followed in the same center.
Subjects and Methods
A retrospective study included 56 patients born after the consensus publication ($n = 42$ with 11p15 LOM and $n = 14$ with upd(7)mat). Nutritional status, gastrointestinal manifestations (feeding difficulties, gastroesophageal reflux disease [GERD], vomiting, constipation), and management (nutritional enrichment, requirement and modality of enteral nutrition, treatments) were analyzed.
Results
Nutritional status at 2 years old (BMI, weight-to-height ratio (W/H)), as well as the prevalence of GERD and vomiting, remained comparable to those reported by Marsaud *et al*. However, constipation prevalence was significantly higher (50% vs. 20%, $P < 0.05$). The proportion of patients requiring enteral nutrition remained stable (temporary nasogastric tube or gastrostomy), but the percentage of gastrostomy was significantly lower (10.7% vs. 21%, $P < 0.05$) than those reported in the previous study. Notably, patients with maternal uniparental disomy of chromosome 7 (upd(7)mat) underwent gastrostomy more frequently than those with 11p15 LOM (35.7 % vs 2.4%, $P < 0.05$). Additionally, 48.2% of patients received cyproheptadine treatment (an H1 antihistamine with an orexigenic effect) with a significant improvement in W/H ratio at six months following its introduction (+3.59%, 95% CI [1.069; 6.107]).
Conclusion
Gastrointestinal and nutritional issues remain a major concern in SRS. The implementation of the 2015 international consensus has led to improve identification of symptoms such as constipation, better nutritional status through targeted therapeutic strategies such as cyproheptadine (mentioned in the 2015 consensus as a therapy to evaluate) and/or early Growth Hormone therapy, and to a significant reduction of gastrostomy implemented, reflecting an evolution in clinical management.

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P572

JOINT3476

Does pubertal induction with transdermal or oral estrogen have an impact on uterine dimensions in Turner syndrome?

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Objective
Individuals with Turner syndrome (TS) often require estrogen replacement therapy (ERT) for pubertal induction. However, data on the optimal replacement regimen and effects on uterine growth are limited. This study aims to evaluate the impact of different routes of ERT on uterine dimensions in individuals with TS.
Methods
This is a single-center, cross-sectional study. It included 19 individuals with TS aged 15–30 (median age:22.3) years who had undergone pubertal induction with transdermal ($n = 15$, initiation dose of 6.25 mg/day) or oral 17β-estradiol ($n = 4$, initiation dose of 0.25 mg/day) preparations, and 20 healthy controls (median age:21.5 years). Uterine length, fundal transverse diameter, fundal anteroposterior diameter, cervical anteroposterior diameter, fundal-cervical ratio (FCR), endometrial thickness, and uterine volume were assessed by transabdominal pelvic ultrasonography. Anthropometric measurements, karyotype, laboratory data, and treatment information were obtained from existing patient records. Those who discontinued ERT after the transition to adult clinics ($n = 5$) were considered non-adherent. The TS group was divided into subgroups according to ERT route (transdermal, 17β-estradiol), treatment adherence (adherent, non-adherent) and karyotype characteristics (45, X=classic, karyotypes other than 45, X=non-classic).
Results
The median height in the TS group was 152 (range:147–161) cm, and the median BMI was 24.6 (range:17.8–42.5) kg/m^2. The median age at initiation of pubertal induction was 13.5 (range:12.0–15.7) years. Uterine volume was significantly lower in the TS group compared to the control group ($P < 0.001$); however, in those who underwent pubertal induction with transdermal estrogen, uterine length was not significantly different from the control group ($P = 0.194$). The oral 17β-estradiol group had significantly lower fundal anteroposterior diameter and uterine volume than the transdermal group ($P = 0.021$ and $P = 0.028$, respectively). Except for the FCR, all uterine dimensions were significantly lower in the non-adherent group compared to those with adherent. There were no statistically significant differences in uterine dimensions between the karyotype groups. Growth hormone therapy (GHT) was administered to 94.7% ($n = 18$) of individuals with TS. A moderate, statistically significant positive correlation was found between duration of GHT and uterine volume ($r = 0.518$, $P = 0.023$).
Conclusion
This study highlights the significant impact of the route of ERT for pubertal induction on uterine development in TS. Underlining the importance of adherence, non-adherent was associated with significantly smaller uterine dimensions. Although our sample size is limited, transdermal estrogen showed superior outcomes in uterine size development compared to oral 17β-estradiol. GH therapy does have a positive correlation with uterine length in both routes of ERT.

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P573

JOINT3695

High diagnostic yield of WES in identifying monogenic causes of severe short stature in consanguineous children across three countries: importance of cellular mechanisms in extreme growth disorders

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Introduction
Severe short stature defined as height below -4 SD is extremely rare and typically indicates a genetic pathology. Despite its clinical significance, data on its genetic aetiology are limited. One of its subtypes, primordial dwarfism is a defect in overall body size determination rather than isolated bone growth. While milder forms of short stature is regulated by the GH–IGF-1 axis and growth plate, severe cases may involve fundamental cellular processes, such as cell division, DNA replication, and genome stability, leading to reduced cell proliferation. This study aims to map the genetic spectrum of severe short stature using next-generation sequencing (NGS) in a unique cohort of children from consanguineous families.
Patients and Methods
Thirty-three probands (16 females) with height $\leq$ 4SD from 1st cousin consanguinity (with/without syndromic features), examined in three centres for paediatric endocrinology in Iraq, Iran and Oman between January 2022 and February 2023, were included in the study. DNA of the proband, both parents, and health/affected siblings (when available) was obtained with informed consent. Probands' DNA was analyzed by Whole Exome Sequencing. Data was processed by a bioinformatic pipeline and SNP and CNV variants were filtered using variant analysis software. Prioritized potentially pathogenic variants were evaluated by the ACMG standards and confirmed using Sanger sequencing.
Results
A monogenic cause of severe short stature was elucidated in 21/33 (64%) probands. Median height was -5.4 SD (IQR -7.3 to -4.6 SD) and median age 8.1 years (IQR 5.2 to 11.2). Pathogenic or likely pathogenic variants were found in genes involved in the GH-IGF-1 axis (*GHR*[2], *GH1*[2]), growth plate and extracellular matrix (*ACAN*, *COL1A2*, *DYM*[2], *FN1*), signal transduction and gene regulation (*NF1*, *ZSWIM6*), DNA repair and chromosomal stability (*NIPBL*, *LIG4*), cytoskeletal structure and cell division (*CUL7*, *PCNT*, *POC1A*), transmembrane transport and metabolism (*SLC4A1*, *SLC7A7*, *SLC34A3*, *GNPNAT1*), and apoptosis regulation (*PDCD6IP*). Homozygous pathogenic variants were prevalent, however there were 3 heterozygous variants, one de novo variant and one compound heterozygous variant. Majority of genes (12/18) were genes involved in fundamental cellular processes.
Conclusion
NGS is a valuable tool for uncovering the genetic basis of severe short stature, particularly in consanguineous populations where recessive inheritance patterns are common. Our findings highlight the genetic heterogeneity of severe short stature, and the presence of majority of variants outside the traditional GH-IGF-1 and growth plate pathways underscores the role of fundamental cellular mechanisms in extreme growth disorders.

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P574

JOINT322

Evolving genetic influences on infant growth: a longitudinal analysis of polygenic scores and growth patterns in infancy

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Background
Infant growth results from a complex interplay of genetic, environmental, and hormonal factors, influencing early development and future health. Large population-based GWAS have identified genetic loci linked to traits such as birth weight, adult height, and BMI, enabling the use of polygenic scores (PGS) to reveal genetic predispositions shaping growth and body composition. Examining these associations in infancy may provide insights into the origins of lifelong growth patterns and health risks, including obesity and cardiometabolic diseases. This study aimed to explore how genetic influences on infant growth develop during the first year of life.
Objective
To investigate the association between PGS for birth weight, adult BMI adult body height and IGF-1 levels with anthropometric measurements as well as IGF-I serum concentrations, as assessed by age-specific standard deviation scores (SDS) , in healthy infants.
Methods
We conducted a longitudinal cohort study (COPENHAGEN Minipuberty Study, 2016-2018) involving 210 healthy, term newborns (female, $n = 101$), with up to six clinical examinations over the first year of life. Publicly available PGS were analyzed alongside with repeated measurement in infants.
Results
PGS for birth weight was significantly associated with birth weight SDS in our cohort (adjusted for gestational age: $P < 0.001$). However, the PGS for birth weight was not associated with the child's weight SDS at one year of age ($P = 0.86$). The PGS for adult BMI was associated with weight SDS at one year of age ($P = 0.02$) as well as with birth weight SDS ($P = 0.03$). The PGS for adult height was associated with height SDS at one year of age ($P = 0.002$) as well as with birth length ($P = 0.04$). PGS for IGF-I were not associated with IGF-I SDS at 1 month (β=0. 40, 95%CI: -2. 01−2. 81) and 2 months (β=1. 84, 95% CI: -0. 65−4. 32), but reached statistical significance at 6 months (β=3. 80, 95%CI: 1. 29 to 6. 31) and 12 months (β=4. 57, 95%CI: 1. 84−7. 31).
Conclusion
Our findings reveal that genetic influences on growth, particularly those linked to adult height and BMI, begin to manifest during the first year of life, while the impact of birth weight genetics gradually diminishes during infancy. Concerning IGF-I, genetic influences appear to be minimal at birth but gradually strengthen as infancy progresses. These results underscore the dynamic interplay between genetic predispositions, IGF-I, and early growth, emphasizing that genetic contributions to physical development are dynamic and unfold progressively throughout infancy.

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P575

JOINT2510

Effects of the ketogenic diet compared to the mediterranean diet in patients with acromegaly

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Background and Aim
The current study aims to evaluate the impact of a ketogenic diet followed by a Mediterranean diet on IGF-1 levels and metabolic parameters in patients with active acromegaly.
Materials and Methods
We conducted a prospective study on 25 acromegalic patients followed at our endocrinology unit on medical treatment (17 were treated with somatostatin analogues alone, 5 were on combined pegvisomant and somatostatin analogues and 3 were on pegvisomant treatment alone). Participants underwent a structured dietary intervention: an initial ketogenic diet (70% fat, 25% protein, 5% carbohydrates) for 3 weeks, followed by a Mediterranean diet (40% carbohydrates, 30% fat, 30% protein) for further 3 weeks. Anthropometric parameters, fasting glucose, insulin, HOMA-IR, HbA1c, lipid profile, liver enzymes, IGF-1 levels, and inflammatory markers (neutrophil-to-lymphocyte ratio, lymphocyte-to-platelet ratio) were assessed at baseline, after the ketogenic phase, and at the end of the Mediterranean phase. In addition, a bioelectrical impedance analysis (BIA) was performed at baseline and after ketogenic diet to evaluate fat and lean masses. Pharmacological treatment for acromegaly was maintaned stable for the duration of the study.
Results
All included patients completed the study. After 3 weeks of ketogenic diet, we observed a significant reduction in weight ($P = 0.001$), BMI ($P = 0.009$), waist circumference ($P = 0.011$), hip circumference ($P = 0.003$), lean mass ($P = 0.01$), fat mass ($P = 0.01$), IGF-1 ($P = 0.02$), blood glucose ($P = 0.004$), and AST ($P = 0.021$), compared to baseline. After we compared the effects of the ketogenic diet vs Mediterranean diet and we found significant higher glucose ($P = 0.045$), insulin ($P = 0.006$) and HOMA-IR ($P = 0.003$) values. At multivariate analysis, IGF-1 positively correlated with weight ($P = 0.014$, beta = 1. 568).
Discussion
Our findings suggest that a ketogenic diet may play a role in modulating IGF-1 levels and improving metabolic parameters in patients with active acromegaly. IGF-1 reduction may be partly mediated by the lower insulin levels induced by KD, as insulin is a known regulator of hepatic IGF-1 production. Furthermore, the significant weight loss observed during the KD phase may have contributed to the decrease in IGF-1, as demonstrated by the positive correlation between IGF-1 and body weight in our multivariate analysis. Our study provides preliminary evidence supporting the use of KD as a potential adjunctive strategy in the metabolic management of acromegalic patients. Further larger-scale, long-term studies are warranted to confirm these findings.

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P576

JOINT951

Comparative efficacy of growth hormone, aromatase inhibitors, and gonadotropin-releasing hormone agonists in idiopathic short stature with advanced bone age

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Background
Idiopathic short stature (ISS) with advanced bone age presents unique challenges in pediatric endocrinology, as accelerated skeletal maturation reduces growth potential and limits final height. Growth hormone (GH) therapy has been widely used, but adjunctive therapies such as aromatase inhibitors (AIs) and gonadotropin-releasing hormone agonists (GnRHa) show promise in optimizing height outcomes by delaying bone maturation. This review evaluates these therapies individually and in combination for managing ISS with advanced bone age.
Objectives
This review aims to assess the efficacy of GH, AIs, and GnRHa, alone or in combination, in improving height outcomes and controlling bone age progression in children with ISS. It also explores the impact of these therapies on height standard deviation scores (HtSDS), growth velocity, and predicted adult height (PAH) to identify the most effective treatment approaches.
Methods
A systematic analysis of 19 studies published between 1994 and 2024 was conducted. The studies included children diagnosed with ISS and advanced bone age, treated with GH, AIs, GnRHa, or combinations of these therapies. Outcomes such as PAH improvement, HtSDS gain, bone age control, and treatment safety profiles were examined to draw Conclusions on therapeutic efficacy.
Results
Across 19 studies, GH monotherapy improved HtSDS modestly, with gains ranging from +0. 62 to +1. 21 over treatment durations of one to three years. Predicted adult height increased by 8. 5 ± 3. 7 cm in some cases, with short-term benefits evident in prepubertal children. However, GH monotherapy often advanced bone age proportionally to height gain, limiting final height outcomes. Combination therapies of GH with GnRHa or AIs consistently outperformed GH alone. These combinations delayed skeletal maturation, prolonged growth periods, and yielded greater PAH gains, often exceeding 10 cm. GH + GnRHa therapy was particularly effective in early puberty, while GH + AI therapy showed substantial height improvements in boys with advanced skeletal maturity. Triple therapy (GH + GnRHa + AI) demonstrated the most robust outcomes, achieving significant PAH gains and effective bone age control, although mild side effects such as acne and mood changes were noted in some cases.
Discussion
Combination therapies provide superior height outcomes by synergistically addressing skeletal maturation and growth stimulation. GnRHa delays puberty and reduces bone age advancement, while AIs inhibit estrogen-mediated-growth plate closure.

Conclusion
Combination therapies involving GH, GnRHa, and/or AIs are highly effective for ISS with advanced bone age, offering substantial height gains and controlled bone maturation. Long-term studies are needed to assess safety and treatment protocols.

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P577

JOINT374

Long-acting PEGYlated recombinant human growth hormone (jintrolong) in short children born small for gestational age: 4-year results from a multicenter, randomized, dose-response trial in china

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Objectives
The efficacy and safety of weekly PEGylated human growth hormone (PEG-rhGH) (Jintrolong) was evaluated over 4 years in children with short stature born small for gestational age (SGA).
Methods
This is a multicenter, randomized, open-label, dose-response trial, including a 52-week main phase (NCT02375620) and an ongoing safety extension phase continuing until reaching near-adult height (NAH), conducted across 9 sites in China. Ninety-six growth hormone (GH)-treatment-naïve, non-GH-deficient, prepubertal short children born SGA were randomized in a 1:1 ration to receive weekly subcutaneous administration of Jintrolong 0. 1 mg/kg/week or 0. 2 mg/kg/week for 52 weeks. Children who completed the 52-week main phase proceeded to the extension phase, while Jintrolong was administered at an initial dose of 0. 2 mg/kg/week. Dose adjustments based on annualized height velocity (AHV; cm/year) and insulin-like growth factor I (IGF-I) response, were made up to a maximum of 0. 4 mg/kg/week until achieved NAH or the patient's voluntary discontinuation. The primary endpoint was the change of height standard deviation score ($\triangle$HT SDS) from baseline to week 52 and every 52 weeks in the extension phase. Other growth-related parameters, along with safety and treatment compliance were also monitored.
Results
The mean (SD) birth weight SDS was -2. 59 (0. 782), the mean age at the start of the study was 4. 3(0. 95) yr, and the mean height SDS at baseline was -2. 658(0. 712). The Jintrolong 0. 2 mg/kg/week group demonstrated significantly greater mean HT SDS increases compared to the 0. 1 mg/kg/week group at week 52 (0. 923 vs. 0. 511, $P < 0.0001$). After 3 years of Jintrolong treatment in the extension phase (a total of 4-Year treatment from baseline), 90. 9% (60/66) of patients reached heights within the normal range for healthy Chinese children ($>$ -2 SDS), and 53. 0% (35/66) of patients' height SDS in conformity with their target height SDS. Additionally, mean AHV remained within the normal range during the 3-year extension treatment. Incidence of adverse events (AEs) and treatment compliance were comparable between two groups during 52-week main phase. Most AEs observed during long-term treatment were mild to moderate and most known GH-related adverse reactions.
Conclusion
Our 4-year data show that long-term continuous Jintrolong PEG-rhGH treatment at an initial dose of 0. 2 mg/kg/week, up to a maximum of 0. 4 mg/kg/week in short children born SGA results in a normalization of height during childhood followed by growth along the target height SDS.

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P578

JOINT2419

Aetiology of short stature in children originally diagnosed with idiopathic growth hormone deficiency: comprehensive genetic investigation of a single centre cohort

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Introduction
Diagnostics of growth hormone deficiency (GHD) is based on stimulation tests, IGF-1 and growth velocity. Children diagnosed with GHD are believed to have heterogeneous aetiology of short stature, frequently independent on GH secretion. Evidence supporting this hypothesis are lacking. The aim of the study was to elucidate genetic aetiology of children with diagnosed GHD.
Methods
Children treated for GHD in our centre with idiopathic GHD and therapy duration $\geq$5 years were enrolled to the study. Children were examined by various genetic methods including next-generation sequencing. Genetic variants were evaluated using ACMG guidelines. Clinical parameters were compared between children with genetically proven GHD and other groups of children based on their genetic aetiology.
Results
In total, 294 children were enrolled to the study. At GH treatment initiation, their median age was 5. 1 years (IQR 3. 5-6. 8 years), height -2. 9 (-3. 2 to -2. 6) SD, IGF1 -1. 7 (-2. 0 to -1. 3) SD, GH_{max} 5. 5 (4. 0-7. 3) mg/l, 32 had combined pituitary hormone deficiency. Of them, 269 (91%) consented with genetic testing. We elucidated genetic aetiology in 56/269 (21%) of them. Fourteen children (25%) had genetically confirmed GHD (genes *OTX2* [4], *GLI2*, *TBX3*, *PROP1*, *POU1F1*, *GHSR*, *GH1*, *CHD7*, *PROK2*, *PMM2*, *SALL4*), 2 (4%) had impaired IGF proteins (genes *IGFALS*, *HGMA2*), 15 (27%) had primary growth plate disorders (genes *NPR2* [3], *FGFR3* [2], *COL2A1* [2], *COL9A2*, *MATN3*, *ACAN*, *EXT2*, *SOX9*, *LTBP3*, *TRPV4*, *ALPL*), 14 (25%) impaired RAS signalling pathway (genes *PTPN11* [8], *SOS1* [3], *NF1* [2], *RAF1*) and 11 (20%) complex genetic disorders (genes *LMNA*, *KMTD2*, *SURF1*, *SOX10*, *MBTPS2*, *TSPAN7*, *FGFR2*, *GNAO1*, *CDC42*, DiGeorge syndrome and Smith-Magenis syndrome). Prior to GH treatment, children with genetically confirmed GHD had lower GH_{max} (median 1. 8 mg/l vs. 4. 5 mg/l [growth plate disorder], 6. 6 mg/l [RASopathies] and 5. 4 mg/l [complex disorders]; $P = 0.05$) and together with RASopathies less affected intrauterine growth (lower of the birth parameters [birth weight/length] -1. 2 SD [GHD] and -0. 8 SD [RASopathies] vs. -1. 8 SD [growth plate disorders] and -2. 0 SD [complex disorders]; $P = 0.009$). After 5 years of therapy, GHD and growth plate disorders groups had better growth outcomes (-0. 7 SD [GHD] and -0. 8 SD [growth plate disorders] vs. -1. 8 SD [RASopathies] and -2. 0 SD [complex disorders] $P = 0.04$).
Conclusions
Genetic aetiology of short stature in children diagnosed with GHD is heterogeneous. Lower stimulated GH concentration, near-normal size at birth, and better response to GH treatment might help to clinically differentiate those with genetically confirmed GHD.

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P579

JOINT3601

Comparison of oral vs intravenous glucose exposure on plasma growth hormone levels: a crossover study in healthy volunteers

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Introduction
It has become increasingly evident that many effects on hormone secretion—most notably for insulin—previously attributed to glucose per se, are partially mediated by hormones released from the gastro-intestinal tract. It is unknown if gastrointestinal tract deviated hormones are involved in the suppression of growth hormone (GH) during oral glucose intake. Interestingly, about 30% of patients with acromegaly show a paradoxical GH increase during an oral glucose tolerance test (OGTT). This phenomenon has been attributed to the presence of GIP receptors on a subset of GH-secreting adenomas, thereby linking GH secretion to gut-hormones.
Materials and Methods
12 healthy controls (6 women, mean age 48 years) underwent a 2-hour OGTT and an isoglycemic intravenous glucose infusion on a separate day, with sequential GH, insulin, glucagon, GLP1 and GIP measurement. The effect of oral vs. intravenous (IV) glucose on plasma GH, insulin, glucagon, GLP1 and GIP was assessed by a mixed-effect model and by area under the curve (AUC).

Results
GH levels were significantly influenced by the route of glucose administration ($P = 0.005$, mixed effect model). During iv glucose, 9/12 participants showed a paradoxical increase in GH within the first 20 minutes post-exposition. The AUC (median (range)) during OGTT was 70 (6-178) vs. 56 (6-474) mg/lxmin during IV glucose ($P = 0.20$). During OGTT, one participant did not reach the threshold (<0.4 mg/l) for excluding acromegaly (nadir GH 0. 66 mg/l), whereas two did not meet the criteria during iv glucose (nadir 0. 72 and 2. 68 mg/l). AUC was significantly reduced during IV vs. oral glucoseload for insulin ($P < 0.001$), glucagon ($P = 0.018$), GLP1 ($P = 0.002$) and GIP ($P < 0.001$) Similar results were obtained using mixed effect models with all P-values < 0.001
Conclusion
Our findings suggest that gastrointestinal-derived hormones may play a physiological role in suppressing GH secretion. As one hypothesis, reduced ghrelin during oral administration may contribute to GH suppression. However, previous studies have reported conflicting results regarding the impact of oral vs. IV glucose on plasma ghrelin levels. We observed significant differences in insulin, glucagon, GIP and GLP-1 levels between the two conditions, which might also influence GH secretion. Further investigations are needed to elucidate the precise mechanisms underlying these observations.

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P580

JOINT577

Epidemiology of disorders associated with tall stature in childhood: a 20-year birth cohort study

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Background
Many primary and secondary disorders in childhood may cause tall stature (height of +2 SD above the mean height for age and sex). Growth-monitoring programs are aimed at early detection of such disorders to avoid permanent health consequences and support children's wellbeing. However, epidemiological data on disorders associated with tall stature in childhood are scarce.
Aim
To specify age- and sex-specific data on the incidence of disorders associated with tall stature and to develop better diagnostic practices.
Materials and Methods
Retrospective population-based study included 1 144 503 children (51% boys) born in Finland between 1998 and 2017 with 16. 5 million register notifications including medical diagnoses. The first occurrences of essential disorders associated with tall stature were identified from multiple registers. The age- and sex-specific cumulative incidences (CMIs) from birth until 18 years of age and the median age at diagnosis were determined.
Results
A total of 3329 children (47% boys) had one of the selected disorders (0. 3% of the whole birth cohort). Central precocious puberty (CMI of 1/894 girls at 8 years, and 1/4856 boys at 9 years) were more common among girls.
Conclusions
This study provided the first age- and sex-specific epidemiological data on several primary and secondary disorders associated with tall stature. These disorders proved to be rather rare yet underdiagnosed in childhood. We suggest that during early childhood, the focus of growth screening should be particularly on Marfan syndrome and congenital overgrowth syndromes, with the addition of Klinefelter syndrome and central precocious puberty thereafter. It is important to distinguish these pathological causes from idiopathic tall stature, which represented half of all cases associated with tall stature.

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P581

JOINT3512

Liver abnormalities in a population of adult women with turner syndrome

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Introduction
Abnormalities in liver function tests (LFA) are frequent in Turner syndrome (TS); nonetheless, the etiopathogenesis of this complication remains unclear, probably being multifaceted. Several potential mechanisms have been suggested, including metabolic syndrome, generalized vasculopathy and autoimmunity.
Objectives
Describe the possible etiopathogenetic factors of LFA in adult patients with TS
M&M
120 adult TS patients, regularly followed-up at our Unit, underwent liver elastometry (FibroScan: Echosens, Paris, France) and hepato-splenic ultrasound. Blood samples were obtained to analyze liver enzymes and other metabolic parameters. Alanino-aminotransferase(ALT), asparate-aminotransferase(AST), gamma-glutamyil-transferase(GGT) and alkaline-phosphatase(ALP) were considered abnormal(LFA) when above 1xULN. Data were retrospectively collected regarding metabolic complications, autoimmune diseases, menstrual history, and hormonal replacement therapies (GH and estrogen-progestin therapy). The presence of structural cardiovascular anomalies and the diameter of the first aortic tract were assessed by retrieving the latest cardiac examination (cardiac MRI and/or transthoracic echocardiography).
Results
74 patients (61. 6%) had at least one LFA, GGT being the most frequent (57. 5%). The prevalence of fibrosis was 6. 7% ($n = 8$). Patients with LFA (LFA-TS) showed significantly higher age, BMI, waist circumference (WC) and waist-to-height ratio than patients with normal liver enzymes (NLE-TS) ($P = 0.008$, $P = 0.046$, $P = 0.005$, $P = 0.002$ respectively). Steatosis was significantly more prevalent in LFA-TS (36. 5% vs 13% in NLE-TS $P = 0.005$). With respect to NLE-TS, LFA-TS showed significantly higher levels of fasting glucose, HbA1c, and total cholesterol ($P = 0.001$, $P < 0.001$, $P = 0.042$, respectively) and were more frequently diagnosed with arterial hypertension and metabolic syndrome ($P = 0.018$, $P = 0.049$). In LFA-TS patients, the diameter of the Valsalva sinuses and the initial aortic segment, as well as the aorta/height index (AHI), were significantly higher compared to NLE-TS patients ($P = 0.045$, $P = 0.032$, $P = 0.025$, respectively). No significant differences were detected in all other variables analyzed (structural cardiovascular abnormalities, autoimmunity, menstrual cycle history, therapies). Performing forward multiple logistic regression analysis, abnormal GGT levels were significantly associated with higher age and WC

P580

Disorder (n)		CMI per 100 000 children Age (years) 0 2 6 10 14					CMI at 18 years	Age at diagnosis (years)
Klinefelter syndrome	Boys (167)	6. 2	13. 2	18. 8	27. 2	34. 0	1/2146	8. 4
47, XYY syndrome	Boys (96)	2. 6	4. 3	11. 0	17. 9	23. 1	1/3837	6. 6
Triple X syndrome	Girls (68)	3. 2	6. 4	10. 3	13. 0	15. 1	1/6277	3. 7
Marfan syndrome	Girls (92)	0. 5	7. 4	12. 0	17. 2	21. 2	1/4307	5. 9
	Boys (65)	0. 5	4. 8	8. 3	10. 5	13. 4	1/5202	7. 1
Congenital over-	Girls (99)	0. 7	10. 9	17. 5	19. 3	21. 2	1/4717	1. 7
growth syndromes	Boys (101)	2. 4	10. 7	16. 3	18. 7	19. 7	1/4925	1. 8
Idiopathic tall stature	Girls (844)	0 0	30. 4	105. 3	176. 3	210. 5	1/436	6. 5
	Boys (844)		35. 4	94. 8	169. 2	200. 9	1/454	6. 6

(OR = 1. 061, 95CI:1. 02-1. 11, $P = 0.005$; OR = 1. 038, 95CI = 1. 01-1. 07, $P = 0.016$ respectively), abnormal ALT with higher WC and HbA1c (OR = 1. 042, 95CI:1. 01-1. 08, $P = 0.018$; OR = 1. 190, 95CI = 1. 08-1. 3, $P < 0.001$ respectively), and abnormal AST with higher HbA1c (OR = 1. 131, 95CI = 1. 04-1. 23, $P = 0.005$)

Conclusions

LFA are highly prevalent in adult TS women; this complication seems tightly related to visceral adiposity and metabolic abnormalities, making their management pivotal in this rare disease. A relation with aortic dilation seems plausible, in the context of a possible generalized vasculopathy: further large-scale studies are needed to clarify and explore this finding in greater depth.

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P582

JOINT792

The growth paradox: unraveling the impact of advanced bone age on height potential in untreated conditions"

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Background

Advanced bone age (ABA) is a critical determinant of linear growth and final adult height in children with untreated conditions such as idiopathic short stature, precocious puberty, and chronic illnesses. This review evaluates the impact of ABA on height outcomes and its contributing factors, categorized into growth potential, primary drivers, untreated risks, and mitigating strategies. Quantified impact scores provide insights into the relative significance of these factors.

Objectives

1. To assess the effects of ABA on linear growth and final height potential in untreated cases.
2. To quantify the relative impacts of growth potential, primary drivers, untreated risks, positive outcomes, and key therapies.
3. To evaluate strategies for mitigating ABA-associated growth deficits.

Methods

A comprehensive review of peer-reviewed studies from 1991 to 2025 was conducted. Studies addressing untreated cases of ABA and its impact on linear growth and adult height were included. The analysis involved calculating percent impacts for key categories, classified as small, medium, or high, to contextualize their significance.

Results

- Impact on Height: ABA had a high impact (32. 8%) on reducing final height potential, primarily due to premature epiphyseal fusion and diminished growth velocity.
- Primary Drivers: Hormonal imbalances, including elevated IGF-I and sex steroids, contributed a moderate impact (28. 7%), influencing bone maturation and growth cessation.
- Untreated Risks: Progressive growth failure, earlier puberty onset, and psychosocial challenges presented a high impact (34. 9%) on overall height potential and quality of life.
- Positive Outcomes: Some untreated cases with slower ABA progression preserved final height within target ranges, contributing a small impact (14. 5%) on mitigating growth deficits.
- Key Therapies: Interventions like GnRH agonists and nutritional management showed potential for reversing growth deficits, though effectiveness in untreated cases remains limited, with a moderate impact (24. 1%).

Discussion

ABA significantly compromises linear growth and final adult height in untreated cases. Its high impact on growth potential and untreated risks highlights the importance of early diagnosis and intervention. Hormonal imbalances and premature epiphyseal closure are primary drivers of height deficits. While positive outcomes are rare in untreated cases, targeted therapies can mitigate risks and preserve growth potential when implemented early.

Conclusion

ABA has a profound impact on final adult height in untreated conditions, primarily through premature growth cessation and progressive risks. Early identification and timely therapeutic interventions are essential to mitigate its effects and improve growth outcomes.

Keywords Advanced Bone Age, Linear Growth, Final Height, Untreated Risks, Growth Potential, Hormonal Imbalances.

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P583

JOINT2922

Efficacy of growth hormone therapy in children with npr2 and acan gene variants: a comparative study

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Introduction

NPR2 and ACAN gene variants are well recognised causes of idiopathic short stature (ISS). Both genes play a crucial role in growth plate regulation; NPR2 through paracrine function of endochondral ossification, while ACAN is a major structural component of the extracellular matrix in cartilage. The study aimed to evaluate and compare the efficacy of growth hormone (GH) therapy in children with NPR2 and ACAN variants.

Methods

Next-generation sequencing was performed in ISS children to identify causal NPR2 and ACAN variants. Eligible children met national guidelines for treatment with GH. The main outcome measure was change (Δ) in height SD score (HtSDS). Comparison was made between:

- Treated and untreated NPR2/ACAN children
- Prepubertal vs. pubertal children receiving GH
- Overall NPR2 vs. ACAN patient outcomes.

Results

A total of 16 NPR2 (11 males) and 17 ACAN (8 males) children were enrolled. Among them 8/16 NPR2 (6 males, mean age 9. 5 ± 3. 8 years) and 10/17 ACAN (5 males, mean age 8. 2 ± 3. 2 years) children received GH (treatment duration: NPR2 3. 2 ± 1. 7 years, ACAN 5. 3 ± 2. 2 years). In the untreated subgroups, the mean Δ in HtSDS was +0. 07 (NPR2) and -0. 23 (ACAN). Children who started treatment at the prepubertal stage (5/8 NPR2, 6/10 ACAN) had greater height gains (Δ HtSDS; +1. 01 in NPR2 and +1. 35 in ACAN) than those who started in puberty (Δ HtSDS; +0. 37 in NPR2 and + 0. 3 in ACAN).

Overall, mean height gain in treated children was:

- NPR2: + 0. 8 ± 0. 4 (mean Δ HtSDS 0. 3 ± 0. 2 per year)
- ACAN +0. 9 ± 0. 8 (mean Δ HtSDS 0. 2 ± 0. 1 per year)

Conclusion

GH therapy significantly improved linear growth in both NPR2 and ACAN groups compared to the untreated children; with a more pronounced effect in ACAN children. Early initiation of GH was particularly effective in both groups.

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P584

JOINT486

Efficacy of somapacitan in treatment-fatigue adults with growth hormone deficiency previously treated with daily GH injections: a 24-week randomized active-controlled trial

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Objective

An important barrier to obtain treatment goals in adult growth hormone deficiency (AGHD) is poor adherence due to the burden of long-term treatment with once daily growth hormone (GH) injections. We aimed to evaluated the efficacy of long acting GH somapacitan in a 24-week, randomized, active-controlled study in treatment-fatigue patients with AGHD, previously treated with once daily GH.

Methods

30 male or female patients with AGHD, previously treated with once-daily GH for ≥ 5 years, reporting fatigue from daily GH injections, were randomized to somapacitan or once-daily GH. Outcome measures were changes in treatment satisfaction assessed by Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9), IGF-1 SDS, glucose and lipid parameters, body composition, bone mineral density (BMD), carotid intima media thickness and reactive hyperaemia index, from baseline to week 24.

Results
At baseline, 38% of patients was sub-optimally treated with daily GH with median IGF-1 SDS outside the range of 0-2 SDS for at least 2 years prior the randomisation. At week 24, median IGF-I SDS was outside the range of 0-2 SDS in 5 patients (35, 7%) in daily GH group and in 1 patient (6. 6%) in somapacitan group. 6 patients receiving daily GH reported missing >5 doses of GH each month, while in the somapacitan group only 1 dose was missed in 1 patient in 24 weeks. TSQM-9 score for convenience increased significantly more with somapacitan vs daily GH (estimated difference, somapacitan-daily GH [95% CI]:23. 2 [7. 9; 38. 4] points, $P = 0.0004$). No significant differences were observed between groups for changes from baseline to week 24 in median values of IGF-1, IGF-1 SDS, glucose homeostasis, lipid profile, visceral adipose tissue, fat mass (%), lean body mass and vascular parameters. There was significant difference between the groups in BMD of lumbar spine (estimated difference, somapacitan-daily GH [95% CI]-0. 036 (-0. 064, -0. 009) gr/cm2, $P = 0.011$).
Conclusion
In the treatment fatigue patients with AGHD, somapacitan was reported to be more convenient than daily GH with better self-reported adherence. The changes in body composition, glucose, lipid and vascular parameters were similar in both groups. A small decrease in BMD when switching to somapacitan may reflect an initial favourable increase in the number of bone metabolic units. A similar effect on BMD was previously observed in treatment naïve patients with AGHD during the first 6 months after initiation of GH treatment, followed by an increase in BMD. Further studies on long-term efficacy and safety of somapacitan in AGHD are needed.

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P585

JOINT1496

Long-term maintenance in the upper normal IGF-1 levels has beneficial effects on body fat and marker of low-grade inflammation in adults with growth hormone deficiency

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Objective
High normal IGF-1 levels may be associated with more favourable outcomes of long-term growth hormone replacement therapy (GHRT) in adult growth hormone deficiency (AGHD). However, the distinctive effects of maintaining the upper (0-2 SDS) vs lower normal (-2-0 SDS) range of IGF-1 SDS in AGHD remain largely understudied.
Methods
We conducted a cross-sectional study with 31 patients with AGHD receiving GHRT with daily GH > 5 years and 2-year mean IGF-1 between -2 to +2 SDS range. Patients were categorized according to their 2-year mean IGF-1 SDS into the upper or lower normal IGF-1 range. Clinical characteristics, anthropometric parameters assessed by dual-energy X-ray absorptiometry, laboratory tests, intima-media thickness (IMT) and reactive hyperemia index (RHI) were evaluated. Associations of those parameters with the mean IGF-1 SDS range over 2 and 5 years were explored.
Results
Over the 2-year period, 18 patients (58. 1 %) had mean IGF-1 SDS in the upper and 13 in the lower normal range. Long-term maintenance of upper normal IGF-1 SDS was more frequent in man than women (72. 2 % vs. 27. 8 %; $P = 0.024$) and in patients with longer GHRT duration (median GHRT duration (25–75 % range): 28 years (16. 5–35) in higher normal group vs. 15 years (5–20) in lower normal; $P = 0.033$). Patients with tumour-related AGHD had a lower 5-year mean IGF-1 SDS than patients with non-tumour etiology. Long-term maintenance of IGF-1 SDS in the higher normal range was associated with lower high-sensitivity C-reactive protein (hs-CRP) levels (median (25–75 % range): 0. 8 (0. 6-1. 1) vs. 1. 8 (0. 8-4. 6); $P = 0.005$) and lower body fat percentage (median (25–75 % range) : (30. 1 % (25. 2-34. 8) vs. 39. 5 % (32. 2-44. 0); $P = 0.008$). A negative correlation was identified between hs-CRP and the 5-year mean IGF-1 SDS ($r = -0.705$, $p < 0.001$). The IGF-1 SDS range was not associated with IMT, RHI, glucose metabolism or lipid profile.
Conclusion
Long-term maintenance in the upper normal IGF-1 SDS was more frequent in male than female patients with AGHD. The upper normal range was associated with lower marker of low-grade inflammation and lower body fat percentage. Prospective randomized studies are needed to evaluate the long-term and sex-specific effects of targeting higher vs. lower normal IGF-1 SDS range in AGHD, for both, daily and weekly GHRT.

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P586

JOINT100

Analysis of functionally uncharacterized variants of the GH1 gene from patients with isolated growth hormone deficiency (IGHD)

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Human growth hormone (hGH), or somatotropin, a 217-amino acid glycoprotein produced by the somatotropic cells in the anterior pituitary, is encoded by the *GH1* gene, located on chromosome 17 (17q22-24). Mutations in *GH1* are associated with Isolated Growth Hormone Deficiency (IGHD), characterized by a spectrum of pituitary hormone deficiencies and growth failure in children, and it can result from mutations in *GH1* or related genes. IGHD is classified into four types based on inheritance patterns: Type IA and IB (autosomal recessive) Type II (Autosomal dominant), and Type III (X-linked), all of which result in short stature. We have investigated five functionally uncharacterized but clinically reported *GH1* missense variants (A39T, R42L, C79G, Q110E, and R160W), identified in patients with IGHD of various types and genetic background s. Pathogenicity analysis tools such as PANTHER, PhD-SNP, SIFT, Meta-SNP, and E-SNPs & GO were utilized to assess the pathogenicity scores for each mutation, highlighting C79G and R42L as the most deleterious mutations. Among the mutations, Q110E is predicted to have the most significant stabilizing effect. Protein free energy ΔΔG calculations (1. 882 kcal/mol) suggested that it enhances protein stability, reducing the likelihood of denaturation or unfolding. Conversely, A39T appears to significantly decrease protein flexibility compared to the other five mutations, as indicated by ΔΔSVib (-4. 925 kcal/mol*K) predictions, which suggests that A39T induces a more rigid and ordered protein structure. Additionally, multiple sequence alignment and phylogenetic analysis with Clustal Omega, phylogenetic analysis with MEGA, domain prediction with SMART, 3D structures modeling, and motif analysis with MEME, confirmed high conservation these residues among primates, underscoring their importance. To complement computational insights, the variants were introduced into the wild-type *GH1* gene via site-directed mutagenesis and expressed in E. coli. Recombinant proteins were purified using immobilized metal affinity chromatography (IMAC), yielding high-quality preparations suitable for downstream functional studies. These findings provide a detailed computational and experimental framework for understanding GH1 variant effects, offering a foundation for future *In vitro* studies aimed at advancing personalized approaches to IGHD diagnosis and treatment.

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P587

JOINT2411

Retrospective evaluation of the phenotypic-genotypic characteristics of patients with short stature who underwent next-generation sequencing analysis

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Background
Short stature is a common pediatric endocrinological disorder with an incidence of 3-5%. The majority of cases have an unclear etiology, which complicates therapy selection and the diagnostic process.
Objective
This study aims to explore the phenotypic-genotypic relationships by retrospectively evaluated patients who underwent targeted next-generation sequencing (NGS) due to short stature.

Materials and Methods
This study included 65 patients (37 male, 28 female) who were followed up for short stature [< -2 SDS (standard deviation score)] between January 2011 and June 2022 at Pediatric Endocrinology Clinic and underwent targeted NGS. The pathogenicity of the variants was evaluated according to the criteria of the American College of Medical Genetics and Genomics (ACMG). Patients with pathogenic or likely pathogenic variants detected in the NGS panel (Group 1) were compared with other patients included in the study (Group 2) in terms of their characteristics.
Results
The mean age at diagnosis of the patients was 7. 93 ± 4. 42 years (min; max: 0. 42; 15. 78), and the mean height SDS was -3. 06 ± 0. 97 (min; max: -7. 37; -2. 00). Among the patients, 15 (23. 1%) had consanguinity between their parents. Forty participants (61. 5%) had at least one individual with short stature in their family. The number of patients with pathogenic or likely pathogenic variants detected in the NGS panel was 19 (29. 2%). These variants were *FLNB* (3 patients), *OBSL1* (2 patients), *FBN1, EXT1, ADAMTSL4, PHEX, LHX3, FLNB, ROR2, ALPL, TTC21B, GHR, SLC26A2, PCNT, NF1, FGFR3, GHRHR*. The birth weight SDS of patients in Group 1 was statistically lower than that of patients in Group 2 (-1.69 ± 1.7 vs. -0.56 ± 1.08, $P = 0.046$). The rate of consanguinity among the parents of patients in Group 1 was 47. 2%, whereas it was 13. 0% in Group 2, and this difference was statistically significant ($P = 0.007$).
Conclusion
In this study, NGS panel screening was used to determine the genetic etiology of short stature in some patients and provided a solid informational basis for clinical phenotype classification and genetic counseling. Additionally, genetic screening can provide a foundation for the development of more effective interventions and help meet the medical needs. Further functional experimental research is required on variants of potential pathogenic significance.

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P588

JOINT2803

The impact of dose modification guided by growth response monitoring on igf-1 levels and height velocity in growth hormone deficiency treatment

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Aim
Growth hormone (GH) therapy is an effective therapeutic modality for children with GH insufficiency. However, in some cases, treatment may yield inadequate responses, limiting the attainment of intended outcomes. Retrospective studies suggest that numerous factors affect the efficacy of GH treatment. The dosage of growth hormone is a critical component influencing growth response. Consequently, if the growth response is suboptimal in the initial year, it is advisable to augment the GH treatment dosage in the guidelines. This study presents the implementation outcomes of the technique indicated in the guidelines.
Material and methods
The study comprised a total of 163 diagnosed instances of GH deficiency. Growth hormone treatment commenced in the instances at a dosage of 25-35 mg per day. During the initial year of treatment, children with mild growth hormone (GH) insufficiency (peak GH between 5-10 ng/dL in stimulation tests) exhibit a 0. 3 standard deviation score (SDS), while those with severe GH deficiency (peak GH <5 ng/mL in stimulation tests) show a 0. 4 SDS. A 100% rise was deemed a sufficient treatment response (Group 1), whereas its absence was regarded as an insufficient response (Group 2). In the inadequately responding cohort, the GH dosage was escalated by 20% per kilogram prior to the second year, and the patients' growth velocities and IGF-1 concentrations were assessed over a period of 3 years.
Results
During the initial year of treatment, it was noted that the height SDS increase was inadequate in 53 out of 163 patients (32. 5%). Both Group 1 and Group 2 had three years of treatment. Table 1 presents the GH doses, height SDS values, IGF-1 SDS values, and alterations in height SDS values from the commencement to the conclusion of treatment for each year. Following the dosage augmentation, growth in Group 2 intensified, and at the conclusion of the third year, overall height rise neared that of Group 1. At the conclusion of the second year, the dosage was necessitated to be reduced in 20 patients from the good response cohort and in 6 patients from the poor response cohort due to elevated IGF-1 SDS values.
Conclusion
In the management of GH insufficiency, monitoring treatment response and adjusting dosages appropriately enhances therapeutic success and provides the individual with an opportunity for growth comparable to those who have a favorable response.

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P589

JOINT3473

Real-world IGF-I variations & its management in children on recombinant human growth hormone (rhGH) therapy (RIGHT study)

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Aim
Serum IGF-I is widely advocated as a tool for monitoring adherence, safety and effectiveness of recombinant human growth hormone (rhGH). However, there is a need to understand the real-world variations in IGF-I levels in children on rhGH and the management of abnormal levels in clinical practice.
Method
Centres participating in the Global Registry for Novel Therapies in Rare Bone and Endocrine Conditions (www. GloBE-Reg. net) were invited to complete the minimum dataset for rhGH therapy. Information on the indications for rhGH therapy, gender, age at diagnosis and rhGH initiation, rhGH doses and serum IGF-I on therapy were collected for analysis. Based on available reference data for 6 different assays, IGF-I SDS were calculated. IGF-I values more than 2SDS below and above the mean were classed as low and high, respectively. Results are shown in median (range).
Results
A total of 2, 697 IGF-I values from 690 children (475 daily/215 LAGH; 429M/261F) were available from 17 centres in 12 countries. The main indications for daily rhGH treatment included growth hormone deficiency (GHD) in 239/475 (50%), small for gestational age (SGA) in 58/475 (12%) and Prader-Willi syndrome (PWS) in 41/475 (9%). The majority were on long-acting GH (LAGH) for GHD 192/215 (89%), with 17/215 for idiopathic short stature (ISS, 8%) and 5/215 for SGA (2%). In those on daily GH, IGF-I SDS were low –2. 4 (-3. 4, -2. 1) in 6% (126/2182) and high +3. 1 (+2. 1, +21. 6) in 10% (218/2182). Noticeably, 73/218 (33%) high IGF-I SDS were within the normal for the centres' laboratory reference range. A quarter of children (49/203) with PWS have high IGF-I with median +3. 15 (2. 2, 21. 6), with variation in the 3 contributing centres. Children with PWS and SGA (both $P<0.001$) were more likely to have high IGF-I, +0. 3 (-3. 4, +21. 6) and +0. 03 (-3. 4, +9. 2) respectively compared to GHD -0. 4 (-3. 4, +6. 2). In those on LAGH, IGF-I SDS were low –2. 2 (-3. 0, -2. 1) in 1. 6% (8/515) and high +2. 7 (+2. 1, +6. 4) in 12% (60/515). Those with high IGF-I were on the recommended LAGH doses 0. 15 (0. 07, 0. 19)

mg/kg or 0. 50 (0. 45, 0. 50) mg/kg for the respective brands. Adherence data were only available in 20%.
Conclusion
Based on this study, 15% (412/2697) of IGF-I values are outwith the recommended +/- 2SDS range. IGF-SDS, as recommended in international guidelines, is underused in routine clinical practice, which often rely on laboratory reference range. Further studies into the implication of high IGF-I in children with PWS and SGA is needed.

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P590

JOINT791

Unexpected high frequency of copy number variations as genetic causes of failure to achieve catch-up growth in small for gestational age children: a multicenter study in Korea

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Background
Small for gestational age (SGA) refers to infants whose size is below the normative range for their gestational age and sex. While up to 90% of these infants experience catch-up growth within the first two years, 10-15% fail to do so and remain short at age 2 (SGA-SS). The causes of this failure remain largely unknown.
Methods
This study investigated the genetic causes of failure to achieve catch-up growth in Korean SGA children. Subjects were recruited from multicenter SGA-SS cohorts across eight hospitals in South Korea. A total of 191 children underwent whole exome sequencing. Copy number variants (CNVs) identified in exome data were validated using chromosomal microarray (CMA). Genetic variants were classified according to ACMG guidelines.
Results
Genetic variants were identified in 36 of 191 children. Half of the genetic abnormalities were CNVs (18/36, 50%). Notably, 22q11. 2 microdeletion syndrome was observed in seven children (7/36, 19. 4%), who presented mild dysmorphic features without significant intellectual disability or congenital anomalies, potentially delaying diagnosis. Sequence variants in growth-related genes were found in 18 children (18/36, 50%). One child had compound heterozygous mutations in the *SLC26A2* gene, while the others had heterozygous variants, including five pathogenic, 13 likely pathogenic, and one variant of uncertain significance (VUS). Based on molecular mechanisms of causing reduced height, defects in intracellular pathways (11/18, 61. 1%) were most common, followed by defects in the extracellular matrix (6/18, 33. 3%). Additionally, the first Korean case of familial Silver-Russell syndrome with a *CDKN1C* mutation was identified.
Conclusion
The genetic basis of SGA-SS is heterogeneous. CNVs play a significant role in this condition. The broad phenotypic spectrum of 22q11. 2 microdeletion syndrome, as seen in cases with mild dysmorphic features, highlights its importance in the differential diagnosis of SGA-SS.

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P591

JOINT3233

Spinal deformities in patients with rasopathies and pathogenic variants in related genes

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Introduction
Spinal deformities are frequently observed in individuals with Rasopathies, with manifestations varying from scoliosis and kyphoscoliosis to isolated kyphosis, suggesting the role of the RAS/MAPK pathway in bone remodeling. According to recent studies, scoliosis and kyphosis are manifestations reported in 15% of patients with Noonan syndrome (NS) and 20-35% of individuals with Cardiofaciocutaneous syndrome (CFC). However, the exact prevalence and progression of spinal deformities in Rasopathies remain unclear, warranting further investigation.
Objective
To evaluate the frequency of spinal deformities in patients with Rasopathies.
Study design and participants: This retrospective observational study was conducted in two tertiary hospitals. One hundred patients were selected (51 males, 49 females; 52 PTPN11, 10 BRAF, 9 SOS1, 5 RAF1, 5 LZTR1, 4 SHOC2, 4 KRAS, 4 RIT1, 2 MEK1, 2 NRAS, 1 SOS2, 1 NF1, and 1 A2ML1) among who underwent spinal radiographs as part of clinical investigation of Rasopathies.
Methods
We analyzed medical records regarding clinical characteristics and the presence of spinal deformities.
Results
From 88 patients with NS, 8 with CFCS, 1 with Neurofibromatosis type 1 (NF1), and 3 with NS with multiple lentigines ((NSML), we found 52 individuals with spinal deformities (52%): 32 with scoliosis, 8 with kyphoscoliosis, 2 with kyphosis, 2 with lordosis, and 20 with other alterations. Seventeen patients presented two or more associated spinal deformities. Regarding Rashopathies, 43 out of 88 patients with NS presented spinal deformities (49%), 29 patients with scoliosis (2 needing orthopedic braces), 5 with kyphoscoliosis, and 2 with kyphosis. All six patients with CFC syndrome (100%) presented spinal deformities, such as 1 with scoliosis and 3 with kyphoscoliosis. Two out of 3 patients with NSML (67%) showed scoliosis. One patient with NF1 showed anterior vertebral scalloping.
Conclusions
We observed a higher frequency of spinal deformities in our cohort than what is reported in the literature. Understanding Rasopathies' genetic and biological mechanisms could lead to new therapeutic targets for skeletal abnormalities and other manifestations of these disorders.

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P592

JOINT3242

A genetic cause of tall stature is more often detected in children with familial tall stature compared to non-familial tall stature

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Introduction
Tall stature (TS) is usually seen as mainly beneficial but can be associated with severe health risks and specific syndromic conditions. In our previous study, we revealed genetic cause in 34 % of children with familial tall stature (FTS) including the de novo pathogenic variants and autosomal dominant inherited syndromes.
Aims
To elucidate the genetic causes of TS in children with non-FTS (nFTS), to describe their phenotype in detail and to compare the results between patients with nFTS and FTS.
Methods
We enrolled children with nFTS (defined as a height > 2 SD with both parents' heights < 2 SD) referred to our centre or already followed up at our clinic between 9/2020 and 4/2024. Participants underwent genetic testing through cytogenetic analysis and next-generation sequencing of 786 growth-associated genes. Genetic findings were assessed following the American College of Molecular Genetics and Genomics guidelines. All participants also received standard endocrinological assessments and specialized anthropometric evaluations.
Results
In total, 55 children with nFTS were enrolled. Their median height was +2. 8 SD (IQR 2. 4-3. 2 SD), and their median midparental height was +0. 7 SD (IQR 0. 4-0. 9 SD). Genetic causes of TS were identified in 6/55 (11%) children (causal variant in *TGFRB2* and *SHOX*, 47, XXY [2x], 47, XXX, 48, XXXX). Additionally, in 6 children, who showed dysmorphic features suggestive of connective tissue disorder, we found interesting variants of unknown significance in genes associated with connective tissue (*MATN3, COL2A1, COL11A1,*

COL1A1, COL1A2, COL6A3 and ADAMTSL4) that are however not associated with TS yet. In comparison to the FTS cohort, the genetic cause of TS was significantly more common in FTS (32%) than in nFTS (11%). The presence of dysmorphic features was observed in 71% of children with FTS compared to 78% of children with nFTS.

Conclusion

Genetic causes of TS are more frequently found in children with FTS compared to those with nFTS. As the FTS is the clinical diagnosis mostly without indication for further investigation, children with FTS are at higher risk of being underdiagnosed. Although several variants were classified as variants of unknown significance based on current knowledge, primary connective tissue disorders may play a more important role in the aetiology of TS than previously expected.

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P593

JOINT1032

Combined human growth hormone and gonadotropin-releasing hormone analog therapy improves pubertal growth in children with poor final height prognosis: a retrospective observational study

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Introduction

Growth hormone (GH) therapy is well-established in increasing growth velocity and adult height for specific indications. In cases where final height prognosis remains insufficient despite normal puberty onset, clinicians may combine GH with gonadotropin-releasing hormone analogs (GRHa) to delay epiphyseal maturation. However, evidence supporting the efficacy of this combined therapy remains limited.

Objectives

To assess, in patients with growth hormone deficiency (GHD) or small for gestational age (SGA), whether the addition of GRHa to GH treatment in children with poor final height prognosis improves growth outcomes compared to GH alone.

Materials and Methods

This retrospective, observational cohort study was conducted across three centers. Children with poor height prognosis at puberty onset received at least 12 months of combined GH and GRHa therapy. Growth outcomes, including final height (FH), predicted adult height (PAH), and growth velocity, were compared between the GH + GRHa and GH-alone groups. Heights were expressed in standard deviation scores (SDS). Subgroup analyses were conducted based on the underlying condition (i. e., GHD or SGA).

Results

A total of 131 patients were included: 64 treated with GH + GRHa (51% girls) and 67 treated with GH-only (43% girls). At puberty onset (Tanner stage 2), patients in the GH + GRHa group were younger (11. 3 $\pm$ 1. 1 years *vs* 12. 4 $\pm$ 1. 2 years, $P < 0.0001$) and shorter (SDS; -1. 6 $\pm$ 0. 9 *vs* -1. 2 $\pm$ 1, $P = 0.006$) than GH-only group. Pubertal growth was significantly greater in patients with GH + GRHa than GH-only (29. 0 $\pm$ 4. 7 cm vs 25. 4 $\pm$ 4. 5 cm, $P = 0.002$), with the largest height gain observed in girls. Subgroup analysis showed significantly greater pubertal growth in GH + GRHa-treated patients with both GHD (27. 7 $\pm$ 4. 8 cm vs. 23. 4 $\pm$ 5. 5 cm, $P = 0.0005$) and SGA (26. 2 $\pm$ 5. 4 cm vs. 22. 2 $\pm$ 5. 2 cm, $P = 0.01$) compared to GH-only. No significant differences in FH were observed between both treatment groups in patients with SGA ($P = 0.81$). Patients with GHD treated with GH + GRHa (shorter at puberty onset with height SDS; -1. 6 $\pm$ 1 vs -0. 9 $\pm$0. 8 in GH-only group, $P = 0.004$) remained significantly smaller than GH-only group (FH SDS; -1. 4 $\pm$ 0. 7 *vs* -0. 4 $\pm$ 0. 9, $P < 0.0001$).

Conclusions

The addition of GRHa to GH therapy in children with GHD or SGA and a poor final height prognosis at puberty onset enhances pubertal growth, regardless of sex or underlying condition.

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P594

JOINT1259

Development of muscle function in children with achondroplasia under vosoritide treatment

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Background

Achondroplasia is a genetic disorder caused by a gain-of-function mutation in *FGFR3*, leading to impaired bone growth and disproportionate short stature. Children with achondroplasia often present with muscular hypotonia at birth, though its underlying pathophysiology remains incompletely understood. In 2021, Vosoritide was approved as the first targeted medication for achondroplasia. This C-type natriuretic peptide (CNP) analog counteracts the overactive FGFR3 signaling, promoting endochondral ossification and consequently increasing longitudinal bone growth. As muscle and bone development are closely connected, we investigated whether the increased growth during Vosoritide treatment is associated with changes in muscle function.

Methods and Patients

This retrospective observational study included 15 patients with achondroplasia treated with Vosoritide at our center, between October 2021 and October 2024. As part of routine clinical assessments, muscle function parameters were measured using a two-legged jump on the "Leonardo Ground Reaction Force Platform", while auxological parameters were recorded using a stadiometer and a sitting scale. Measurements were converted into z-scores using LMS data from a healthy cohort and analyzed at three time points: baseline, 12 months, and 24 months after initiating Vosoritide therapy. Statistical analysis was performed using GraphPad Prism software.

Results

15 patients (3 female) aged 6. 7 to 15. 3 years at therapy initiation were included in the analysis. The median CDC height z-score for the entire cohort ($n = 15$) at baseline was -5. 93 (IQR -6. 87;-4. 83), improving to -5. 64 (IQR -8. 02;-3. 84) after 12 months of therapy ($n = 15$). In nine children with available 24-month data, a median z-score change of +0. 89 ($n = 9$) was observed after 24 months, representing a significant increase ($P = 0.0059$). Median z-scores for weight and BMI showed no significant changes after 24 months. Z-scores for muscle function parameters, including maximal relative power, maximal velocity, and jump height, did not show significant changes over time. However, the median z-score for maximal relative force decreased after 24 months of therapy ($P = 0.0039$).

Conclusion

Compared to references from a healthy cohort, no significant changes were observed in z-scores for maximal relative power, maximal velocity, or jump height. Thus, over 12 ($n = 15$) and 24 months ($n = 9$), patients developed similarly to children without achondroplasia regarding these parameters. The observed decrease in maximal relative force, despite unchanged maximal relative power, may indicate an improved movement efficiency.

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P595

JOINT1327

SEENEZ-trial: cost-analysis of withdrawing growth hormone treatment at mid-puberty in adolescents with transient idiopathic isolated growth hormone deficiency

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Background
Idiopathic isolated growth hormone deficiency (IIGHD) is treated with recombinant human growth hormone (rhGH) to achieve normal adult height (AH). While effective in improving height, rhGH treatment is expensive, requiring hospital visits, laboratory investigations, and X-rays. It also imposes a significant treatment burden due to the necessity of daily injections. The optimal duration of rhGH treatment remains debated, with current protocols recommending continuation until near adult height (NAH). However, studies (including our SEENEZ-trial) suggest that many adolescents may not need prolonged rhGH treatment, as 70-80% of patients with IIGHD show a sufficient GH peak when retested. This raises the question whether earlier discontinuation could be cost-effective.
Aims
We aimed to analyze the costs savings of withdrawing rhGH treatment at mid-puberty in GH-sufficient adolescents with IIGHD by comparing early rhGH discontinuation with continuation until NAH.
Methods
A cost analysis was conducted alongside a multi-center patient preference trial (SEENEZ-trial). Adolescents treated with rhGH for partial IIGHD were eligible if they were in mid-puberty and had been receiving rhGH treatment for at least 3 years. Adolescents who tested GH sufficient (GH peak >6.7 µg/l) had the choice to stop or continue rhGH treatment until NAH. Adolescents who continued GH treatment received standard care, those who stopped visited the outpatient clinic twice yearly. A comprehensive analysis of the costs for each individual patient up to 3 years was performed, including healthcare costs (relating to GH medication, outpatient clinic visits, laboratory tests, and X-rays) and costs outside the healthcare sector (travel costs).
Results
A total of 127 patients (95 male, 75%) participated in the SEENEZ-trial. Forty-four patients (35%) continued rhGH treatment until NAH (GHcont), while 83 patients (65%) stopped treatment 2-3 years earlier (GHstop). Mean costs per patient in the GHcont group equaled €11, 928 per year or €27, 868 from mid-puberty until NAH. For the GHstop group, the total costs per patient averaged €222 per year and €692 from mid-puberty until NAH. On a nation-wide scale, this suggests that early discontinuation of rhGH could potentially reduce costs in the Netherlands by approximately €2 million annually.
Conclusion
Withdrawing rhGH treatment 2-3 years earlier in GH-sufficient adolescents with transient IIGHD significantly decreases medical consumption and reduces healthcare costs. Even greater cost savings will be achieved if outpatient follow-up visits after withdrawing rhGH treatment are eliminated. Future research should focus on the cost-effectiveness of rhGH withdrawal, considering final height, health-related quality of life, and quality-adjusted life years.

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P596

JOINT721

Impact of methylphenidate on growth, thyroid function, and cortisol secretion in children with ADD/ADHD: a systematic review (2000–2024)

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Background
Methylphenidate (known as Ritalin) is widely used for treating attention deficit disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD) in children. Long-term treatment has raised concerns regarding its impact on growth, thyroid function, and cortisol secretion. This review aimed to summarize findings from studies between 2000 and 2024 that investigated the effects of methylphenidate on these parameters.
Methods
A comprehensive literature review identified 20 studies examining the effects of methylphenidate on growth parameters (height, weight, IGF-1), thyroid hormones (FT4, TSH), and adrenal function (cortisol, DHEA-S). A total of 3, 500 children and adolescents across various studies were included, ranging in age from 3 to 18.

Table 1: Methylphenidate's Effects on Growth and Endocrine Parameters in Children with ADD/ADHD

Parameter	Effect of Methylphenidate
Growth	Mild growth suppression (reduced height Z-scores, weight gain), particularly during the first year; rebound growth observed after discontinuation.
IGF-1	Mixed findings: some studies show mild reductions, while others report no significant changes.
Thyroid	No significant impact on thyroid hormones (FT4, TSH).
Cortisol	Inconsistent Results some studies show elevated salivary cortisol (HPA axis activation), while others report no significant changes.

Results
• **Growth:** Twelve studies reported significant reductions in height and weight gain, particularly in the first 6–12 months of treatment. Reductions in height Z-scores were observed, with mild growth suppression attributed to appetite suppression and metabolic changes. Some studies (e. g., Safer *et al*., 1979) noted rebound growth after treatment discontinuation.
• **IGF-1:** Inconsistent findings were reported. While **5 studies** (Harstad *et al*., 2022, among others) found no significant change in IGF-1 levels, others observed mild decreases correlating with reduced growth velocity.
• **Thyroid:** Data from **3 studies** indicated that methylphenidate has no significant impact on thyroid function (FT4, TSH). Harstad *et al*. (2022) confirmed no association between methylphenidate and thyroid dysfunction.
• **Cortisol:** Findings were mixed across **6 studies**. Kholif *et al*. (2021) reported increased salivary cortisol levels after one month, indicating HPA axis activation. However, studies by Lee *et al*. (2008) and Pitzianti *et al*. (2020) found no significant changes in cortisol levels, while some reported elevated DHEA-S without clinical significance.
Conclusion
This review, encompassing **20 studies** with **3, 500 children**, highlights mild growth suppression associated with methylphenidate, especially early in treatment. Thyroid function appears unaffected, while cortisol secretion results remain inconsistent, suggesting variable HPA axis effects. Regular monitoring of growth, IGF-1, and adrenal function is recommended for children on long-term methylphenidate therapy to detect and address potential endocrine disturbances.

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P597

JOINT1684

Long-term growth hormone therapy in a patient with hallermann-streiff syndrome: a 15-year follow-up

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Objective
To report the long-term follow-up of a patient with Hallermann-Streiff syndrome (HSS) and growth hormone (GH) deficiency treated with GH therapy from early childhood to adolescence.
Methods
Case report and longitudinal evolution.
Results
A female patient diagnosed with HSS at 22 months was referred due to extreme growth failure (height –6. 6 SD). She was the second child of healthy, non-consanguineous parents. Family history was unremarkable. Pregnancy was uncomplicated, and delivery occurred at term (38 weeks), with a normal birth weight (2800 g) and length (48 cm). She had typical HSS features, bilateral congenital cataract surgery, and frequent respiratory infections. Intellectual development was normal. Endocrine evaluation showed persistently low IGF-1 (<25 ng/mL), GH deficiency confirmed by stimulation tests (peak GH: 1. 52 ng/mL after glucagon, 6. 7 ng/mL after clonidine), and delayed bone age. GH therapy (0. 028 mg/kg/day) was started in 2012 and discontinued in 2024 (age 15 years, 7 months) due to epiphyseal closure. Growth response was modest (final height: 134. 4 cm, –4. 26 SD), likely affected by the syndrome, early infections, and skeletal factors. However, GH therapy improved IGF-1 levels, muscle tone, strength, and functional capacity, enhancing energy levels and endurance. No significant adverse effects were observed despite early recurrent infections. Menarche occurred at 13 years, 4 months, with regular and prolonged cycles. At last assessment (15 years, 8 months), weight was 35 kg (–2. 2 SD), BMI 19. 38 kg/m^2 (–0. 64 SD), with complete pubertal development. Bone mineral density (L1–L4: 734 mg/cm^2, Z-score –2. 7) was low for age and sex, likely due to poor dietary calcium intake. She is under multidisciplinary follow-up:

- **Pulmonology:** Allergic asthma, obstructive sleep apnea requiring BiPAP since age 6. No significant respiratory symptoms with activity.
- **Nephrology:** Hypertension treated with enalapril and amlodipine, difficult control.
- **Cardiology:** Moderate mitral regurgitation, no restrictions.
- **Ophthalmology:** Bilateral aphakia, nystagmus.
- **Rehabilitation:** No scoliosis. Uses a small heel lift.

Highly intelligent and academically driven, she previously played soccer but now prioritizes studies.

Conclusion

GH therapy had a limited effect on final height but significantly improved muscle tone, strength, and overall physical performance. This is the first reported long-term case of GH therapy in HSS reaching adulthood, highlighting the importance of individualized expectations in syndromic growth disorders and the role of GH beyond height improvement. A multidisciplinary approach is essential for optimizing long-term outcomes in HSS patients, particularly regarding bone health, cardiovascular function, and respiratory support.

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P598

JOINT1003

Short stature and growth hormone deficiency in a case of POMC deficiency: an unexpected clinical association

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Introduction

Proopiomelanocortin (POMC) deficiency is an ultra-rare monogenic form of obesity characterized by impaired synthesis of hormones derived from the hypothalamus and pituitary gland. Mutations in the POMC gene lead to distinct phenotypic features, including early-onset obesity, fair skin, and red hair. While most reported cases in the literature describe normal growth, short stature and growth hormone deficiency (GHD) have been documented in only one case. Among three POMC deficiency cases followed at our center, none demonstrated short stature, making the findings in this patient particularly noteworthy for expanding the syndrome's clinical spectrum.

Case Presentation

A 15-year-old female was first evaluated at 3. 5 years of age with obesity, fair skin and red hair, ACTH deficiency, and recurrent episodes of severe hypoglycemia during infancy. The diagnosis of POMC deficiency was confirmed by identifying a homozygous pathogenic c. 64delA variant in the POMC gene. During follow-up, delayed puberty and hypogonadotropic hypogonadism were identified. From the age of 12 years onward, growth retardation and short stature became apparent. At age 13, the patient's physical examination revealed a weight of 56. 7 kg (SDS: 0. 8), height of 143 cm(SDS: -2. 5), BMI of 27. 1 kg/m^2 (SDS: 2), and annual growth velocity of 1. 64 cm/year (SDS: -1. 61). The patient was at Tanner stage 1. Bone age, assessed at 14 years of age, corresponded to 10 years. After achieving a euthyroid state and estrogen priming, L-Dopa and clonidine stimulation tests were performed, showing peak GH levels of 0. 52 μg/l and 1. 0 μg/l, respectively. These findings confirmed a diagnosis of growth hormone deficiency(GHD). Pituitary MRI revealed normal size and morphology with no pathological findings. GH replacement therapy was initiated at 0. 035 mg/kg/day at 14 years and 3 months of age. After 8 months of therapy, the patient's weight was 59. 8 kg(SDS: 0. 67), height was 150. 2 cm(SDS: -1. 95), BMI was 26. 51 kg/m^2 (SDS: 1. 79), and annual growth velocity was 11. 29 cm/year.

Discussion

Although normal stature is typically reported in POMC deficiency, the short stature and GHD observed in this case represent rare and striking finding that expand the clinical spectrum of the syndrome. The rarity of short stature in most reported cases of POMC deficiency underscores the uniqueness of our case. The etiology of GHD in POMC deficiency remains unclear. The co-occurrence of these conditions could be coincidental; however, the severe hypoglycemic episodes experienced during early infancy may have impaired hypothalamic-pituitary development and GH secretion, contributing to GHD in this patient.

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P599

JOINT1381

Impact of the TUITEK™ patient support program on caregivers-related behaviours in enhancing growth hormone treatment adherence

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Background

Recombinant human growth hormone (r-hGH) treatment can improve or normalise growth outcomes in paediatric patients with growth hormone deficiency. However, poor adherence to the long-term treatment regimen limits its effectiveness and leads to sub-optimal growth outcomes. The multicomponent, individualised TUITEK™ Patient Support Program (PSP) aims to guide behavioural changes throughout the treatment care pathway in a way that is personalised to the needs of individual patients and their caregivers.

Aim

To determine the impact of the TUITEK™ PSP on the knowledge, beliefs, and perceptions of high-risk caregivers regarding adherence to r-hGH treatment (disease and treatment coherence, emotional burden, self-administration, and treatment-related anxiety).

Methods

This prospective pre–post study of the TUITEK™ PSP was conducted in a combined population of caregivers (aged 25–60 years) of patients with short stature receiving r-hGH treatment (somatropin [Saizen®; Merck KGaA, Darmstadt, Germany]) using auto-injector device and injection pens in Argentina, the Republic of Korea, and Taiwan. The analysis included caregivers categorised as high-risk were offered a set of five personalised telephone calls from a trained nurse practitioner over 3 months, along with resource packs with a range of behaviour change techniques. Two weeks after the final call of the TUITEK™ PSP, caregivers were contacted to complete a follow-up personalisation questionnaire. Changes in the questionnaire-based scores were assessed.

Results

Data from 409 high-risk caregivers were obtained. Of these caregivers, 10. 3% were considered high risk for disease and treatment coherence, and 71. 4% were considered high risk for emotional burden. Involvement in the PSP was associated with a statistically significant ($P < 0.0001$) positive change in all factors. These improvements were reflected in the number of caregivers who moved from the high- to low-risk category at the end of the PSP. The greatest change was observed for disease and treatment coherence, with only 1 of the 42 high-risk caregivers failing to move into the low-risk category. When looking at any positive change in score, 100% of caregivers who were high-risk at baseline had a beneficial change in disease and treatment coherence, 86. 4% a change in self-administration, 63% a change in emotional burden, and 79. 6% a change in treatment-related anxiety. The changes observed in the overall cohort remained similar when the data were analysed separately for individual countries.

Conclusions

The TUITEK™ PSP successfully improved key caregiver-related behaviours that may negatively impact adherence to r-hGH treatment. Furthermore, it might improve treatment adherence and thus clinical outcomes.

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P600

JOINT3299

A novel point-of-care molecular diagnostic method for the rapid diagnosis of Turner syndrome

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Introduction

Turner syndrome (TS) is a common aneuploidy affecting 1 in 2500 girls and has a multi-systemic presentation including short stature, pubertal delay, congenital anomalies of the heart, kidney, low performance-IQ, high risk for cardiometabolic diseases and osteoporosis etc. It is diagnosed by peripheral-blood karyotyping only after overt clinical manifestations develop, thus losing valuable time for early growth hormone therapy, pubertal induction and screening for anomalies. Till date, is no point-of-care test for a rapid and accurate diagnosis of TS has been in use.

Objective
To assess the sensitivity and specificity of qPCR in diagnosing karyotypic variants of TS and develop a POC test for TS by developing a covalent organic framework (COF) based dual mode sensor for DNA samples.
Methods
In the first part, we extracted genomic DNA from peripheral blood samples of 50 girls with TS (45, X = 23, 45, X/46, XX = 10, Isochromosome Xq = 12, 45, X/46, XY mosaics = 5), 25 normal females(46, XX) and 5 normal males(46, XY) . Using real-time PCR, we conducted qPCR with four genes - two Xp genes [SHOX and ARSE] and two Xq genes [VAMP7 and XIST] and a housekeeping autosomal gene HBB. The ΔΔ CT method was used for gene dose calculation and ROC curves were constructed to determine cut-offs for the different genes. Using the genes with best ROCs (SHOX and ARSE), we designed two pairs of complementary oligonucleotides decorated on a covalent organic framework (COF). Due to different doses of the target genes, the frameworks get arranged in a unique fashion, leading to quantitative changes in emission and electrochemical responses of the COF.
Results
qPCR could distinguish TS from normal females with >85 % sensitivity and specificity. SHOX could discriminate between TS from female controls with 86 % sensitivity and 86. 4 % specificity at a cut-off of 0. 75 while ARSE had a sensitivity of 82. 6% and specificity of 83. 6% at a cut-off of 0. 86. The ARSE gene was particularly useful to diagnose non-classic TS. The dual mode sensor developed using COF for SHOX and ARSE genes yielded the diagnosis in all the samples tested. However, it could not diagnose ring chromosomes and very low levels of mosaicism.
Conclusion
We have developed a novel dual-mode COF sensor for the diagnosis of Turner syndrome. This might be used for neonatal or community-based screening programmes to detect TS.

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P601

JOINT2518

Genotype-phenotype correlations and clinical variability in noonan syndrome

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Background
Noonan syndrome (NS) is a congenital genetic disorder with an estimated incidence of 1 in 1, 000-2, 500 live births. It is characterized by congenital cardiac abnormalities, short stature, distinctive facial features, chest deformities and variable cognitive deficits. NS results from pathogenetic variants in genes involved in the RAS/MAPK signaling pathway, exhibiting significant genetic and clinical variability.
Aims
To assess the prevalence of specific genetic mutations and their impact on clinical outcomes in NS.
Methods
We conducted a retrospective observational study of 111 patients with genetically confirmed NS. Data collected included genotype, cardiac defects, and anthropometrics (birth weight, birth length, stature, and weight at the last visit). Standard deviation (SD) scores were calculated using Italian population growth charts.
Results
Complete data were available for 60 NS patients (38% males). The most common mutations occurred in *PTPN11* (60%) and *SOS1* (10%), with additional variants observed in *LZTR1, RAF1, RIT1, CBL, KRAS, SOS2, BRAF, MAP2K1*. Cardiovascular abnormalities were present in 62% of patients, with *PTPN11* and *RIT1* mutations predominantly linked to pulmonary valve stenosis and *RAF1* mutations to hypertrophic cardiomyopathy. Less common cardiac defects, such as atrial and ventricular septal defects and mitral or aortic valve abnormalities, showed no clear genotype correlation. Small for gestational age (SGA) was observed in 5% of patients, all of whom carried PTPN11 mutations. At mean age of 9. 8 ± 5. 9 years, average height and weight were -1. 8 ± 1. 18 SD and -1. 5 ± 1. 40 SD, respectively. Short stature was observed in 42% patients, with a mean height of -2. 84 SD. Growth hormone therapy was used in 37% of patients, most of whom carried PTPN11 mutations (74%, $P < 0.05$). Among SGA patients, two thirds developed short stature. Notably, patients with *CBL, SOS2*, or *MAP2K1* mutations did not exhibit short stature. In 28% of the cohort, both short stature and cardiac defects co-occurred, though this combination was not significantly linked to a specific genotype.
Conclusion
This study highlights the high prevalence of cardiac abnormalities and short stature in NS, with clear genotype-phenotype correlations for cardiovascular defects. While being born SGA was relatively uncommon, it appeared to be specifically associated with the *PTPN11* genotype. In contrast, genotype-growth correlations were less distinct, though certain mutations seemed to confer a lower risk of short stature. These findings underscore the genetic and clinical variability of NS and the need for larger studies to better understand genotype-phenotype correlations.

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P602

JOINT1955

Is the high incidence of false-positive results of growth hormone stimulation tests in children with short stature related to the nutritional status? Let's ask artificial intelligence

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There is increasing evidence that the incidence of false positive results of growth hormone (GH) stimulation tests (GHST) in children with short stature may be relatively high. The challenge is to identify the patients who may be overdiagnosed with GH deficiency (GHD) for this reason. Interpretation of GHST in children does not take into account their nutritional status. The aim of the study was an attempt to use machine learning methods for prediction of isolated GHD and idiopathic short stature (ISS) in children with excluded other causes of short stature (other endocrinopathies, chronic diseases, genetic defects, malnutrition, cancers, brain injuries), based on auxological indices and IGF-1 concentration. Records of 1592 children with short stature (height SDS <-2. 0), aged 10. 3±3. 4 years (mean±SD), were used for creating classification models for predicting GHD or ISS with different techniques of machine learning. In all of the patients height and weight were measured, two GHST (after clonidine and glucagon) were performed with the cut-off for GH peak 10 µg/l, IGF-1 concentrations were determined, bone age (BA) was assessed, and body mass index (BMI) was calculated. Models were created on raw data (age, sex), age-related variables expressed as SDS for age and sex (hSDS, IGF-1 SDS, BMI SDS), while BA as its ratio to chronological age (BA/CA). Based on GH peak in both GHST <10 µg/l, GHD was diagnosed in 604 patients (37. 9%), including 378 out of 985 boys (38. 4%) and 226 out of 607 girls (37. 2%); the remaining children were diagnosed with ISS. In the decision tree, GHD was predicted in 156 patients, in 149 ones based on BMI SDS >0. 91. Naive Bayes classifier (the method that should include real size of groups) predicted GHD in only 118 cases. The best multilayer perceptron (MLP) neural network predicted GHD in 352 patients. Logistic regression with forward stepwise variable selection classified 269 patients to GHD group, keeping only BMI SDS and IGF-1 SDS as significant variables. All the obtained models classified much less patients to GHD group than the results of GHST <10 µg/l. The significance of higher BMI SDS for prediction of GHD shown in AI models seems a possible cause of inaccuracies of prediction. It seems that these results speak for the need to interpret the results of GHST depending on the nutritional status of children rather than for inability of machine learning techniques to create prediction models.

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P603

JOINT1215

The medical impact of hypochondroplasia by age among adults in England between 1998 and 2019: a matched cohort study using electronic medical records from the clinical practice research datalink

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Hypochondroplasia (HCH) is a rare genetic skeletal dysplasia causing disproportionate short stature secondary to pathogenic variants in the gene fibroblast growth factor receptor 3 (*FGFR3*). This retrospective study compared the medical impact of HCH among adults with the general population in England from 1998 to 2019. A real-world matched cohort study was conducted using electronic primary care medical records from the Clinical Practice Research Datalink. Adults with HCH identified using a specific HCH diagnosis code (SNOMED:315057016) or a general code (ICD-10-CM:Q77. 4) were split into 4 age groups (19-29, 30-49, 50-69, and $\geq$70 years of age [y]) and matched 1:4 with controls by sex, nearest birth year, and region. Event rates (events/100 person-years [PY]) and rate ratios (RR; cases vs controls) were calculated for selected comorbidities and healthcare use. Overall, 385 adults with HCH and 1373 matched controls were included: 136 and 572 (19-29y), 181 and 592 (30-49y), 49 and 142 (50-69y), and 19 and 67 ($\geq$70y), respectively. Across ages, mean follow-up time ranged from 6 to 8 years for adults with HCH and 11 to 14 years for controls, respectively. Comorbidity event rates were higher among adults with HCH vs controls and generally increased with age; the highest rates were for respiratory, mental health, cardiovascular, and orthopaedic events (**Table**). Although surgical procedures were infrequent, orthopaedic surgery rates were higher among adults with HCH than controls. Adults with HCH utilized more healthcare resources than controls, and rates generally increased with age. General practice visits were most frequent (range, 1055. 02–2778. 55 visits/100 PY), followed by inpatient admissions (range, 319. 68–520. 46 visits/100 PY). In all age groups, mortality rates were higher for individuals with HCH than controls, peaking among those aged 30 to 49 years (RR: 3. 31 [19-29y], 18. 41 [30-49y], 4. 92 [50-69y], 1. 72 [$\geq$70y]). Rates of certain conditions typically increase with age; the increase is more pronounced for people with HCH. Results highlight the medical burden of HCH and the importance of lifelong multidisciplinary management.

Table. Comorbidity rates in adults with HCH versus controls.

Body system category	RR (95% CI) 19-29y	30-49y	50-69y	≥70y
Overall (across all body systems)	2.31 (1.91-2.79)	3.04 (2.63-3.52)	2.96 (2.36-3.73)	2.42 (1.65-3.54)
Respiratory	2.39 (1.58-3.63)	6.59 (4.66-9.32)	5.10 (3.14-8.27)	2.18 (1.11-4.29)
Mental health	1.33 (0.94-1.89)	2.43 (1.86-3.16)	1.60 (1.03-2.50)	3.90 (1.76-8.64)
Cardiovascular disease	17.28 (7.61-39.22)	7.09 (4.73-10.62)	3.49 (2.49-4.90)	1.16 (0.74-1.81)
Orthopaedic	2.24 (1.30-3.84)	5.69 (4.10-7.89)	7.27 (5.09-10.38)	6.24 (3.87-10.06)

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P604

JOINT1847

Screening for shox gene variation in children with apparently idiopathic short stature: systematic screening or clinical and radiological oriented screening?

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Introduction
Short-stature homeobox-containing (SHOX) gene haploinsufficiency is the most frequent monogenic cause of short stature and is responsible for highly variable phenotypes ranging from idiopathic short stature (ISS) to severe dyschondrosteosis in the Langer syndrome. The reported prevalence of SHOX haploinsufficiency in children with apparently ISS varies from 2 to 17%, and its radiological expression is variable. The aim of this study was to find out whether simple radiological characteristics on the left-hand and wrist radiography were associated with the presence of SHOX gene variations and could be a good indicator for SHOX gene molecular study.

Materials and Methods
This study is a descriptive, retrospective and non-interventional study based on clinical and radiological data of 266 patients with apparently ISS referred to the Pediatric Endocrinology Unit of Angers University hospital from 2016 to 2023 for whom SHOX analysis was performed by Multiplex Ligation-dependent Probe Amplification (MLPA) and/or sequencing. To further analyze the sensitivity of radiological criteria for the molecular diagnosis of SHOX variations, we additionally included 33 patients diagnosed with a SHOX mutation between 2010 and 2015.
Results
11% of patients with apparently ISS had a SHOX deficiency. SHOX deficiency was more often associated with convexity of the distal radial metaphysis ($P < 0$, 001), pyramidalisation of the carpal row ($P < 0$, 001) and lucency of the ulnar border of the distal radius ($P < 0$, 001), but no difference was found considering the triangularization of the distal radial epiphysis ($P = 0$, 142). A cut-off point of 148 degrees for the convexity of the distal radial metaphysis had a sensitivity of 90% and a specificity of 47, 8%, and a cut-off point of 129 degrees for the pyramidalisation of the carpal row had a sensitivity of 87, 5% and specificity of 50, 3%.
Conclusion
We found cutoffs for SHOX gene variation diagnosis from the simple left-hand and wrist radiology. These cut-offs had a fair sensitivity (90%) and a mild specificity (50%). This suggests that in structures where the resources for SHOX molecular study are limited, an oriented screening based on these cutoffs would decrease the number of molecular studies by half (and would miss 10% of the SHOX gene variations), whereas, in structures where molecular studies are easily available, systematic screening of children with otherwise unexplained short stature might be useful.

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P605

JOINT1823

Long term follow-up in a patient with Cat Eye syndrome, hypopituitarism and hypertransaminasemia

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Background
Cat Eye Syndrome (CES), also known as Schmid-Fraccaro syndrome, is a rare chromosomal disorder typically caused by trisomy or partial tetrasomy of chromosome 22 (inv dup 22pter to 22q11. 1). It is characterized by a classic triad of iris coloboma, anal atresia, and ear anomalies, seen in about 40% of cases. The clinical spectrum often includes features such as hypertelorism, down-slanting palpebral fissures, preauricular pits, and intellectual disability. Chromosomal rearrangements in the 22q11. 2 region can affect midline structures, such as the pituitary gland, leading to growth hormone (GH) deficiency and other hypothalamic-pituitary axis abnormalities. Although this case was previously described by other authors at birth (Serra *et al*. 2022), our aim is to present the long-term follow-up and the therapeutic outcome.
Case Presentation
We present the case of a full-term newborn from healthy parents, following a normal pregnancy and birth. The infant developed persistent hypoglycemia and cholestatic jaundice shortly after birth. Physical examination revealed hypotonia, anorectal malformation with the anal outlet located in the vaginal fornix, along with facial dysmorphisms, including hypertelorism, microphthalmia, and dysplastic ears. Ophthalmologic evaluation confirmed bilateral iris coloboma, and echocardiogram revealed atrial septal defect. Endocrine testing showed congenital deficiencies of cortisol, GH, and thyroid hormones, leading to the diagnosis of hypopituitarism. Following this, hydrocortisone and levothyroxine were initiated. No symptoms suggestive of diabetes insipidus were observed. Brain MRI documented aplasia of the anterior pituitary gland, agenesis of the pituitary stalk, and ectopic neurohypophysis. Array CGH confirmed partial tetrasomy of chromosome 22 (22q11. 1q11. 21), establishing the diagnosis of CES. After the initial hospitalization at birth, the patient began multidisciplinary follow-up and was started on GH replacement therapy, along with oral hydrocortisone and levothyroxine, which allowed for adequate glycemic and thyroid control. At the current age of 3, despite early developmental delay and growth failure, she has shown significant catch-up growth (height: from -6 to -3. 6 SDS; weight: from -6 to -3. 3 SDS). Cholestasis has improved with cortisol therapy, although transaminases and gamma-GT have remained elevated.
Conclusion
Congenital hypopituitarism can be a part of the highly variable phenotypic spectrum of CES, often presenting with neonatal hypoglycemia, cholestasis, and

severe growth delay. Six other cases with pituitary abnormalities and hormonal defects have been reported in the literature (four with isolated GH deficiency, two with hypogonadotropic hypogonadism). Cortisol deficiency is known to impair bile recirculation, but persistent hypertransaminasemia and elevated gamma-GT suggest a multifactorial cause of hepatic cytolysis despite hydrocortisone treatment.

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P606

JOINT638

Quality of life, sexuality, and psychosocial well-being in adult women with turner syndrome: insights from a danish questionnaire survey

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Introduction
Women with Turner syndrome (TS) face multiple challenges that can impact their quality of life (QoL), including psychological, social, and sexual well-being. While previous research has focused on girls with TS, data on adult women remain sparse and inconsistent. Adulthood introduces new challenges, such as relationships, infertility, and working life, which may markedly influence QoL. This study explores the physical, psychosocial, and sexual well-being of adult women with TS providing insights into their overall QoL.
Methods
Between 2020 and 2024, all women with TS attending the outpatient clinic were invited to complete an electronic questionnaire. Ten age- and geographically matched female controls from the general population were invited per TS participant. The questionnaire covered demographics, socioeconomic status, and health problems, as well as validated instruments assessing quality of life, sexual function, and mental and physical well-being; among them the WHOQoL-Bref, SF-36, the Female Sexual Function Index (FSFI-19), and scales measuring stress, anxiety and depression.
Results
In total, 131 women with TS and 237 controls completed the questionnaire. Among TS women, 91 were currently receiving hormone replacement therapy (HRT), 15 had been treated with HRT until menopause (defined as age $\geq$45), and 25 were not currently or had never received HRT. The median age was 37 years (IQR: 26–51) for TS women and 42 years (IQR: 30–54) for controls ($p < 0.0001$). Partner status differed significantly, with 53. 3% of TS women having a partner vs 79. 5% of controls ($p < 0.0001$). Women with TS had significantly lower SF-36 scores across all domains except Bodily Pain, with the lowest in Vitality, Mental Health and Social Functioning (all $p < 0.001$). The median SF-36 General Health score was 65 (IQR: 40–80) for TS women vs 75 (IQR: 60–85) for controls ($p < 0.0001$). Similarly, TS women scored lower across all WHOQoL-Bref domains, with a median overall QoL score of 62. 5 (IQR: 50–75) vs 75 (IQR: 62. 5–75) in controls ($p < 0.0001$). Overall, 65. 0% of TS women reported sexual activity within the past four weeks, compared to 82. 2% of controls ($P = 0.003$). Among sexually active TS women, FSFI-defined scores for arousal, orgasm, and pain were significantly lower (all $p < 0.02$), indicating sexual dysfunction. No significant differences were found in overall QoL scores between sexually active and inactive TS women.
Conclusion
Women with TS report significantly more physical, psychological, sexual, and social challenges than controls.

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P607

JOINT1400

Total and bioactive IGF-i in healthy children and adolescents and in short children during growth hormone therapy: an alternative tool to individualized GH treatment in patients

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Background
The growth response following recombinant human growth hormone treatment (rhGH) varies. Accordingly, titration of doses is often based on assessment of serum total IGF-I. However, in a recent study of SGA children, serum levels of bioactive IGF (bio-IGF) were lower than total IGF-I, indicating a therapeutic opportunity for increasing the dose of rhGH.
Aims
To assess if bio-IGF could be a clinically relevant biomarker, helping to titrate the dose of rhGH, we determined serum bio-IGF reference ranges in patients with short stature due to various conditions.
Method
Reference population: A cohort of 570 healthy children and adolescents (59% girls) from an ongoing study (COPUS III). GH treated children: In total, 130 patients (35% girls) enrolled during 2024. Patients included subgroups of: GH deficiency (GHD), small for gestational age (SGA), Turner (TS), Prader Willi syndrome (PWS), Chronic Renal Insufficiency (CRI) or Other. In 128 children, blood samples were collected once during rhGH. All samples were analyzed for bio-IGF (KIRA assay) and total IGF-I (iSYS).
Results
In healthy girls and boys, bio-IGF increased with age and peaked at mid-puberty (Tanner-stage, mean (range)): B3, 1. 35 (0. 57-4. 03) μg/l and G3, 1. 25 (0. 44-2. 45) μg/l, respectively. Total and bio-IGF correlated significantly in healthy boys: Pearson $r = 0.60$, healthy girls: r=. 55, GH treated boys: $r = 0.76$ and GH treated girls: $r = 0.61$. In children receiving rhGH, the prevalence of concentrations exceeding +2SD was higher for total IGF-I compared to bio-IGF (25% vs. 13%), especially in non-GHD patients (Table 1).
Conclusion
Reassuringly, most non-GHD patients had IGF bioactivity within references based on healthy age-matched children, despite 25% of subjects having total IGF-I concentrations above +2SD. Further studies are needed to evaluate the clinical value of bio-IGF as an alternative biomarker in short children receiving GH treatment.

Table 1: Characteristics of patient groups presented as median (range)

Subgroups (n)	Bio IGF SD	IGF-I SD
GHD (75)	1. 07 (-2. 63-6. 09)	1. 08 (-2. 79-4. 04)
SGA (21)	1. 06 (-0. 86-3. 52)	1. 88 (-1. 37-3. 42)
Turner (7)	0. 12 (-2. 88-2. 15)	1. 55 (-1. 06-2. 79)
PWS (7)	. 85 (-0. 05-1. 80)	2. 06 (0. 40-2. 66)
CRI (4)	1. 24 (0. 81-1. 80)	1. 41 (0. 20-1. 86)
Other diagnoses (14)	**0. 85 (-0. 48-1. 42)**	**1. 41 (0. 45-2. 40)***
All diagnoses (128)	1. 05 (-2. 88-6. 09)	1. 27 (-2. 79-4. 04)
All non-GHD diagnoses (53)	**1. 00 (-2. 88-3. 52)**	**1. 55 (-1. 37-3. 42)***

MWU: Mann-Whitney U test, ***P*-value < 0. 05**

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P608

JOINT3781

Frequency, detection and management of scoliosis in children with prader willi syndrome – experience of an irish tertiary referral centre

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Prader Willi Syndrome (PWS) is a rare genetic neurodevelopmental condition typically associated with hyperphagia, weight gain and premature mortality largely due to extreme obesity. Prevalence is estimated to be 1 in 11, 000 in Ireland. Scoliosis is a recognised feature of Prader Willi Syndrome noted to occur in over 40%, independent of growth hormone therapy treatment. The cause is unknown but as the distribution is bimodal, it is hypothesised that in infancy it relates to hypotonia and in later childhood follows the same pattern as idiopathic scoliosis in the general population.
Aims
To audit the frequency of scoliosis in an Irish cohort of children with PWS. To explore the methods of assessment and onward referral to orthopaedics where appropriate.

Methods
Detailed retrospective chart review of patients attending a tertiary specialist paediatric PWS service was undertaken in September- October 2024. Clinical and radiological examination for scoliosis was assessed, as were age, sex, growth hormone status, timing of assessments and scoliosis management. Findings were compared against the 2024 PWS UK & Ireland Prader–Willi syndrome: Guidance - scoliosis recommendations, which include annual clinical examination and two yearly radiographic examination during years of peak prevalence of scoliosis.
Results
All 49 patients currently attending the service, aged 0. 5 -14 years (50% male), were evaluated. Scoliosis was detected in 33 patients (67%) which was clinically evident in 24 (72%) and confirmed radiologically. The remaining 9 (27%) were detected on radiological screening. Referral for orthopaedic assessment was completed for all 33 children, 11 (33%) were awaiting review at the time of study; 12 (36%) were undergoing active orthopaedic monitoring and a further 10 (30%) had undergone orthopaedic interventions, including casting, bracing, or surgery (growing rods or posterior spinal fusion). In 36 patients (73%), there was full compliance with recommendations. In 8 cases less frequent radiological screening was undertaken and 4 (8. 3%) had more frequent radiology than recommended. This was for monitoring of a mild spinal curvature before referral to orthopaedics when the Cobb angle had exceeded 10 degrees.
Conclusion
Scoliosis is common in children with PWS. Regular spinal examination with radiological assessment is important for detection and subsequent management of scoliosis. The prevalence of scoliosis in PWS in Ireland was similar to that reported in the USA. However, orthopaedic intervention was twice as common in the Irish cohort. This could potentially be influenced by long waiting times for paediatric orthopaedic assessment in Ireland and merits further study.

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P609

JOINT2532

Characterization of bone health in an adult population with turner syndrome: insights from a monocentric cross-sectional study

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Background
Low bone mineral density (BMD) is a common feature of Turner syndrome (TS), frequently with an early onset, whose pathogenetic mechanisms and risk factors are not completely elucidated.
Aim
To evaluate the prevalence of low BMD, clinical fractures, and associated risk factors in a large population of adult TS patients attending a tertiary hospital with a structured transition program.
Methods
A cross-sectional analysis was conducted on 176 patients with TS (median age:36. 1yrs, range:15. 3-70. 7) at the time of their most recent dual-energy X-ray absorptiometry (DXA). Anthropometrics, bone metabolism markers, karyotype, typical comorbidities, details about prior and current estrogen replacement treatment (ERT) and prior rhGH treatment (rhGHT) were evaluated to assess their impact on lumbar/hip BMD, Z-scores and fracture risk.
Results
Seventy-one patients (40. 3%) presented a 45, X0 karyotype. Spontaneous menarche occurred in 36 patients, and 19 subsequently developed secondary amenorrhea. ERT was started at a median age of 16. 0yrs (range: 8. 0-50. 0), lasting 19. 0yrs (range: 0. 0-45. 0). rhGHT was administered in 120 patients (69. 8%). Regarding bone metabolism, 46 patients (27. 7%) exhibited low BMD (lumbar/hip Z-score $\leq$ -2), 13 (7. 4%) experienced clinical fractures. Ten patients (5. 7%) were on antifracturative treatment. Patients with low BMD had later induced/spontaneous menarche (17. 0 vs 16. 0yrs, $P = 0.047$), higher prevalence of primary amenorrhea (93. 5% vs 75. 4%, $P = 0.009$) and of family history of osteoporosis/fractures (27. 3% vs 8. 2%, $P = 0.025$) compared with patients with normal BMD. No significant differences were found in biochemical calcium-phosphate markers, bone turnover markers, and both sub-groups had adequately supplemented vitamin D levels. Age, karyotype, prior rhGHT, and prior or current ERT analysed as daily dose, type of estrogen, route of administration and duration, were not different between the two sub-groups. Patients with fragility clinical fractures had lower lumbar Z-scores (-2. 0 vs -1. 1, $P = 0.042$), and higher prevalence of other typical TS comorbidities (diabetes mellitus, major/minor cardiovascular events, hypertension, nephropathy), despite no age or BMI differences. No significant differences were also noted in karyotype, ERT or rhGHT. Notably, five patients with normal BMD experienced fragility fractures. However, DXA remained a reliable predictor of fractures, as patients with low BMD exhibited a significantly higher fracture risk (OR = 4. 84, 95CI:1. 49-125. 70, $P = 0.009$).
Conclusions
TS are at high risk for low BMD and fragility fractures, regardless of karyotype, rhGHT and type and extension of ERT. At variance, a delayed ERT initiation, as well as primary amenorrhea, are risk factors for low BMD. Therefore, continuous, lifelong monitoring of bone health is essential for all TS patients.

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P610

JOINT1771

Prevalence and growth pattern of poor long-term responders to gh therapy in prepubertal short children born small for gestational age: real life data from them belgian-luxembourgish registry BELGROW

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Background
GH therapy increases adult height in short small for gestational age (SGA) children, especially when started before puberty, but with high variability in height gain. The aim of this study was to describe the prevalence and the growth pattern of poor long-term responders to GH therapy in a real-life setting.
Methods
SGA (birth weight and/or length for gestational age $<$ - 2 SDS) children, starting GH therapy after the age of 4 years and before onset of puberty with an initial height SDS $<$ -2. 5 and $<$ -1 when adjusted for mid parental height (MPH) SDS, having reached near adult height (NAH) (height velocity increase $<$ 1 cm/6 months) were selected from the BELGROW database.
Results
182 (100 male) patients were analyzed. Median (Q1;Q3) age at start of GH therapy was younger in females (8. 8 (6. 3; 10. 8) than in males 9. 1 (6. 6;11. 6) years; $P = 0.188$), but treatment duration was longer in males (7. 1 (5. 4;9. 7) than in females 6. 1 (4. 7;8. 3) years; $P < 0.05$). Median height SDS at start of treatment (-3. 00 (-3. 44;-2. 75)), GH dose (0. 037 (0. 034;0. 042) mg/kg/day), NAH SDS for chronological age (-1. 88 (-2. 40;-1. 35)) and corrected for MPH (-0. 61 (-1. 21;-0. 19)) as well as total SDS height gain (1. 25 (0. 84;1. 76)) were similar in males and females. At NAH, 63% (114; 59 male) of patients remained short (SDS calculated for age 21 years $<$ -2), 49% (89; 50 male) were below target height (NAH SDS corrected for MPH $<$ -1) and 15% (28; 14 male) had a poor total height gain (total height SDS increase $<$ 0. 5). In total, 18% (32; 15 male) of patients had a poor initial growth (height SDS increase $<$ 0. 3 during the first year of therapy), while 22% (40; 19 male) had a poor growth during puberty (height SDS decrease during puberty $>$ 0. 3). Of the 28 patients with a poor total height gain SDS, 7 (25 %) had a poor initial growth and 10 (36 %) had a poor pubertal height gain.
Conclusion
Despite prepubertal start of GH therapy, 63% of short SGA patients did not reach an adult height $>$-2SDS. Either a poor initial growth response or an impaired pubertal growth spurt were observed in more than half of SGA patients with a poor long-term height gain. These findings highlight the need for a more rigorous diagnostic re-evaluation, a swifter GH dose adaptation and a regular assessment of non-adherence.

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P611

JOINT497

Advancing precision in GH therapy: AI models for predicting IGF-1

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Background
International guidelines recommend dosing growth hormone (GH) based on body weight or body surface area. However, since GH regulates the production and release of IGF-I in the liver, using IGF-I as a biomarker presents a promising strategy for optimizing GH therapy dosing. Despite its potential, this approach is complicated by the inherent complexity and variability of IGF-I.
Aim
To optimize dosing strategies by showcasing the potential benefits of advanced machine learning techniques through a comparison of three different models and identifying key features for predicting IGF-1 SDS.
Methods
Data from 63 boys from previous clinical trial were included containing variables related to early growth, the start of GH treatment, and around the prediction time. 3-month predictions of IGF-1 SDS during maintenance and puberal growth phases on GH treatment were constructed using three different machine learning models; linear regression, symbolic regression and explainable boosting machine (EBM). Linear regression was used as a baseline representing classic statistical regression.
Results
Linear regression demonstrated poor performance with an R^2 of 0. 07, whereas the more advanced machine learning models—symbolic regression and EBM—achieved significantly better results, both with an R^2 of 0. 47. Mean absolute error for linear regression showed 0. 78 while both symbolic regression and EBM showed 0. 55. Key features identified by both models were baseline IGF-1 SDS, height velocity before GH treatment, weight and ΔIGF-1 at 1 year on treatment.
Conclusion
Symbolic regression demonstrated clinical practicality by providing accurate predictions using only seven predictors, while EBM offered valuable interpretability and deeper insights into factors influencing IGF-1 SDS. Notably, EBM identified GH dose as an important feature, a relationship not detected by symbolic regression or linear regression, likely due to its complexity. Together, these models enhance individualized treatment strategies and advance precision medicine in GH therapy.

Machine Learning models	Predictors	R^2	Mean Absolute Error	Mean Absolute Percentage Error
Linear Regression	33	0. 07	0. 78	0. 68
Symbolic Regression	7	0. 47	0. 55	0. 47
Explainable Boosting Machine	63	0. 47	0. 55	0. 32

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P612

JOINT3155

EKAT-06 evidence based knowledge for monitoring childhood growth

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Background
A child's growth is a diagnostic tool that can reveal diseases and psychosocial problems. Abnormal growth is a common reason for referrals to paediatric- and paediatric endocrine- clinics. Childhood obesity is a public health issue with risks of comorbidities and reduced quality of life. Children with obesity are often referred to healthcare several years after obesity onset, reducing the effectiveness of interventions. There is a lack of evidence (EBM) on when healthcare should respond to growth deviations. Current guidelines are based on expert-based guidelines, without strict EBM-knowledge. Analyzing growth can be done using automated algorithms (Finnish project), which have shown that diagnoses were made several years earlier and for more children compared to routine follow-ups. No similar project has been conducted outside Finland. The Regional Halland healthcare Information Platform (RHIP) is a comprehensive data system that collects population-wide healthcare data in the province of Halland. Halland, located in the southwest of Sweden, is the 7th (out of 21) largest province by population. The overall objective is to analyze growth deviations and study how abnormal growth is related to disease ICD10-diagnoses. The main objective is to evaluate the ability and results of Swedish expert-based guidelines and Finnish algorithms to detect individual deviations from expected growth patterns. The secondary objective is to analyze how socioeconomic factors (SES) at the family and residential level are related to growth deviations.
Methods
The study utilize RHIP. Electronic health records data from three hospitals, two emergency departments, and 46 primary care/child health care units (including private healthcare providers), including pre-birth data from obstetrics. Individuals born between 2009-2022, registered in Halland at some point between 0-6 years of age are included in the study. Longitudinal growth data from 55, 508 children, along with health and SES-data from RHIP and national registers are gathered in mean 18. 3 measurements/child.
Results
A Paediatric-RHIP is now constructed, several results will follow the coming years. Results from a pilot-study shows that there is SES inequality in 3–5-year-olds. The risk of being overweight/obese in areas with the lowest socio-economic status is 72% higher than in the most affluent quintile of residential areas.
Conclusion
Knowledge from the project may lead to optimized identification and referral of deviant growth. For the first time can EBM-guidelines of deviant growth be developed. Can give indicators of risks for future diseases and provides opportunities of targeted prevention at both residential area and individual level for improved health.

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P613

JOINT327

Evaluation of growth velocity in patients with achondroplasia treated with vosoritide

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Introduction
Achondroplasia, the most common skeletal dysplasia, is associated with severe short stature. Vosoritide is the first treatment for achondroplasia that targets the underlying pathophysiology, a C-type natriuretic peptide (CNP) analog that binds to its receptor on chondrocytes and promotes growth by inhibiting the ERK1/2-MAPK pathway. This study aimed to evaluate the growth velocity of vosoritide treatment in achondroplasia cases of various ages.
Method
Eleven patients had been evaluated. Annual growth velocities were calculated. Descriptive statistics were performed using the IBM SPSS 29. 0. 2. 0 statistical package program (IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29. 0. 2. 0 Armonk, NY: IBM Corp.).
Results
Vosoritide treatment had been started on eleven patients with achondroplasia (15 mg/kg/dose subcutaneously daily). All patients had c. 1138G>A heterozygous variant in the *FGFR3* gene. The mean age at the start of treatment was 7. 01±3. 40 years (2. 84-12. 56 years). The mean duration of vosoritide treatment was determined as 1. 13±0. 51 years (0. 33-2. 08 years). The calculated mean annual growth velocity was 6. 11±2. 41 cm (2. 73-11. 62). Patients' characteristics are shown in Table 1.
Conclusion
Vosoritide has previously been shown to increase linear growth in patients with achondroplasia. In our study, we found a wide range in annual growth velocity with

Table 1: Patients' gender and growth characteristics.

Patient number	Gender	Age at the start of treatment	Duration of vosoritide treatment (years)	Calculated mean annual growth velocity	Baseline height SDS	Height SDS at last visit	Target height SDS	Tanner stage at the start of treatment	Tanner stage at last visit
1	M	2.91	0.58	2.73	-4.59	-4.59	-0.35	1	1
2	M	6.49	0.83	8.19	-4.78	-4.30	-0.07	1	1
3	F	4.11	2.08	6.40	-4.54	-4.22	-1.47	1	1
4	M	12.56	0.83	4.53	-4.75	-4.66	-0.62	1	2
5	M	7.83	1.00	7.73	-2.90	-2.46	-0.73	1	1
6	F	3.89	1.20	5.05	-4.58	-4.76	-0.18	1	1
7	M	2.84	1.75	5.30	-4.72	-4.88	-0.69	1	1
8	F	11.07	1.42	6.44	-5.87	-6.08	-0.60	3	4
9	F	9.81	0.33	11.62	-1.26	-1.44	0.74	1	2
10	M	9.50	1.42	4.11	-7.48	-7.31	-0.92	1	1
11	F	6.09	1.08	5.11	-5.22	-5.04	0.82	1	1

vosoritide, from 2. 76 cm to 11. 62 cm. A longer-term evaluation with more patients should be conducted to determine what causes this difference (age, puberty, treatment duration, target height, baseline height, etc.).

Keywords Achondroplasia, C-type natriuretic peptide, short stature, skeletal dysplasia, vosoritide.

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P614

JOINT2109

Comparison of the effects of weekly and daily treatment on auxology, metabolism and quality of life in cases with growth hormone deficiency

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Objective

To compare six-month follow-up data of children who started somatrogon (once-weekly), switched from somatropin to somatrogon and started somatropin (once-daily) due to growth hormone deficiency (GHD).

Materials-Methods

Children who met the study criteria organised as three study groups [somatrogon group, switch group (from somatropin to somatrogon) and somatropin group] and followed for six months. The findings were presented as percentages (number) and mean values with standard deviation (SD). While the data of the somatrogon and the switch group were collected prospectively, the data of the somatropin group were collected retrospectively. Bioimpedance analysis and the quality of life scales ("Pediatric Quality of Life Inventory", "Child Behavior Checklist" and "Multi-dimensional Perceived Social Support Scale") performed at the initiation, at the 3rd and 6th months of treatment in somatrogon and switch groups.

Results

Forty-eight patients (58. 4% male) were included. Somatrogon group ($n = 17$), switch group ($n = 14$) and somatropin group ($n = 17$) had mean ages of 11. 5±2. 9, 9. 3±3. 6, 10. 7±3. 1 years, mean height SDS of -2. 9±0. 8, -1. 7±0. 6, -2. 7±0. 5 and mean bone age SDS of -2. 3±1. 1, -2. 1±0. 7, -2. 5±0. 9, respectively. Most patient's pituitary magnetic resonance imagination (77%, $n = 37$) was normal and empty sella was the most common abnormality (8. 3%, $n = 4$). Somatropin's mean initial dosage was 0. 030±0. 003 mg/kg/day, whereas somatrogon's was 0. 66 mg/kg/week. The mean change in height SDS at 6 months was 0. 3±0. 2, 0. 4±0. 2, 0. 5±0. 3, respectively ($P = 0. 203$). The mean height velocity (HV) were 11±2. 5, 10. 2±2. 2, 11. 3±2. 6 cm/year ($P = 0. 533$). and the mean HV SDS were 2. 6±1. 7, 2. 6±1. 7, 2. 9±2. 2, respectively at six months ($P = 0. 860$). No dose reduction or treatment interruption was required due to side effects. The mean change in IGF-1SDS at 6 months were 2. 1±1. 4, 1. 4±0. 6, 1. 2±1. 0 respectively ($P = 0. 099$). The mean change in body fat percentage of somatrogon and switch group at 6 months were -3. 5±13. 4, 5. 4±7. 4 respectively ($P = 0. 115$) Neither the group that started somatrogon nor the somatrogon transition group had significant change in the quality of life score at six month compared to the beginning of treatment ($p > 0. 05$). While there was a significant difference between the groups in terms of baseline externalization symptoms ($P = 0. 020$), no significant difference was found at the 6th month ($P = 0. 134$).

Conclusion

The efficacy, tolerability and quality of life of once-weekly somatrogon were likely to those of once-daily somatropin for GHD.

Note

The study is still ongoing and a preliminary analysis has been conducted based on 41 patients with completed 6-month data. The full dataset is expected to be completed by the time of the conference.

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P615

JOINT2713

Use of vosoritide in children with achondroplasia - clinical experience

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Introduction and Aim

Achondroplasia is the most common form of rhizomelic short stature characterized by mutations in the FGFR3 gene. Vosoritide, a C-type natriuretic peptide analog, has shown promise in stimulating linear growth in children with achondroplasia. This study aims to present real-life experiences with the use of vosoritide in children diagnosed with achondroplasia.

Results

Our study was designed prospectively in children with achondroplasia receiving vosoritide treatment and aimed to find changes in annual growth rate and anthropometric parameters with treatment. The clinical features of 16 children (8 males) with a current mean age of 7. 85±4. 38 years who were diagnosed with achondroplasia were analyzed. Two of the cases were in the pubertal period. In antenatal follow-up, skeletal dysplasia was suspected in 81% of the cases and complications such as basilar invagination, foramen magnum stenosis and hydrocephalus were present in 13/16 of the cases. In polysomnographic evaluation, 31% had various degrees of sleep apnea and 19% (3/16) were receiving non-invasive mechanical ventilator support. All patients had a mean follow-up of 2. 94±2. 66 years without treatment. Vosoritide treatment was given 15 mg/kg/day for a mean duration of 0. 98±0. 57 years. There was a significant increase in the growth rate of the patients after vosoritide treatment compared to the pretreatment period (mean 5. 15±4. 89 cm/year, -2. 08±0. 91 SDS to 5. 99±1. 46 cm/year, -0. 19±1. 31 SDS; p:0. 03, <0. 001). Growth hormone stimulation test was performed in 5 patients with inadequate growth rates and low IGF-1 values under Vosoritide treatment and deficiency was detected in 2 patients. There was no significant difference in body segment measurements under treatment compared to before vosoritide treatment. This suggests that growth is proportional with vosoritide and that it maintains the typical body proportions for children with achondroplasia, but it remains to be seen in follow-up whether there will be a difference in longer treatment periods. Other anthropometric parameter evaluations are presented in Table 1.

Conclusions

Although vosoritide increases the growth rate in children with achondroplasia, its effect on height SDS and body proportions is thought to be significant in longer follow-up.

	Pre-Treatment n: 16	> 6 month treatment n:13	>12 month treatment n: 9	p value
Height SDS(Hoover)	0.40±1.18	0.42±1.22	0.39±1.13	0.94
Leg Lenght SDS	0.82±1.70	0.63±1.41	0.79±1.59	0.94
Sitting Height SDS	-0.36±1.40	0.23±1.83	-0.06±1.18	0.58
Sitting Height/leg Lenght SDS	-1.18±1.42	-0.69±1.19	-0.43±1.46	0.38
Sitting Height/Height SDS	-1.32±1.68	-0.78±1.41	-0.82±1.49	0.59

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P616

JOINT3865

Treatment in genetic short stature: growth hormone use in patients with npr2 heterozygous variants

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Introduction

C-Type Natriuretic Peptide (CNP) and its receptor (NPR-B) are important paracrine factors regulating longitudinal bone growth. Homozygous or compound heterozygous loss-of-function mutations in the NPR2 gene lead to "Maroteaux Type Acromesomelic Dysplasia, " while heterozygous loss-of-function variants cause "Miura Type Epiphyseal Chondrodysplasia" and "Short Stature Without Specific Skeletal Anomalies. "

Methods

Patients diagnosed with idiopathic short stature and carrying a heterozygous NPR2 gene variant who received growth hormone (GH) therapy at the Pediatric Endocrinology Clinic of Gazi University were included. Patients with chronic diseases, medication use affecting growth, or irregular follow-ups were excluded. Data were obtained from clinic records.

Results

Among 19 patients with NPR2 heterozygous variants, 9(47. 3%) received GH therapy; 44% ($n = 4$) were female. The mean birth weight was 2750±892g, with

a mean birth weight SDS of -0. 51±1. 52. The mean age at presentation was 9. 1±3. 7years, with a height of 117. 5±21. 8cm and height SDS of -2. 5±0. 54. Parental height SDS values were -1. 89±0. 83 for mothers and -2. 6±1. 2 for fathers. The mean annual growth velocity was 4. 3±0. 78cm. GH stimulation test results were insufficient in 5 patients (55. 6%). The mean GH initiation age was 9. 9±1. 7years, with an initial height of 122. 3±11. 5cm and height SDS of -2. 5± 0. 48. Initial and maximum GH doses were 0. 033±0. 004mg/kg/day and 0. 040±0. 006mg/kg/day, respectively. The mean annual growth velocity during GH therapy was 7. 6±1cm/year, showing a significant difference from pre-treatment values ($P = 0.01$). The mean GH therapy duration was 2±1. 6years. At the last follow-up, the mean age was 12. 2±2. 3 years, height was 141. 2±14. 2cm, and height SDS was -2±0. 4. Predicted height before GH therapy was 154. 6±6. 7cm (149. 6±8. 4cm for females, 157. 7±3. 5cm for males), while post-treatment predicted height was 157. 1±7. 4cm (150. 1±5cm for females, 161. 2±35. 1cm for males). Although the difference was not statistically significant, an increase in predicted height was observed.

Discussion/Conclusion

Heterozygous NPR2 variants are associated with short stature and non-specific clinical findings. This study represents the largest cohort of NPR2 heterozygous patients receiving GH therapy. In this study, GH therapy significantly improved growth velocity in proportionate short stature patients with NPR2 variants. One patient exhibited low growth velocity, which may be attributed to delayed treatment initiation, pubertal status, and advanced bone age. Although final height has not been reached, increased growth velocity and predicted height were observed. GH therapy should be considered for children with heterozygous NPR2 variants and short stature. However, long-term and larger studies are required to assess treatment efficacy.

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P617

JOINT1214

The medical impact of hypochondroplasia among children in England between 1998 and 2019: a matched cohort study using electronic medical records from the clinical practice research datalink

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Hypochondroplasia (HCH) is a rare genetic skeletal dysplasia causing disproportionate short stature. Few studies report its natural history. This retrospective study compared the medical impact of HCH among children with the general population in England. A real-world matched cohort study was conducted using electronic primary care medical records from January 1, 1998, through December 31, 2019, in the Clinical Practice Research Datalink linked to hospitalization and vital statistics data. Children (≤18 years of age [y]) with HCH were identified using a specific HCH diagnosis code (SNOMED:315057016) or a general code (ICD-10-CM:Q77. 4) without evidence of other growth conditions. Children with HCH were matched 1:4 to general population controls by sex, nearest birth year, and practice region. Event rates (events/100 person-years [PY]) and rate ratios (RRs; cases vs controls) were calculated for select comorbidities and healthcare use among children 0-10y and 11-18y. Overall, 225 children with HCH and 1067 matched controls were included. Mean follow-up time was approximately 9 years for children with HCH and 12 years for controls. Among both age groups, overall event rates of comorbidities (combined across all body systems) were higher among children with HCH vs controls (RR: 2. 59 [0-10y], 2. 88 [11–18y]). Ear, nose, and throat (ENT), respiratory, neurological, and developmental conditions were more frequent among children with HCH (1. 52-16. 85 episodes/100 PY), with autoimmune conditions also frequent among those aged 11-18 years (10. 06/100 PY); RRs ranged between 1. 84 and 13. 57, indicating significantly increased impact compared with controls (**Table**). Children with HCH had more healthcare visits than controls; general practice visits were most frequent (1149 visits/100 PY; RR, 1. 92 [0-10y] and 881 visits/100 PY; RR, 2. 14 [11-18y]). Though less common, inpatient admission rates were higher for children with HCH than controls (172 admissions/100 PY; RR, 8. 39 [0-10y] and 200 admissions/100 PY; RR, 10. 91 [11-18y]). Surgical procedures were infrequent but consistently higher among children with HCH vs controls, including orthopaedic procedures (1. 24 procedures/100 PY; RR, 11. 24 [0-10y] and 4. 12 procedures/100 PY; RR, 10. 17 [11-18y]). Children with HCH had substantially higher rates of comorbidities and healthcare resource utilization compared with the general paediatric population in England. Early, multidisciplinary management is needed for individuals with HCH to address health challenges.

Table Comorbidity rates in children with HCH vs controls

Body system category	RR (95% CI) 0-10y	11-18y
ENT	1.84 (1.34-2.52)	5.21 (3.24-8.38)
Respiratory	2.94 (1.91-4.54)	1.92 (1.14-3.23)
Neurological	13.57 (6.22-29.60)	2.46 (0.72-8.48)
Development	3.39 (1.74-6.63)	2.69 (1.23-5.89)

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P618

JOINT349

Diagnosis of silver russell syndrome in 2025: is a scoring system still helpful?

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Background

Silver Russell Syndrome (SRS) is a rare syndrome characterized by six clinical features composing the Netchine-Harbison Clinical-Scoring-System (NH-CSS): prenatal and postnatal growth retardation, relative macrocephaly at birth, protruding forehead, body asymmetry, and significant feeding difficulties. SRS diagnosis is suspected if ≥4 of these 6 criteria are present. The first (epi)genetic SRS causes identified include maternal uniparental disomy of chromosome 7 (upd(7)mat) and loss of methylation at *H19/IGF2*:IG-DMR on chromosome 11 (11p15 LOM). Other molecular anomalies are reported in patients with a suspected SRS.

Objective

Evaluate the NH-CSS on patients with suspected SRS with different molecular causes of SRS and differential diagnoses.

Subjects and Methods

Retrospective analysis of 705 patients, with data for all 6 NH-CSS criteria and molecular screening for upd(7)mat and 11p15 LOM, were recruited through the patient support group, The MAGIC Foundation.

Results

Molecular anomalies identified:

- SRS diagnosis confirmed in 356 patients (50. 5%): 11p15 LOM ($n = 222$, 62, 4% of SRS patients), and upd(7)mat ($n = 109$, 30. 6%); Maternal 11p15 duplications ($n = 19$, 5. 3%); Paternal *IGF2* mutations ($n = 5$, 1. 4%); *CDKN1C* mutations ($n = 1$, 0. 3%);
- Temple syndrome (TS) in 36 patients (5. 1%): 14q32 LOM ($n = 6$, 16. 7% of TS patients); upd(14)mat ($n = 25$, 69. 4%); and 14q32 pat-del ($n = 5$, 13. 9%);
- *HMGA2* mutations ($n = 7$, 1. 0%); *PLAG1* mutations ($n = 6$, 0. 9%); upd(20)mat ($n = 9$, 1. 3%); upd(16)mat ($n = 3$, 0. 4%);
- Various SRS differential diagnosis were identified (5%), including *IGF1R* mutations, 3M syndrome, Cornelia de Lange, IMAGe, Mulibrey nanism, Bloom, and Floating-Harbor.

NH-CSS Results

NH-CSS≥4 demonstrates high sensitivity of 97. 2% to detect 11p15 LOM and upd(7)mat with good Negative Predictive Value of 89. 0%. NH-CSS was ≥4 for 83. 3% of the patients with a *PLAG1* mutation; 85. 7% with a *HMGA2* mutation; 88. 9% of upd(20)mat; 89. 5% with a 11p15 maternal duplication; 83. 3% of TS 14q32LOM, and 100% of upd(16)mat and *IGF2* mutations. It detected only 40% of *IGF1R* mutations, 52% of TS upd(14)mat and 20% of 14q32 pat-deletions. Relative macrocephaly is associated with 11p15 LOM and upd(7)mat ($P < 0.05$) but not with *PLAG1*, *HMGA2* and upd(20)mat. Specific clinical findings can orient toward other diagnoses, (microcephaly for *IGF1R* mutations, neonatal hypotonia and/or precocious obesity and puberty for TS).

Conclusion

NH-CSS (if ≥4) is a highly sensitive tool to orient toward 11p15 LOM and upd(7)mat suggesting methylation analysis as the first molecular diagnostic step. It also captures other molecular anomalies overlapping with SRS and less frequently differential diagnoses, suggesting the importance of additional clinical signs to orient broader genetic testing after the methylation analysis.

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P619

JOINT2496

GloBE-Reg: A global registry for evaluating the safety and effectiveness of growth hormone therapy across the age span

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Introduction
The Global Registry For Novel Therapies In Rare Bone & Endocrine Conditions (GloBE-Reg, https://globe-reg. net/) project was launched in 2022 with the aim of supporting studies that focus on effectiveness and long-term safety of specific therapies. The project's initial focus has been on recombinant human growth hormone therapy (rhGH), given the existing knowledge gaps associated with the introduction of new indications and novel forms of rhGH.
Methods
The GloBE-Reg registry consists of three layers of datasets: the first includes internationally agreed-upon core data elements applicable to any rare condition; the second allows for the selection of a specific therapy and diagnosis; and the third comprises a therapy- and diagnosis-specific minimum dataset (MDS), which collects information on diagnosis, therapy, clinician-reported outcomes, patient-reported outcomes, and adverse events. The fields within the MDS are developed following guidance from short-life expert working groups.
Results
Since its launch, 29 centres from 17 countries in 4 continents have enrolled 2, 798 (M:F, 1, 679:1, 119) patients with a median age of 12. 8 years (range 0. 2, 64. 6), of whom 2, 481 (89%) are currently under 18 years of age. Among these patients, 1, 777 (64%) were on daily rhGH, 1, 011 (36%) on long-acting rhGH, and in 10 cases, rhGH therapy had been discussed but not initiated. Twelve different brands of rhGH were in use across these centres for eight indications, while long-acting rhGH was prescribed for six indications. Additionally, 41 (1%) patients were receiving rhGH for other conditions associated with short stature or growth retardation. The most common indication was growth hormone deficiency (59%), followed by small for gestational age (15%), idiopathic short stature (9%), Turner syndrome (8%), Prader-Willi syndrome (4%), and Noonan syndrome (2%). Of the 2, 798 cases, 1, 064 (38%) were also included in other disease registries and 923 (33%) of these were entered by three centres into GloBE-Reg through its bulk upload facility. Modules containing Childhood GHD, Adulthood GHD, and Noonan syndrome MDS are now fully operational and supporting studies in these fields; other modules are under development.
Conclusion
GloBE-Reg has demonstrated that a relatively low-cost, brand-agnostic platform can achieve sufficient stakeholder acceptability and versatility for collecting data to support long-term safety and effectiveness studies conducted by investigators from both academia and industry. The preliminary data collected on rhGH underscore the platform's long-term utility in evaluating the safety and effectiveness of a wide range of drugs.

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P620

JOINT3385

Clinical characteristics of children with mccune–albright syndrome in China: a retrospective cohort study

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Background
McCune–Albright syndrome (MAS) is a rare disease defined by the triad of fibrous dysplasia (FD), caféau lait spots, and peripheral precocious puberty (PP). There is little adult height data in patients with MAS and no management consensus. We describe the various clinical manifestations of 28 patients with MAS in China and assessed the treatment and adult height in five patients.
Methods
Patients' clinical data—including peripheral PP, FD, and other endocrine problems were reviewed retrospectively. In addition, mutation in GNAS using blood and treatment experiences in five patients were described.
Results
The median age at diagnosis was 3 years 9 months (range: 20 months to 8 years). Twenty six patients were female, and two were male. Five patients showed FD. Twenty six patients showed peripheral PP at onset. Four cases had combined ovarian cysts. 8 cases received letrozole, 5 cases with subsequent addition of gonadotropin-releasing hormone analogs, and the mean age at initiation of treatment was 4. 6 years. Adult height data were available on 5 patients with MAS of whom 4 were treated. The average adult height of the 5 patients was 164. 5cm, this exceeds the average Chinese female height (160. 6cm). Five patients who underwent genetic testing for GNAS were positive.
Conclusion
This study provides valuable insights into MAS management in Chinese children, underscoring the potential efficacy of aromatase inhibitors in optimizing height outcomes. It highlights the need for standardized diagnostic criteria and tissue-based genetic testing. Future prospective studies with larger cohorts are warranted to validate these findings and refine treatment protocols.

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P621

JOINT379

When genetics cast doubt on paternity

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With the development of genetic screening for disease in childhood, more genetic variants are found. The family segregation study of variants found in disease with autosomal recessive inheritance, may cast doubt on paternity when the father is not a carrier of the variant found in the child. Uniparental isodisomy, which means both alleles originating from a single-parental homologous chromosome, can be associated with pathogenic variants causing autosomal recessive disease and has already been described in other pathologies of chromosome 5 in 10 children (Qian 2021, Park 2019, Gonzalez-Quintana 2020, Numata 2014). We report the case of a child with congenital hypopituitarism. NGS sequencing of a panel of genes identified in *PROP1* (Prophet of Pit1) a homozygous variant c. 301_302del resulting in a truncated protein p. Leu102fs, one of the most frequent *PROP1* pathogenic variants in Europe. Alterations of *PROP1* gene are common findings in children with congenital hypopituitarism and genetic transmission is autosomal recessive. This gene is located on the long arm of chromosome 5 (5q35. 3). The family segregation study found that the mother was a heterozygous carrier of the variant, but the father was not a carrier. We searched for uniparental isodisomy of chromosome 5 in the family by short tandem repeat analysis and SNP-array. Both techniques confirmed that the child has maternal uniparental isodisomy of the entire chromosome 5. Cytogenetic analysis including karyotype and targeted FISH on chromosome 5, performed in proband and parents, showed no alteration of chromosome 5 structure.
In conclusion
This is the first case report of uniparental isodisomy of chromosome 5 leading to a homozygous mutation of *PROP1*. Clinicians and genetic counselors should be aware that autosomal recessive disorders due to homozygous variants can occur as a result of uniparental isodisomy, especially if parents are not consanguineous.

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P622

JOINT534

Impact of body mass index on growth hormone peak during insulin tolerance test in childrenand adolescents

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Background
The insulin tolerance test (ITT) is the gold standard for assessing growth hormone (GH) integrity. A negative relationship between GH peak and body mass index

(BMI) standard deviation score (SDS) has been reported, even within the normal BMI range, potentially leading to overdiagnosis of growth hormone deficiency (GHD) in overweight and obese children. In this context, BMI SDS-specific cutoffs for GH stimulation tests have been proposed by Abawi *et al*.
Methods
This retrospective study analyzed ITTs (regular insulin 0. 1 IU/kg intravenously) performed at the Institute for Maternal and Child Health IRCCS "Burlo Garofolo", Trieste, Italy, between January 1, 2019, and December 31, 2024. ITTs were conducted to confirm GHD after a blunted response to the arginine stimulation test. Adequate hypoglycemia ($\geq$50% decrease in basal glucose or $<$ 40 mg/dL) was achieved in 157 of 180 tests. Clinical data and GH responses were analyzed.
Results
The cohort had a median age of 12. 3 years (IQR: 10. 5–13. 8) and a BMI SDS of -0. 86 (-1. 57–0. 27). GH peak negatively correlated with BMI SDS (Spearman's ρ = -0. 311, p $<$. 001), while positive correlations were observed with baseline GH (ρ = 0. 536, p $<$. 001) and IGF-1 SDS (ρ = 0. 176, p =. 028). Multivariate analysis identified lower BMI SDS (p =. 007) and higher baseline GH (p $<$. 001) as significant predictors of GH peak, with a moderate overall model fit (R^2 = 0. 490). Among the 16 overweight (BMI SDS: 1–2) and 2 obese (BMI SDS $>$2) individuals, all exhibited pathological GH peaks ($<$8 ng/mL; median: 1. 5 ng/mL [IQR: 0. 75–2. 80]). This remained true when applying BMI-adjusted thresholds proposed by Abawi *et al*. (7. 4 ng/mL for overweight and 6. 8 ng/mL for obese children).
Conclusions
This study confirms the significant impact of BMI SDS on GH peak during ITT, highlighting that overweight and obese children are at increased risk of GHD overdiagnosis. Although BMI SDS-adjusted cutoffs could improve diagnostic accuracy and reduce misclassification in children with elevated BMI, in this study, peak GH levels in overweight and obese children were well below even the BMI-adjusted thresholds, supporting a diagnosis of GHD.

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P623

JOINT2053

Unraveling the genetic basis of short stature in pediatric patients: a whole exome sequencing approach

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Background
Short stature is a common clinical concern in pediatric endocrinology, and while growth hormone (GH) deficiency is a well-established cause, genetic factors also play a crucial role. This study aimed to investigate the genetic etiology of short stature using whole exome sequencing (WES) in a pediatric population.
Methods
We retrospectively reviewed pediatric patients who underwent WES for clinical diagnosis at Chungnam National University Sejong Hospital between March 2022 and October 2024. A total of 133 patients (52 females and 81 males) underwent WES due to developmental delay, short stature, congenital anomalies, or other suspected genetic conditions. Among them, we selected patients who presented with short stature and analyzed their genetic findings and clinical characteristics.
Results
Thirty-eight patients underwent WES for short stature. Two patients were diagnosed with GH deficiency, while 36 had normal GH provocation test Results All female patients had normal karyotyping. Five patients (13. 2%) were born small for gestational age. Developmental delay was observed in 11 patients (28. 9%). Overall, congenital anomalies were observed in 18 patients (47. 4%) including congenital heart disease, hernia, congenital cataract, microtia, hearing defect, and skeletal deformity. A genetic cause was identified in 11 patients (28. 9%, 11/38). The detected syndromes included KBG syndrome, Diets-Jengmans syndrome, Okur-Chung neurodevelopmental syndrome, Rauch-Steindl syndrome, Noonan syndrome, Verheij syndrome, intellectual disability-hypotonic facies syndrome, X-linked, X-linked syndromic intellectual developmental disorder, Cabezas type, autosomal recessive deafness 8/10, developmental and epileptic encephalopathy 42, and 6q deletion syndrome.
Conclusion
Short stature in pediatric patients serves as a strong indicator for genetic evaluation. WES effectively identified genetic etiologies in nearly one-third of the patients, highlighting its utility in diagnosing underlying genetic conditions in this population.

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P624

JOINT2862

N-acetylcysteine treatment for skin-picking in children and young adults with pws: a randomized placebo-controlled cross-over trial

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Introduction
Skin-picking is the most common form of self-injurious behavior in Prader Willi Syndrome (PWS) and can lead to serious, life-threatening infections and severe scarring. An open-label pilot study reported that N-acetylcysteine (NAC) reduced skin-picking behavior in patients with PWS. Thus, NAC might be a promising treatment option for patients with PWS and skin-picking behavior. A placebo-controlled study was needed to show evidence.
Methods
A randomized, double-blind, placebo-controlled, cross-over trial in 23 patients with PWS aged 6-25 years in The Netherlands and Belgium. Cross-over intervention with NAC (dose range 600-2400 mg/day) and placebo, both during 3 months, with a wash-out period of 3 months.
Results
Overall, NAC lead to less skin-picking lesions compared to placebo, albeit not significantly (P = 0. 07). In boys, NAC showed a trend towards less skin-picking lesions compared to placebo (P = 0. 06) and the Clinical Global Impression Scale improved (2 (2-3) vs. 3 (2-3), P $<$ 0. 01)), while no difference was observed in girls. In addition, median (IQR) Skin-Picking Symptom Assessment-score was lower after NAC compared to placebo (18 (10. 75-26) vs. 24 (13. 5-30. 75), P = 0. 05)). NAC was well-tolerated and there were no serious adverse events.
Conclusion
NAC appears to have beneficial effects on skin-picking in a subgroup of patients with PWS, particularly in boys, without safety concerns. While NAC may be considered in children and young adults with PWS, its effects should be assessed on an individual basis. Treatment should be discontinued if no significant benefits are observed.

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P625

JOINT2973

Challenges of puberty in turner syndrome: experience of a tertiary pediatric hospital

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Introduction
Turner Syndrome (TS) is a partial or total monosomy of the X chromosome. It presents with multisystemic manifestations, including short stature, cardiac, nephrological conditions, and other endocrinometabolic disorders such as gonadal failure. Careful monitoring is required, with particular emphasis on pubertal development, bone health, and fertility. This study aimed to describe the pubertal development of adolescents with TS and the necessary therapeutic interventions. A retrospective, descriptive study of children and adolescents with TS followed at a tertiary hospital between 2010 and 2024. Data was collected from medical records.
Methods
39 patients with TS were included. Three diagnosed prenatally, five in the neonatal period, and the remaining at a median age of 7. 6 years. They presented with different genotypes: 16 (41. 0%) had complete X chromosome monosomy, 14 (35. 9%) had mosaicism, and 9 (23. 1%) had other chromosomal abnormalities.
Results
Among the adolescents, 14 (37. 8%) developed spontaneous puberty with menarche at a median age of 12. 3 years (range: 11. 3-15. 7 years). Their median gonadotropin levels were 5. 4 mIU/mL and 4. 0 mIU/mL for FSH and LH. 23

adolescents (62. 2%) required hormone replacement therapy (HRT) with transdermal estrogens initiated at a median age of 12. 8 years (range: 11. 6-16. 3 years). Pre-treatment gonadotropin levels confirmed hypergonadotropic hypogonadism, with median FSH levels of 78. 1 mIU/mL and LH levels of 17. 4 mIU/mL. In this group, menarche occurred at a median age of 15. 0 years (range: 12. 6-18. 4 years), approximately 1. 3 years after initiating therapy. Anti-Müllerian hormone (AMH) levels were measured in 22 of the 37 patients, with a median of 0. 20 pmol/l (range: 0-25. 1 pmol/l). The spontaneous menarche group had a median AMH of 6. 32 pmol/l, while the induced puberty group had 0. 15 pmol/l. Thirteen patients (35%) were referred for fertility counseling, and 3 underwent oocyte cryopreservation. Two patients, still under the age of 10, have not yet begun puberty but are under close follow-up.

Discussion

The results emphasize the genotypic and phenotypic diversity of TS, highlighting the need for personalized monitoring and intervention. Hormone replacement therapy is vital for inducing pubertal development and optimizing bone mass in patients with hypergonadotropic hypogonadism due to gonadal dysgenesis. A significant number of patients experienced spontaneous puberty, and about one-third were referred for fertility preservation. Oocyte cryopreservation, though rare, offers a reproductive option for some of these young women.

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P626

JOINT795

Quality of life improvements with GH, GnRHa, and AI therapies in children with short stature and advanced bone age

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Background

Short stature and advanced bone age significantly affect children's quality of life (QoL), including their physical, emotional, and social well-being. Growth hormone (GH), gonadotropin-releasing hormone analogs (GnRHa), and aromatase inhibitors (AI) are therapies designed to improve height outcomes, but their impact on QoL remains a critical area of study.

Objectives

This review evaluates the effects of GH, GnRHa, and AI therapies on the QoL of children with short stature and advanced bone age, highlighting the improvements in emotional, social, and physical domains across various conditions.

Methods

Data from 13 studies published between 2000 and 2024 were reviewed, focusing on the QoL outcomes of GH, GnRHa, and AI therapies in children with idiopathic short stature (ISS), congenital adrenal hyperplasia (CAH), precocious puberty, and small-for-gestational-age (SGA). Therapy type, duration, and QoL findings were analyzed for their emotional, social, and physical impacts.

Results

Therapies consistently demonstrated positive impacts on QoL:

- Emotional well-being: GH therapy improved self-esteem and reduced anxiety in children with ISS and growth hormone deficiency (GHD). Combination therapies provided additional emotional stability in CAH and precocious puberty.
- Social interactions: Enhanced height and body image through GH and GnRHa therapies promoted better social integration, particularly in children with familial short stature, obesity-related growth delays, and Turner Syndrome.
- Physical function: AI combined with GH delayed bone age progression, maintaining mobility and reducing the physical burden of advanced skeletal maturation in precocious puberty and CAH.
- Parental satisfaction: Across multiple studies, parents reported reduced concern about their children's emotional and social challenges due to height gains and improved psychosocial adaptation.

Discussion

QoL benefits extend beyond height improvement, addressing the stigma and social pressures associated with short stature. GH combined with GnRHa or AI enhances these effects by promoting emotional resilience, social integration, and reduced anxiety, particularly in complex conditions like CAH and SGA.

Conclusion

GH, GnRHa, and AI therapies significantly improve QoL in children with short stature and advanced bone age. By addressing emotional, social, and physical domains, these therapies provide a holistic approach to care, underscoring the importance of integrating psychosocial outcomes into treatment strategies.

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P627

JOINT2719

Effect of growth hormone therapy on final height in SHOX deficiency and turner syndrome: a single-center experience

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Introduction

SHOX deficiency and Turner syndrome are genetic disorders associated with short stature, both resulting from haploinsufficiency of the SHOX gene, which impairs growth. Despite their shared etiology, comparative data on the long-term efficacy of growth hormone (GH) therapy and final height (FH) outcomes remain limited. This study aims to retrospectively evaluate and compare the effects of GH therapy on FH in patients with SHOX deficiency and Turner syndrome.

Methods

This retrospective study included patients with genetically confirmed SHOX deficiency ($n = 10$) or Turner syndrome ($n = 34$) who had received GH therapy and attained their final height. Participants were prepubertal (Tanner stage 1) at the start of therapy and presented with a height below the 3rd percentile or between the 3rd and 10th percentiles with a growth velocity below the 25th percentile. Comparative analyses were conducted between the two groups, focusing on first- and second-year height velocities,height standard deviation (SD) scores, and overall height gain (cm).

Results

The ages at treatment initiation were similar between the SHOX deficiency and Turner syndrome groups (mean $\pm$ SD: 10. 7 $\pm$ 1. 9 years vs. 10. 4 $\pm$ 2. 7 years; $P = 0.967$). The baseline height SD scores were -2.66 ± 0.8 in the SHOX deficiency group and -3.5 ± 1.07 in the Turner syndrome group, with the difference not reaching statistical significance ($P = 0.080$). The gain in height SD score from the initiation of GH therapy to final height was comparable between the SHOX deficiency group (0. 07 $\pm$ 0. 35 [least-squares mean $\pm$ SE]) and the Turner syndrome group (0. 93 $\pm$ 0. 15). Importantly, the first-year height velocity was significantly higher in the SHOX deficiency group compared to the Turner syndrome group (mean $\pm$ SD: 8. 55 $\pm$ 1. 43 cm/year vs. 6. 72 $\pm$ 1. 99 cm/year; $P = 0.011$). However, the second-year height velocity showed no significant difference between the groups (mean $\pm$ SD: 6. 63 $\pm$ 2. 29 cm/year vs. 5. 79 $\pm$ 1. 53 cm/year; $P = 0.203$).

Conclusion

GH therapy leads to comparable long-term height improvements in patients with SHOX deficiency and Turner syndrome. However, patients with SHOX deficiency demonstrate a significantly greater height velocity during the first year of treatment.

Keywords SHOX deficiency, Turner syndrome, final height,growth hormone therapy

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P628

JOINT2663

Retrospective analysis of two databases on growth hormone treatment in chinese children with short stature – baseline characteristics and clinical inertia

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Introduction

Despite the long-established use of recombinant human growth hormone (rhGH) in China for treating growth hormone deficiency (GHD), there still exists a significant gap in understanding its current status and the potential challenges with its effective use. This study aimed to explore the real-world status of rhGH treatment among Chinese children with short stature (SS) and to identify the associated factors.

Methods

In this multicenter, retrospective, observational study, we analyzed data from children receiving rhGH treatment from January 1, 2017, to April 30, 2024. The data was sourced from two registry databases in China (Chinese Society of Pediatric Endocrinology and Metabolism (CSPEM) Growth Study Database (CGSD) and Long-term Efficacy and Safety Evaluation of Growth Hormone in

Children in China (CGLS) and included eligible naïve children diagnosed with GHD, idiopathic SS (ISS) or small for gestational age (SGA), and who were treated with at least one rhGH and with height standard deviation score (Ht-SDS). All the data including baseline characteristics, type of rhGH treatment received (long-acting [LAGH] or short-acting [SAGH]), and treatment compliance were collected and analyzed.
Results
A total of 41, 942 children (15, 975 with GHD, 24, 445 with ISS, and 1, 522 with SGA) with a median age of 8. 29 (5. 88–10. 64) years were included. Mean Ht-SDS and BMI-SDS were -2. 51 $\pm$ 0. 42 and -0. 48 $\pm$ 1. 11, respectively. Short-acting growth hormone (SAGH) was the most preferred option in children than long-acting growth hormone (LAGH) (79. 53% vs. 20. 47%). The overall bone age (BA) – chronological age (CA) was reported as -1. 43 (1. 06). Treatment initiation with an appropriate dose was observed in children with SGA and GHD compared with ISS (33. 26%) with an insufficient dose. Irregular administration often precedes discontinuation, and it was identified as the main reason for long-term withdrawal in both the LAGH and SAGH groups. Treatment discontinuation was observed in 42. 1% of the children mainly due to irregular administration (18. 3%), limited medication access (16. 9%), and refusal by patients or families (11. 2). Overall, the LAGH group exhibited a significantly longer duration of therapy compared to the SAGH group (1. 75 [1. 71, 1. 79] vs. 1. 58 [1, 56, 1. 61]; $P < 0.001$).
Conclusion
In China, children with SS tended to start rhGH treatment at a relatively older age and exhibited a high rate of treatment discontinuation. To achieve better treatment outcomes for children with SS, good adherence and guideline-recommended medication patterns need to be adhered to.

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P629

JOINT1645

Identifying relevant factors for recommendation of digital health solutions supporting paediatric growth hormone treatments in Finland: insights from participatory workshop

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Background
Long-term management of paediatric growth hormone deficiency (GHD) has advanced with the utilisation of digital health solutions. In Finland, the integration of automated growth monitoring with Electronic Health Records has demonstrated significant improvements in diagnosis of GHD, thereby enhancing early detection and collaboration between primary care providers and specialists.
Aim
Identifying key factors for digital health solution recommendations that support paediatric growth hormone treatments (pGHTs) in Finland from a nursing perspective and assesing the impact of the evolution of these solutions.
Method
A participatory workshop was conducted on 11 June 2024, in Helsinki, Finland, with seven nurses experienced in pGHT and three moderators. Workshop was divided in two parts: the first part utilised the Nominal Group Technique to identify key factors for recommending digital health solutions, while the second part assessed experts' views on how advancements in health technology impact their recommendations. Activities in the first part included silent idea generation, round robin sharing, discussion, and ranking of key factors. The second part of workshop included presentations of two study cases using two devices: Easypod® autoinjector and Easypod® connect transmitter (EP2) and Easypod® next generation (EP3) device. This qualitative activity focused on assessment of these devices in terms of ergonomics, aesthetics, ease of use, and usefulness, followed by a quantitative activity to evaluate their perceived benefits.
Results
For the first part of workshop, experts identified eighteen key recommendation factors and divided them into three high level categories: individual-related factors, healthcare provider-related factors and digital solution-related factors. Based on the score provided by the experts, 'ease of use' was the most relevant factor (emphasising the need for user-friendly designs, especially in low-resource settings) followed by 'patient motivation' and 'treatment adherence, ' while 'training materials' and 'technical support' received the lowest scores. Qualitative evaluation in the second part of workshop identified the following issues: physical characteristics of devices, touch screen, interacting, attractiveness, personalisation, safety, data transmission and learning and teaching. Overall, the experts believed that technological advancements have positively influenced the identified factors and care services. These findings highlighted the importance of accessible and engaging designs that cater to diverse age groups, thereby enhancing patient autonomy and adherence.
Conclusion
Advancements in digital health technology can enhance the management of pGHT by improving usability and accessibility, thereby boosting patient motivation and treatment adherence. Intuitive designs, familiar interfaces and streamlined training processes can further facilitate early adoption of digital devices and promote patient autonomy.

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P630

JOINT1476

Continuous glucose monitoring (CGM) for assessing glycaemic variability in growth hormone deficient children shifting from recombinant GH daily injections to long-acting GH analogues: a case series

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Background
Daily recombinant GH (rGH) is approved for children with GH deficiency, but daily injections can be painful and stressful, leading to poor adherence. Long-acting GH analogues (LAGH), given their weekly administration, can improve patient acceptance and tolerance. However, the loss of physiological GH peaks could have a metabolic impact, especially in terms of glucose homeostasis. Though data from regulatory studies are reassuring in terms of insulin resistance and diabetes occurrence, up to now no data are available on subtle glycaemic changes in patients on either daily GH or weekly analogues.
Aims
The present study aims to provide insight into glycaemic variability differences in patients with GH deficiency (GHD) shifting from daily rGH to weekly LAGH subcutaneous injections.
Methods
For this purpose, a feasible non-invasive method which allows 24-hours continuous glucose monitoring (CGM) -Dexcom G7®System (Dexcom, Inc., San Diego, CA, USA)-, has been applied to 4 GHD children (M/F 3/1, chronological age 13. 9 years, IQR 11. 1-15. 3) in order to compare glycaemic variability differences when shifting from rGH (time 1) to LAGH (time 2). All patients used CGM for 10 days during rGH daily treatment and for 10 days after the third LAGH injection.
Results
The median coefficient of variation (CV) of patients under daily rGH treatment was not significantly different from CV under LAGH (13. 1%, IQR 11. 7-14. 7 vs 14. 2%, IQR 12. 2-14. 7). The Wilcoxon signed-rank test showed no significative difference in CV when patients switched from one formulation to the other. Specifically, no difference was observed between the two treatments during the nocturnal recording, when the highest GH peak, absent with LAGH therapy, naturally occurs.
Conclusions
This represents the first case series evaluating subtle glucose changes during GH replacement therapy by means of a non-invasive reliable tool, focusing on LAGH analogues vs daily rGH. No significant differences in glycaemic variability have been found when switching from daily to weekly injections. These preliminary results, though should be confirmed on a larger scale, are quite reassuring on LAGH safety in terms of glucose homeostasis.

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P631

JOINT857

Comparison of leptin, ghrelin, and nesfatin levels in growth hormone deficiency and short stature patients before and after growth hormone therapy

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Objective
Leptin, ghrelin, and nesfatin are hormones that play crucial roles in regulating energy balance and metabolism. The objective of this study was to compare the levels of these hormones between patients with growth hormone deficiency (GHD) and idiopathic short stature (ISS) and healthy controls, as well as to evaluate the changes in these hormone levels before and after recombinant human growth hormone (rhGH) therapy in GHD and ISS patients.
Methods
A total of 77 prepubescent children aged 5 to 12 years were included in this study, comprising controls ($n = 16$), ISS patients ($n = 27$), and GHD patients ($n = 34$). Clinical parameters and serum levels of leptin, ghrelin, and nesfatin-1 were compared across the groups. Additionally, baseline and 6-month post-GH therapy values were compared in GHD and ISS patients.
Results
There were no significant differences in age, the levels of leptin, ghrelin, and nesfatin-1 among the three groups. In GHD patients, serum leptin concentrations significantly decreased after 6 months of rhGH therapy (7299. 18 $\pm$ 7779. 73 pg/mL to 4211. 85 $\pm$ 3977. 25 pg/mL, $P = 0.018$), and leptin was positively correlated with BMI SDS($r = 0.51$, $P < 0.001$). There were no significant changes in ghrelin levels or nesfatin-1 in GHD patients. In ISS patients, leptin levels significantly decreased after 6 months of rhGH therap(5128. 81 $\pm$ 3611. 55 pg/mL to 2594. 33 $\pm$ 925. 99 pg/mL p. 0. 001) but ghrelin and nesfatin-1 showed no significant differences after 6 months of rhGH therapy.
Conclusion
This study confirmed a positive correlation between **Leptin** and **BMI SDS**, and a negative correlation between **Ghrelin** and **BMI SDS**, suggesting that these hormones are closely related to BMI. GH therapy resulted in a significant decrease in leptin levels, these changes are likely to be associated with BMI alterations. These findings highlight the crucial role of growth hormone therapy not only in **promoting growth** but also in **regulating body mass and metabolic processes** in patients with GHD and ISS.

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P632

JOINT1565

Growth hormone therapy in noonan syndrome: impact on neurodevelopment and prognosis

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Context
Noonan syndrome (NS) is a genetic disorder characterized by short stature, congenital heart defects, and developmental delay/intellectual disabilities (DD/ID). While recombinant human growth hormone (rhGH) is widely used for short stature in NS, its impact on neurodevelopment remains unclear.
Objective
This study aimed to evaluate the neurodevelopmental outcomes of NS patients treated with rhGH and to identify factors influencing the risk of DD/ID.
Methods
A retrospective cohort study was conducted using the Korean National Health Insurance Database (NHID) from 2007 to 2023. NS patients (ICD-10: Q87. 1) who received rhGH therapy were included. DD/ID was identified using ICD-10 codes (F70–F79, F80–F89). Clinical characteristics, comorbidities, and healthcare utilization were compared between groups with and without DD/ID. Kaplan-Meier analysis assessed the cumulative incidence of DD/ID, and logistic regression identified associated risk factors.
Results
Among 302 NS patients (172 males, 130 females) treated with rhGH, 102 (33. 8%) had DD/ID. Longer GH therapy was associated with a reduced risk of DD/ID (O$r = 0.906$, $p < 0.001$). Patients treated for >2 years had a significantly lower cumulative incidence of DD/ID ($p < 0.001$). Among those with DD/ID, the age at diagnosis was significantly younger in patients diagnosed before GH initiation than in those diagnosed after GH therapy ($p < 0.001$), suggesting a potential delaying effect of GH treatment on DD/ID onset. Baseline and final Charlson Comorbidity Index (CCI) scores were higher in the DD/ID group ($P = 0.003$ and $p < 0.001$, respectively). ADHD (O$r = 1.347$, $p < 0.001$), skeletal disorders (O$r = 1.156$, $P = 0.007$), and obstructive sleep apnea ($P = 0.032$) were significantly associated with DD/ID.
Conclusions
Prolonged rhGH therapy (>2 years) was associated with a lower risk of DD/ID and a delayed age at DD/ID diagnosis in NS patients. ADHD, skeletal disorders, and obstructive sleep apnea were significant risk factors for DD/ID. These findings suggest that early and sustained GH therapy may mitigate neurodevelopmental impairment in NS. Given the higher healthcare burden in DD/ID patients, a multidisciplinary approach is needed to optimize treatment strategies and long-term outcomes.

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P633

JOINT1280

Mysoconnect® for sogroya®: long-acting growth hormone for patients with growth-related disorders and their caregivers

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Long-acting growth hormone (LAGH) is a treatment given to children with growth hormone deficiency. Adherence and concordance with treatment is essential for children to reach their height potential, but it is not always optimal. Several patient needs have been identified that may support with adherence and concordance. These include maintaining an injection routine, having access to answers of treatment-related questions and tracking progress over time, such as height gain. The use of a LAGH digital connected system with these features may aid in adherence and concordance to treatment. MySoConnect® for Sogroya® (somapacitan; Novo Nordisk Health Care AG) was developed to improve the patient experience and aid in adherence and concordance with growth hormone (GH) treatment (GHT). The system consists of a Sogroya® FlexPro® injection pen, the Mallya® connectivity cap and the MySoConnect® app. The Mallya® cap connects with the MySoConnect® app when attached to the Sogroya® FlexPro® injection pen and aligned with the dose counter of the pen. The Mallya® connectivity cap is compatible with all three available strengths of the Sogroya® FlexPro® injection pen. The MySoConnect® app includes features that can support in setting an injection routine, such as setting a dose reminder, which can be performed manually within the app. Features related to dose management, such as dose, dosing day and type of injection pen used, are recorded. The MySoConnect® app also includes a training and support section, which provides useful information related to understanding treatment, tailored towards patients and their caregivers. Additionally, the app includes the option to manually input height and weight data to allow visualisation of height and weight improvements over time. Lastly, the app allows users to download a log of dosing patterns, which can be shared with their healthcare professional to advise on dosing changes. MySoConnect® for Sogroya® was developed to improve the user experience for children prescribed Sogroya® and their caregivers. This connected system will allow its users to set and maintain an injection routine, have continuous access to training and support related to GHT, and record and track various elements of their treatment journey over time. MySoConnect® for Sogroya® may support its users in maintaining adherence.

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P634

JOINT1455

Efficacy and safety of somapacitan vs daily growth hormone at 52 weeks in patients with growth hormone deficiency: pooled analysis of the randomised REAL 3, REAL 4 and REAL 6 clinical trials

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Objective
Somapacitan is a long-acting reversible albumin-binding growth hormone (GH) derivative approved for once weekly administration in children with growth hormone deficiency (GHD). We present outcomes from a pooled analysis of data from three clinical trials (REAL 3 [NCT02616562], REAL 4 [NCT03811535] and REAL 6 [NCT04970654]) assessing the efficacy and safety of somapacitan vs daily GH (Norditropin®, Novo Nordisk).
Methods
In each trial, pre-pubertal, GH-treatment-naïve children with GHD were randomised to treatment with somapacitan (REAL 3: 0. 04 vs 0. 08 vs 0. 16 mg/kg/week; REAL 4 and 6: 0. 16 mg/kg/week only) or daily GH (all: 0. 034 mg/kg/day) for 52 weeks. REAL 3 and 4 were conducted internationally, and REAL 6 was conducted in China. For this analysis, efficacy comparisons were conducted vs patients treated with somapacitan 0. 16 mg/kg/week only. Mixed models of repeated measurements were used for comparisons of height velocity (HV), change in height standard deviation score (SDS) and change in insulin-like growth factor-I (IGF-I) SDS. An analysis of covariance model was used to compare changes in bone age/chronological age (BA/CA). Treatment, study, sex, age group, region, GH peak group and sex by age group by region interaction term were included as factors in each model, with the baseline of each respective efficacy measure used as the covariate (for HV, baseline height was used instead).
Results
The analysis included 220 patients treated in total with somapacitan and 118 patients treated with daily GH. Efficacy data are mean (SE). After 52 weeks, HV was 11. 2 (0. 1) cm/year vs 11. 1 (0. 2) cm/year in the pooled somapacitan and daily GH groups, respectively. Change in height SDS from baseline to week 52 was 1. 25 (0. 03) in the pooled somapacitan group and 1. 20 (0. 04) in the pooled daily GH group. Change in IGF-I SDS after 52 weeks was 2. 34 (0. 08) and 2. 10 (0. 11) in the pooled somapacitan and daily GH groups, respectively. Change in BA/CA after 52 weeks was similar between the pooled somapacitan and daily GH groups (0. 06 [0. 01] vs 0. 07 [0. 01], respectively). Differences between groups were non-significant for measures reported above ($P > 0.05$). Similar rates of adverse events per 100 patient years of exposure (294. 6 for somapacitan and 289. 0 for daily GH) were reported.
Conclusions
Outcomes from a pooled analysis of REAL 3, REAL 4 and REAL 6 demonstrate similar efficacy of somapacitan compared to daily GH over 52 weeks of treatment, with comparable safety and mean IGF-I SDS change in treatment-naïve children with GHD.

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P635

JOINT3485

Evaluation of features for a digital application for growth hormone therapy using perceptions gathered from patients, caregivers and healthcare professionals

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Growth hormone therapy (GHT) may be administered to children with growth-related disorders to enable them to reach their expected target height. This study was designed to assess the features of a digital application (app) that would support patients at different stages of GHT. Insights from patients, caregivers and healthcare professionals (HCPs) were gathered to inform the development of MySoConnect® for Sogroya® (Novo Nordisk Health Care AG). German-speaking Swiss patients/caregivers ($n = 21$) and HCPs ($n = 5$) were invited to participate. Patients were current users of the Norditropin® (somatropin) FlexPro® pen (Novo Nordisk Health Care AG). Each participant undertook three 60-minute online interviews, conducted at study start, after 1 month of app use and after new app features were developed. The overall experience and features of the app were discussed. Perceptions and needs related to GHT were also gathered at the first interview. All interviews were conducted between June and November 2022. Average patient age was 12 years. Based on response patterns, GHT journey stages were defined as "pre-therapy", "initiation of therapy", "injection by parents", "transition to self-injection", "self-injection" and "end of therapy". Perceptions and needs identified as relevant to all stages of GHT were reminders for injection, progress tracking of height and training/support related to treatment. Perceived benefit of the app by patients/caregivers was dependent on their GHT journey stage. Patients at "initiation of therapy" considered an app to be highly beneficial. For patients at "injection by parents", "transition to self-injection" and "self-injection", an app was considered beneficial. When asked about specific app features, most participants considered the ability to set reminders for injection and track height gain over time to be beneficial. Most participants indicated that having access to supporting information, such as instructional manuals, training videos and frequently asked questions, would be beneficial. In particular, patients at "initiation of therapy" and "transition to self-injection" stages deemed these supporting information features as very beneficial. The lack of connectivity between the pen and the app was considered critical by the participants. HCPs were strongly in favour of adding an automated dose-logging feature, which corresponds to a connectivity element between the injection pen and the app, to encourage app use. Insights gathered from patients, caregivers and HCPs indicate that the use of an app for GHT may support adherence to treatment, with features such as tracking height gain over time, setting reminders and accessing instructional manuals and other relevant supporting information considered beneficial.

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P636

JOINT2060

Real-world data: effectiveness and safety of vosoritide in the treatment of achondroplasia in chinese population

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Background
Achondroplasia (ACH) is the most common form of hereditary skeletal dysplasia, caused by activating mutations in the FGFR3 gene. It leads to severe disproportionate short stature and multiple complications. Current management strategies focus on multidisciplinary care, but effective pharmacological treatments are limited. Vosoritide, a CNP analogue, is the first available molecular therapy for ACH in China, showing significant improvement in annual growth rate in children.
Methods
This retrospective cohort study collected data from 30 ACH patients treated with vosoritide at the Hainan Boao Lecheng International Medical Tourism Pilot Zone from June 2022 to August 2024. After excluding four cases due to irregular medication, 26 cases were analyzed. Inclusion criteria included a diagnosis of ACH confirmed by genetic testing and open or partially closed growth plates. Vosoritide was administered at 15 μg/kg by subcutaneous injection once daily. Data on physical conditions, growth measurements, and biochemical indices were collected and analyzed using SPSS 22. 0 software.
Results
The study included 26 patients (11 males, 15 females) from 3. 4 to 11. 7 years old. Significant improvements were observed in height SDS, annual growth velocity (AGV), and BMI SDS after 12 months of treatment. Height SDS increased by 0. 4, and AGV increased by 2. 3 cm/year. The SH/H ratio decreased, indicating improved body proportions. No significant difference was found in BA-CA. Vosoritide treatment was well-tolerated, with no serious adverse events reported.
Conclusion
Vosoritide effectively promotes linear growth and improves body proportions in Chinese children with ACH, providing an optimized treatment option. Further studies with larger sample sizes are needed to confirm these findings and explore potential racial differences in treatment efficacy.

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P637

JOINT2668

Long-acting PEG-RHGH: insights from five-year outcomes in pediatric patients with growth hormone deficiency from CGLS database

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Introduction
Growth hormone deficiency (GHD), an endocrine disorder, caused due to insufficient production of growth hormone (GH), thereby affecting children's growth. Currently, pegylated recombinant human growth hormone (PEG-rhGh) is the only long-acting treatment approved for treating pediatric GHD (PGHD) in China. Long-term Efficacy and Safety Evaluation of Growth Hormone in Children in China (CGLS) is a large, surveillance registry database comprising information on participants with short stature treated with recombinant human growth hormone (rhGH) or PEG-rhGH in a real-world setting.
Methods
In this study, we analyzed the data from the CGLS database to evaluate the safety and effectiveness of PEG-rhGH over five-years in children with PGHD in China. Key outcomes such as adverse events (AEs), serious AEs (SAEs), and height gain were assessed.
Results
A total of 1207 participants were included in the safety analysis set, of which 339 received PEG-rhGH for five years and were included for efficacy analysis. Safety assessment indicated that 563 participants exhibited 1328 AEs with an incidence rate of 46. 64%. In addition, SAEs were reported in 0. 99% of participants (n = 12) with none being related to PEG-rhGH treatment. During the treatment period, a significant increase in mean change in height-SD score (**Δ**Ht-SDS) was observed with a mean ΔHt-SDS of 2. 11 ± 0. 87 in five years. Over the treatment course of five years, the mean Ht-SDS showed a consistent increase i. e., from baseline (−2. 43 ± 0. 94) to five years (−0. 33 ± 0. 83). The highest height velocity was highest at 1st year (10. 21 ± 2. 52 cm/y), which stabilized by the fifth year (6. 72 ± 1. 74 cm/y). A more favorable response in height improvements was observed in the age subgroup analysis (2-6, 6-8 and >8 years) when treatment was initiated at an early age.
Conclusion
Data from the CGLS database confirmed that participants with PGHD treated with PEG-rhGH for five years demonstrated a satisfactory safety profile and consistent improvement in height.

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P638

JOINT308

Clinical delineation and genotype-phenotype correlation in 104 pediatric patients with kabuki syndrome: a large longitudinal cohort from a single center in china

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Purpose
Kabuki syndrome is a monogenic genetic disorder affecting multiple systems, with an incidence rate of 1 in 32, 000 to 1 in 86, 000. This study provides a detailed genotype and phenotype analysis of a large longitudinal cohort of Kabuki Syndrome (KS) from a single center in China.
Methods
From July 2017 to July 2024, participants were enrolled at Shanghai Children's Medical Center. Variants in KMT2D or KDM6A were identified through whole exome sequencing. Phenotype data included prenatal and perinatal history, neonatal, childhood and adolescence evaluations.
Results
A total of 104 KS individuals fullfiled 362 outpatient visits, with an average follow-up of 2. 58 years. Growth curves were plotted based on 545 follow-up height data points. Among the patients, 27. 08% had congenital heart defects (CHD), and 3 patients were identified with anomalous pulmonary venous connection as a new KS phenotype. KS patients showed facial feature heterogeneity, patients with atypical facial features associated with a older diagnosis age and a more diverse and severe phenotype. The Face2gene software correctly identified the facial photographs of all 85 KS patients.
Conclusion
This study offered a comprehensive description of a Chinese KS cohort. And provided the first growth curves for Chinese KS patients and a detailed CHD phenotype spectrum. Our findings also suggest that artificial intelligence (AI) - assisted facial diagnostic criteria will be a valuable in the clinical diagnosis of KS.

Key words
Kabuki syndrome, Growth curves, Congenital heart defects, Artificial intelligence
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P639

JOINT1748

Early growth hormone treatment enhances growth and nutritional status in silver-russell syndrome

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Context
Silver-Russell syndrome (SRS) is an imprinting disorder characterized by severe intrauterine and postnatal growth retardation, feeding difficulties, and risk of hypoglycaemia. Recombinant growth hormone (rGH) therapy has shown its positive effect on adult height in SRS.
Objective
We aimed to assess the short-term effects of rGH therapy on the growth and nutritional status of these patients.
Design, patients and settings
Retrospective monocentric data of growth and nutritional characteristics of 77 prepubertal patients with molecularly proven SRS during the first two years of rGH therapy were analysed.
Results
The mean age at the initiation of rGH therapy was 3. 7 (1. 4-10. 3) years. The mean height gain was 0. 8 standard deviation score (SDS) after one year of treatment and 1. 3 SDS after two years. The ideal weight for length/height (WfH), reflecting the nutritional status, increased from a mean of 81% at rGH initiation, to 84% after one year of treatment ($p < 0.001$) and 86% after two years ($p < 0.001$). The proportion of SRS patients below a WfH of 75% decreased from 22. 1% at rGH therapy initiation to 7. 8% after two years of treatment. Starting rGH therapy before the age of four years was associated with a greater increase in height after two years, 1. 5 *vs* 1. 1 SDS, $P = 0.012$.
Conclusions
In prepubertal SRS patients, the first two years of standard-dose rGH therapy significantly enhance both height and nutritional status. Early initiation of treatment, before the age of four years, further optimizes height gain.

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P640

JOINT3532

The impact of growth retardation on quality of life

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Introduction
Children diagnosed with growth retardation (nanosom) face the same social and psychological challenges during their development as their healthy peers, with the difference that they also must cope with difficulties arising from their condition.
Objective
The aim of our study was to assess the impact of growth retardation on quality of life, paying particular attention to differences between hormone-treated and follow-up children, and to compare data from two chronic diseases—nanosom and diabetes mellitus (1TDM) - both treated similarly with subcutaneous injections.
Method
The sample consisted of children treated at the Endocrinology and Diabetology outpatient clinic of University of Debrecen between 2007 and 2023. The nanosom sample consisted of 110 individuals, including 69 boys/41 girls, of whom 58 were treated and 52 were followed up. The average age of the children was 12 (SD ± 4. 3). The 1TDM group consisted of 114 children. To assess quality of life, we used the Pediatric Quality of Life Inventory™ (PedsQL™) questionnaire. To evaluate the long-term effects of treatment, we assessed the quality of life of 32 growth hormone-treated children two years after their initial examination.

Results
According to the survey results, the average quality of life for nanosom children was 76. 2%. Contrary to expectations, the quality of life for hormone-treated children - 74. 8% did not show a significant difference compared to untreated patients 77. 8% ($P = 0.317$). Regarding gender, boys (77. 4%) experienced negative effects less than girls (74. 2%), but no significant difference was found ($P = 0.301$). Based on the aggregated results was confirmed that children under 12 years of age (77. 5%) rated their condition more positively than their older (75. 0%) counterparts ($P = 0.404$). Responses to the modules showed that the most negatively affected factors were emotion and school functioning. Regarding injection treatment, children with 1TDM (76. 7%) showed better scores than their growth hormone-treated counterparts (74. 8% - $P = 0, 773$). The only significant difference ($P = 0.001$) between the two group's data was observed in the social module. Examining the long-term effects of hormone treatment, children showed an improving trend (73. 59% to 77. 92%); however, this difference was not statistically significant ($P = 0.285$).
Conclusion
The results for the nanosom population fall short of the full 100%, but the long-term positive effects of hormone therapy were confirmed in this study. Considering injection treatments, no significant differences were found between the nanosom and T1DM control groups. Our research highlights the need for greater attention to emotional support therapy and school acceptance for children diagnosed with growth retardation.

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P641

JOINT3429

Assessing skeletal maturity in indian children: a comparative study of GP, GR, and TW3 methods

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Background
Bone age (BA), a critical measure of growth and skeletal maturity, is influenced by several factors, including ethnicity, gender, race, geographic distribution, environmental conditions, socioeconomic status, systemic diseases, and secular trends. Most BA assessment methods have been predominantly developed and validated in upper-class Caucasian populations. Literature comparing the accuracy and validation of different methods, especially in Indian population, is scanty. The objective of this study was to compare the accuracy of GP Atlas, GR Atlas, and TW-3 method to identify the most reliable tool for BA assessment in Indian children.
Methods
280 healthy children of both sexes, aged 2-16 years, with normal anthropometric parameters were included in the study and sub grouped equally into: 2–5 years, 5. 1–8 years, 8. 1–12 years, and 12. 1–16 years. Clinical history, pubertal status, accurate date of birth and chronological age at time of hospital visit were recorded for all participants. Digital X-rays of the left hand and wrist were obtained and analysed for BA using above three methods. BA of each was then compared to the chronological age (CA) using mean difference (BA-CA) and Bland Altman agreement analysis.
Results
All three methods underestimated CA across all age groups. TW3 method had the smallest mean difference from chronological age (-0. 24 $\pm$ 1. 02 years) overall and particularly in the 2–5-year age subgroup (-0. 07 $\pm$ 0. 71 years). Additionally, it had the narrowest limits of agreement across all age groups (-2. 24 to 1. 76 years). The GP atlas highly underestimated the Bone age (-0. 44 $\pm$ 1. 07 years), particularly in pre-pubertal males (-0. 54 $\pm$ 1. 0 years). In the prepubertal group, the TW3 method was found to have the lowest mean difference (-0. 19 $\pm$ 0. 94 years) overall and in both sexes individually, especially in females. In contrast, in the pubertal age group, GR atlas was found to have the best results with the lowest mean difference overall (-0. 13 $\pm$ 1. 33 years) and in both males (-0. 15 $\pm$ 1. 27 years) and females (-0. 11 $\pm$ 1. 39 years).
Conclusion
The GP atlas exhibited significant underestimations across all age groups, so may not be suitable for Indian children without population-specific adaptation. The TW3 method emerged as the preferred choice for detailed clinical evaluations, particularly in the prepubertal age group and showed the highest percentage of correct classifications. GR atlas, while less commonly used, offers potential as an alternative for bone age assessment in older children and adolescents.

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P642

JOINT1282

Factors influencing growth trajectory and adult height in children born small for gestational age and treated with growth hormone: a single center study

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Background
treatment with growth hormone (GH) has been approved by many countries for short children born small for gestational age (SGA) with no postnatal growth recovery. To date, optimization of the efficacy of GH treatment has not been achieved in SGA patients.
Aim
to investigate the impact of GH therapy on growth trajectory (GT) and adult height (AH) in children born SGA and to identify factors influencing the efficacy of GH therapy in terms of height gain (HG).
Methods
the study population consisted of 38 SGA children (20 M, 18 F) length without postnatal growth recovery and treated with GH for at least 5 years (mean age at GH start: 7. 65$\pm$ 3. 26 years; mean height (H): -3. 05$\pm$0. 55 SDS) and followed in our Center between 2010 and 2023. Clinical and anthropometric data [age, bone age, H (SDS), weight (SDS), BMI (SDS), SG and delta H -target height (H-TH)] at the start (T0), during GH treatment [at 1 (T1) and 2 years (T2) of therapy, during puberty onset (P0), first (P1) and second year (P2) of puberty] and at the reaching of AH were collected.
Results
HG increased during the first years of GH treatment (mean H at T1 and T2 were -2. 47$\pm$0. 55 SD and -2. 07$\pm$0. 57 SDS respectively). H at P0 was -1. 89$\pm$0. 76 SDS, at P1 it was -1. 61$\pm$0. 84 SDS and at P2 it was -1. 50$\pm$0. 78 SD. HG resulted greater in males (1. 21$\pm$0. 96 SDS) than females (0. 53$\pm$0. 49 SD; $P < 0.005$). Mean total HG (THG) was 0. 95$\pm$0. 87 SDS. Delta H-TH reduced from the start of therapy until the first two years of puberty: H-TH was -1. 63$\pm$0. 74 SDS at T0, -1. 03$\pm$0. 77 SDS at T1, -0. 66$\pm$0. 87 SDS at T2, -0. 10$\pm$1. 07 SDS at P1, and -0. 01$\pm$1. 13 SDS at P2. However, AH resulted reduced (-2. 11$\pm$0. 88 SDS), although within the TH range in 83% of patients. Only 3 patients had an AH below the lower limit of TH. AH was higher in males than females (-1. 70$\pm$0. 85 SDS vs -2. 77 $\pm$ 0. 39 SDS; $P < 0.005$). HG during T1, H at T0 and at P0 did not significantly influence AH.
Conclusions
GH treatment improves GT in SGA children. AH results within TH limits in the majority of patients, even in cases with delayed start of therapy. Sex and timing of GH initiation can influence AH in SGA children. Early selection of SGA patients for GH therapy could further improve their GT.

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P643

JOINT1604

Childhood-onset growth hormone deficiency: transition from pediatric to adult endocrine care in the Netherlands

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Background
Childhood-onset growth hormone deficiency (CO-GHD) can vary in cause and severity. Managing the transition of patients with CO-GHD into adulthood can be challenging with regard to reconfirming GHD (when and how) and continuing GH treatment (dosing) as well as determining transition readiness.
Objective
A survey was performed amongst all accredited pediatric endocrinologists in The Netherlands aiming to gather valuable insights into current practices regarding the transition of care for adolescents with CO-GHD.
Results
The survey was completed by 33 respondents (67%). Of them, 58% works in a university hospital and 42% in a general hospital. All participants indicated to stop GH in adolescents with idiopathic isolated GHD and reconfirm the diagnosis.

In case of pathogenic gene variants causing isolated GHD, the majority would stop (65%). Also, in tumor-related GHD (even after high dose radiation (>40 Gy)) and adolescents with midline abnormalities, the majority would stop GH and retest (68% and 79%, respectively). However, in case of ≥2 additional pituitary hormone deficiencies 65% indicated they would continue GH. If indicated, GHD is reconfirmed using serum IGF-I levels and/or GH provocation tests. Forty-four percent of the participants indicated that an IGF-I level >0 SDS excluded adult GHD. The most frequently performed GH provocation test was the GHRH-arginine test, but since GHRH is no longer available, most use either arginine or clonidine provocation test (65%) and 14% use the insulin tolerance test. In case of persistent GHD, GH dosages vary widely, from 0. 3 mg/day (39%) to restarting with 0. 7 mg/m^2/day and slowly lowering the dose (18%) or GH titration aiming at IGF-I levels being -1 to +1 SDS (43%). Transition readiness is assessed in consultation with the patient (83%), with the majority indicating that there are no clear guidelines and/or programs used (80%). Most patients are transferred to adult endocrine care at 18 years of age (93%), either using a referral letter (59%) or during a single JOINT consultation (35%).

Conclusion

There are considerable differences in local policies with regard to confirming persistent GHD and GH dosing after adult height attainment. Furthermore, the transition of care to adult services is not uniformly organized. It is important to also evaluate the consequences of different approaches in terms of e. g. body composition and bone development and develop a national guideline.

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P644

JOINT944

Effects of growth hormone (GH) and sex steroid therapy on brain structure and pituitary function in turner syndrome (TS)

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Background

Turner Syndrome (TS) is characterized by complete or partial loss of one X chromosome, leading to a range of physical, cognitive, and neurodevelopmental abnormalities. Therapeutic interventions such as GH and sex steroid therapy have shown promise in addressing these deficits, but their effects on brain structure and pituitary function remain under scrutiny.

Objectives

To investigate the effects of GH and sex steroid therapy on brain structure, pituitary function, and associated clinical outcomes in individuals with TS.

Methods

This review synthesizes findings from studies involving TS patients, comparing brain structure, pituitary function, and clinical outcomes with healthy controls (HC). Data include sample sizes ranging from 9 to 65 individuals, with a focus on neuroimaging, hormonal levels, and cognitive performance metrics.

Detailed Results:

• Brain Structure: TS individuals exhibit smaller hippocampus, caudate, thalamic nuclei, and parieto-occipital brain volumes compared to HC (Murphy *et al*., 1993). GH and sex steroid therapies influence these metrics, with estrogen deficiency linked to reduced gray and white matter development (Li *et al*., 2019). Enhanced basal ganglia and cerebellar growth during adolescence was observed with combined therapies (O'Donoghue *et al*., 2019).

• Pituitary Function: GH therapy increases adrenal steroid responsiveness (Balducci *et al*., 1998), reduces fat mass, and improves lean body mass (Gravholt *et al*., 2002). GH-IGF axis irregularities in TS can be normalized with sex hormone replacement (Gravholt *et al*., 1997).

• Cognitive Outcomes: Oxandrolone, a common adjunct with GH, improves working memory but GH alone does not significantly affect cognitive performance [(Ross *et al*., 1997)](https://consensus. app; (Ross *et al*., 2003).

Discussion

GH and sex steroid therapies have significant impacts on TS-associated deficits. GH improves growth and body composition, while sex steroids address estrogen deficiency, critical for neurodevelopment. The findings underscore the importance of therapy timing and individualized approaches to maximize outcomes. Limitations include small sample sizes and heterogeneity in therapy protocols across studies.

Conclusion

GH and sex steroid therapies positively impact brain structure and pituitary function in TS, with combination therapy yielding the most substantial benefits. Tailored interventions and rigorous monitoring are essential to optimize clinical and neurodevelopmental outcomes in TS patients.

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P645

JOINT781

Growth hormone therapy in children with congenital acyanotic heart disease and short stature: balancing growth and cardiac health

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Background

Children with congenital acyanotic heart disease (CAHD), including atrial septal defect (ASD) and ventricular septal defect (VSD), frequently experience growth failure due to energy deficits, malnutrition, and altered hemodynamics. Growth hormone (GH) therapy is a potential treatment for short stature in this population; however, its effects on cardiac function warrant careful evaluation.

Objectives

To assess the real impact of GH therapy on growth velocity and cardiac function in children with CAHD and short stature, focusing on benefits and risks to inform safe and effective treatment practices.

Methods

A systematic review of 20 studies published between 2000 and 2025 was conducted, involving 2, 300 children with CAHD and short stature. Real impacts on growth outcomes (height velocity and z-scores), cardiac stability, and adverse events were calculated based on pooled study data.

Results

• Growth Outcomes: GH therapy improved height velocity by an average of 39. 1%, demonstrating significant benefits for growth failure in this population.

• Cardiac Stability: Cardiac function remained stable in 86. 6% of cases, with no significant deterioration in ejection fraction or ventricular dimensions reported.

• Mild Cardiac Changes: Transient mild cardiac changes, such as slight increases in left ventricular mass, were observed in 13. 4% of cases but did not impact overall heart function.

• Metabolic Risks: Mild metabolic side effects, including fluid retention and insulin resistance, occurred in 10. 2% of cases and were manageable with routine monitoring.

Discussion

GH therapy significantly benefits growth outcomes in children with CAHD while maintaining an acceptable safety profile. The findings underscore that cardiac changes are mostly mild and transient, particularly when therapy is monitored appropriately. Improved growth outcomes contribute to better overall health and quality of life in this population. Coordination between pediatric cardiologists and endocrinologists is crucial to optimize treatment outcomes.

Conclusion

GH therapy is a safe and effective intervention for short stature in children with CAHD when administered with careful cardiac monitoring. Its significant growth benefits and manageable risks make it a valuable option for addressing growth deficits in this vulnerable population.

Growth Hormone Therapy in Children with CAHD

Aspect	Key Findings	Number of Studies	Number of Patients
Growth Velocity Improvement	39. 1% improvement in height velocity	20	2300
Cardiac Stability	86. 6% cases with stable cardiac function	18	2100
Mild Cardiac Changes	13. 4% cases with mild cardiac changes	12	1500
Metabolic Side Effects	10. 2% cases with mild metabolic side effects	10	1300

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P646

JOINT2365

Should the initial dose of long-acting growth hormone therapy somatrogon for pediatric growth hormone deficiency be standard for each child?

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Background

The Long-Acting Growth Hormone (LAGH) therapy, Somatrogon, has been available in Turkey since October 2023 for children with growth hormone deficiency (GHD). LAGH demonstrates equal efficacy compared with daily GH,

with the added advantage of reduced injection frequency. Although clinical studies have highlighted the efficacy and safety of Somatrogon, the standard initial dose for each child may present difficulties in dose titration.
Objective
The aim of this study was to evaluate dose titrations based on insulin-like growth factor 1 (IGF-1) levels in children initiated on Somatrogon therapy for pediatric growth hormone deficiency (PGHD)
Methods
A single-center, retrospective study was conducted including children initiated on Somatrogon therapy with a diagnosis of PGHD between April 1, 2024, and October 31, 2024. A total of 56 children with GHD (37 males), mean age 12. 42 ± 2. 88 years were commenced on LAGH therapy (initial dose 0. 66 mg/kg/week). 20 patients were GH naïve, and 36 were switched from daily GH to LAGH. Auxology, pubertal stage, laboratory findings including IGF-1 levels (measured 96th hours post-weekly injection) were obtained retrospectively from medical records.
Results
The mean duration of Somatrogon therapy was 0. 46 ± 0. 13 years. Dose reduction was achieved in 55. 5% of individuals due to high IGF-1 SDS, and this rate was similar to patients who were GH naïve and switched from daily GH to LAGH. Dose reductions were made in 33. 3% of 21 prepubertal individuals, 76. 9% of 13 with pubertal stage Tanner 2, 50% of 16 with Tanner 3, and 100% of individuals with Tanner 4/5 (6 patients). Children with Tanner stage 4/5 had a mean dose of 0. 51 ± 0. 02 mg/kg/week and a mean dose reduction of 22. 47 ± 3. 51 %. Children were divided into 4 groups according to their peak growth hormone response to stimulation tests. Dose reduction was made in 56. 5% of those with hormone levels between 7 and 10 ng/mL, 54. 4% of those with levels between 5 and 7 ng/mL, 41. 7% of those with levels between 3 and 5 ng/mL, and 80% of those with levels < 3 ng/mL (severe GHD). The children with severe GHD had a mean dose of 0. 56 ± 0. 08 mg/kg/week and a mean dose reduction of 14. 54 ± 12. 33 %.
Conclusion
Somatrogon may be a suitable option in PGHD patients, but the recommended initial dose of 0. 66 mg/kg/week may need to be individualized, particularly in children with severe GHD and in Tanner stage 4/5 of puberty. Careful monitoring and dose adjustment based on IGF-1 levels are necessary to maintain safety and efficacy.

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P647

JOINT1217

Design of a phase 2, randomized, controlled, multicentre study of vosoritide treatment in children with idiopathic short stature

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Idiopathic short stature (ISS) is diagnosed in individuals with height 2 to 2. 25 standard deviations below age- and sex-matched populations with no other defined aetiology. Evidence suggests that C-type natriuretic peptide is a master regulator of growth. Its analogue vosoritide is an approved targeted therapy for achondroplasia, a condition in which fibroblast growth factor receptor 3 (FGFR3) overactivity causes impaired endochondral ossification and growth. Preliminary experience from an ongoing phase 1/2 proof-of-concept study (NCT04219007) supports that vosoritide may offer benefits in a broad spectrum of short-stature conditions beyond achondroplasia, including children with short stature attributed to variants in natriuretic peptide receptor 2 (*NPR2*) and aggrecan (*ACAN*). Study 111-210 (NCT06382155) is a phase 2, randomized, controlled, multicentre study designed to compare efficacy and safety over a range of vosoritide doses vs placebo (short-term) and human growth hormone (hGH; long-term) in children with ISS. Study 111-210 aims to recruit approximately 100 prepubertal children with ISS aged ≥3 to <10 years (females) or <11 years (males) with a height Z-score less than or equal to −2. 25 from US Centers for Disease Control and Prevention average-stature references. Participants must also be naïve to growth-promoting agents. Baseline annualized growth velocity (AGV) will be established prospectively during a 6-month pretreatment growth-assessment phase. Participants will then be randomized 1:1:1:1:1 to 7. 5, 15. 0, or 22. 5 µg/kg/day vosoritide, 0. 24 mg/kg/week (starting dose) of daily hGH (US only), or placebo in the dose-finding phase of the study. Participants and investigator/study-site personnel will be blinded to vosoritide and placebo. Participants will complete a minimum of 6 months of blinded treatment (maximum 6 months of placebo), followed by open-label treatment with the selected therapeutic dose of vosoritide until they reach near-final adult height in the long-term phase. Participants randomized to hGH will receive open-label hGH for a minimum of 4 years, after which they may transition to open-label vosoritide at the therapeutic dose, if desired. The objectives of the dose-finding phase are to evaluate the safety and efficacy of 3 doses of vosoritide compared with placebo as measured by change from baseline in AGV after 6 months of treatment. The objectives of the long-term phase are to evaluate the safety and efficacy of the therapeutic dose of vosoritide vs hGH on height and height Z-score after long-term treatment.

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P648

JOINT315

Phase 3 pivotal trial design of daily oral LUM-201's efficacy and safety in treatment-naïve children with growth hormone deficiency (GHD) in randomized, double-blind, placebo-controlled study

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Objectives
The primary objective of the OraGrowtH Phase 3 study is to evaluate the efficacy of daily oral LUM-201 (1. 6 mg/kg) in improving growth velocity over 12 months in prepubertal children with GHD. LUM-201, an oral growth hormone secretagogue (GHS), acts on the GHS receptor 1a in the pituitary and hypothalamus to stimulate GH release. Clinical evidence suggests that LUM-201 increases GH pulse amplitude, resulting in increased insulin-like growth factor 1 (IGF-1) and growth. The FDA has acknowledged that, due to LUM-201's unique mechanism of action, its efficacy can be compared to placebo or injectable GH, which delivers GH concentrations about five times greater than physiological levels. 1. 6 mg/kg/day dose was selected based on prior pediatric studies. This study seeks to clinically validate the predictive enrichment marker (PEM) classification, which identifies patients who respond to LUM-201, by assessing changes in growth velocity, IGF-1 SDS, and height SDS over 12 months.
Methods
The OraGrowtH Phase 3 Trial, (global, multicenter, 12-month, randomized, double-blind, placebo-controlled) will enroll treatment-naïve, prepubertal children with GHD who test positive for PEM at screening. A positive PEM result is defined as a baseline IGF-1 concentration > 30. 0 ng/mL and a peak serum GH concentration ≥ 5. 0 ng/mL following a single dose of LUM-201. 150 subjects will be randomized in a 2:1 ratio to receive either daily LUM-201 or placebo (identical capsules) for 12 months. Subjects will attend clinic visits every three months until Month 12. At 12 months subjects will be eligible for an extension trial receiving LUM-201 for up to three years. During the trial, measurements such as height, body weight, and vital signs will be tracked. Safety assessments will include laboratory tests, ECGs, and pharmacokinetic and pharmacodynamic data. Bone age will be evaluated with standard X-rays at screening and Month 12 visits. Adverse events and the use of concomitant medications will be monitored and documented at each visit.
Results
The detailed study design will be presented at the meeting.
Conclusions
LUM-201 represents a novel investigational treatment option for patients with GHD. By stimulating endogenous GH release via the GH-releasing hormone pathway and reducing somatostatin activity, LUM-201 preserves the physiological feedback loop, distinguishing it from exogenous GH injections. The OraGrowtH Phase 3 trial aims to further evaluate LUM-201's efficacy and safety as an oral treatment for GHD.

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P649

JOINT187

Changes in body composition, ghrelin, adipokines, and FGF23 in growth hormone deficient children during rhGH therapy

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Introduction
Growth hormone (GH) therapy not only accelerates growth but also improves body composition of children with GH deficiency (GHD) by modulating lipid and

carbohydrate metabolism. This effect is potentially mediated through adipokines secreted by adipose tissue and ghrelin. Additionally, maintaining proper phosphate balance is crucial for linear growth. Fibroblast growth factor 23 (FGF23), a key regulator of phosphorus levels in the blood, may contribute to the increased renal phosphorus reabsorption observed during recombinant human GH (rhGH) therapy. This study explored the effects of one year of rhGH therapy on body composition, adipokines, acylated/unacylated ghrelin (AG/UAG), and FGF23 in children with GHD.
Materials and Methods
This prospective observational study of 42 prepubertal, non-obese children with GHD undergoing their first year of rhGH replacement therapy. Changes in body composition, adipokine levels, AG/UAG, and FGF23 were evaluated at baseline and compared to results after 6 and 12 months of treatment.
Results
The participants, with an average age of 9. 2 ± 2. 6 years, experienced significant growth acceleration. Over the 12-month period, total body fat decreased markedly, the lipid profile improved, and bone mineral density (BMD) showed a significant increase. Leptin and UAG levels dropped substantially, while adiponectin and AG concentrations increased. Plasma cFGF23 and IGF1 levels rose significantly, correlating with higher serum phosphate levels. However, FGF23 concentration changes did not affect BMD. The observed correlation between FGF23, IGF1, and height SDS suggests a potential role of FGF23 in linear growth. Regression analysis indicated that rhGH therapy influenced leptin and adiponectin levels independently of lean or fat mass but had no direct impact on ghrelin.
Conclusions
GH replacement therapy improves body composition and modifies adipokine profiles in GHD children. It also directly affects leptin and adiponectin levels regardless of body composition. Additionally, GHD children show increased serum phosphate levels, which appear linked to an upregulation of FGF23 rather than suppression, challenging the conventional understanding of FGF23's phosphaturic role. Further studies are necessary to uncover the molecular pathways through which the GH/IGF1 axis regulates adipokine secretion and alters FGF23 plasma levels.
Keywords GH deficiency, adipokines, ghrelin, IGF1, body composition, FGF23.
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P650

JOINT129

Big data as a strategy in the development of population auxological studies

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Introduction
To date, knowledge of population dynamics and its repercussions on health required complex, long and expensive field studies. Big data tools are nowadays postulated as a tool of first magnitude for weighted population changes observed in real time if reliable sources of collection and adequate mathematical and computer tools for their assessment are available.
Main objective
Carry out a methodological approach to the use of big data applications to prepare auxological growth tables in our population with high statistical power, as a first step to infer the measurement for the entire CCAA. Assess how our population is in the auxological variables with respect to the current Orbegozo 2011 standards and Spanish growth studies 2010.
Material and methods
Data collected from episodes of computerized medical records, studying the variables sex, age, weight, height, place of residence (PC, health center, neighborhood) of our population between 01/01/2020-03/31/2020 (avoiding effect pandemic) To calculate the curves and percentile tables we have used the Cole-Green LMS algorithm with penalized likelihood, implemented in the RefCurv 0. 4. 2 (2020) software, which allows managing large amounts of data. The hyperparameters have been selected using the BIC (Bayesian information criterion). To calculate population deviations from the reference, being above 1. 5 standard deviations from the mean according to age has been taken as a reference.
Results
66, 975 computerized episodes of children under 16 years of age and a total of 1, 205, 000 variables studied are collected. Although data is available, individuals $>16^{a}$ are excluded due to low N. The graphs of our population are represented with respect to the standards, observing that there are differences with Orbegozo 2011 and Spain 2010. We present the data and percentages of overweight/obesity by age and sex. There are significant differences of more overweight in the entire sample of men and women in our population than the usual standards. Big data technology surpasses classic population studies in power and is an innovative tool compared to auxological studies (limited in N) carried out to date. The development of these new strategies in auxology will allow us to know almost in real time the epidemiological situation of the population in different variables, being able to infer health actions in a more effective way.
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P651

JOINT740

Non-evidence-based and off-label growth therapies - observations from consultations and practice patterns

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Introduction
Growth assessments do not always lead to established diagnoses and respective therapeutic options. This can cause considerable stress for patients and families. Some ask for alternative (or additional) non-evidence-based or off-label methods (e. g. growth hormone) for growth stimulation. However, the possibility of such off-label treatment has led to a change in the way the diagnosis of 'short stature' has been approached in recent years. A trend from 'growth medicine' to 'growth engineering' is currently being observed. There is no reliable data on the frequency and content of such enquiries.
Methods
An anonymous international online survey was conducted with paediatric endocrinologists from the Young European Society for Paediatric Endocrinology ("YES-Group"). The response rate was 47. 8 % (total 65 participants). The relevance of this topic from the perspective of paediatric endocrinologists was surveyed. In addition, the frequency/thematic content of corresponding enquiries and the attitudes of colleagues were surveyed. Specific prescription frequencies of off-label use treatments with growth hormone (GH), aromatase inhibitors (AI) /Gonadotropin-Releasing-Hormone (GnRH) analogues or both were queried separately.
Results
In 44. 6 % of cases, non-evidence-based methods were requested in every fifth to second consultation by patients or parents. 96. 9 % of colleagues considered the topic to be relevant. Most clarify the ineffectiveness (76. 9%) or potential risks (47. 7%). Most people asked about 'special diets/optimisation of nutrition' and 'food supplements', among other methods. 29. 3% prescribed off-label GH, 50. 8 % refused (for AI 15. 4 % and 33. 9 % respectively/for GH plus AI or GnRH analogues 19. 9 % and 33. 9 % respectively).
Conclusion
Non-evidence-based and off-label methods for growth stimulation play a significant role in patient counselling. A proactive approach in counselling for non-evidence-based methods could prevent disappointments or even risks. The off-label use of GH or GH plus AI/GnRH is frequent and the subject of ongoing societal, ethical and medical discourse.

Table 1: Which types of non-evidence-based methods have your patients or parents inquired about this year? Select all that apply (n = 65, multiple choice, below 5 % not shown).

Non-evidence based method	Ratio of requests
Food supplements	75.0%
Special diets/optimisation of nutrition	59.4%
Off-label use of Growth Hormone	40.6%
Sports (e. g. swimming)	35.9%
Medical drugs (other than GH and/or AI)	34.4%
Physiotherapy (e. g. stretching exercises) /physical thrp./manual thrp.	26.6%
Herbal remedies/phytotherapy	26.6%
Sleep regulation	25.0%
Zinc	18.8%
Arginine suppelment	17.2%
Strength/weight training	14.1%
Homeopathy	7.8%
Stress reduction	7.8%
Aromatase inhibitors	6.3%

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Metabolism, Nutrition and Obesity

P19

JOINT1763

Dysregulation of RNA-Exosome machinery component EXOSC4 in MASLD-HCC progression

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Metabolic-associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease and can progress to hepatocellular carcinoma (HCC). Understanding the molecular mechanisms underlying MASLD progression to HCC is essential for developing effective therapeutic strategies. Previous studies have suggested that RNA processing and metabolic machinery, including the RNA-Exosome complex, may play a pivotal role in MASLD-HCC progression. However, the specific role and contributions of the RNA-Exosome complex in HCC development remain poorly understood. The aim of this study was to characterize the dysregulation and putative role of the RNA-exosome machinery, specifically the component EXOSC4, in MASLD-HCC progression to identify new diagnostic/prognostic biomarkers and/or potential therapeutic targets. Bioinformatic approaches were implemented to analyze the dysregulation of the RNA-exosome machinery and to characterize, in silico, the expression of EXOSC4 at mRNA/protein levels in MASLD, MASLD-related HCC, Metabolic Dysfunction-Associated Steatohepatitis (MASH), HCC and control (normal or adjacent tissue) samples in 16 cohorts (2 retrospective and 14 in silico). Correlations between EXOSC4 expression and clinical parameters relevant to MASLD-HCC progression were evaluated. Pathway enrichment analyses were performed to identify associated cellular and molecular processes. Finally, the role of EXOSC4 was characterized in vitro (proliferation, migration, clonogenic and tumorosphere formation assays) by modulating its expression (silencing and overexpression) in two liver-derived cell lines (Hep3B and SNU-387) and in vivo through a preclinical model of Hep3B-induced xenograft tumors. These analyses revealed that the RNA-exosome machinery is dysregulated in MASLD and HCC. Specifically, the EXOSC4 component was consistently overexpressed in the cohorts studied, wherein high EXOSC4 expression was associated with clinical parameters of malignancy, such as poor survival, increased invasion and recurrence capacity. Consistently, high EXOSC4 expression was associated with the enrichment of oncogenic pathways, such as cell cycle regulation or DNA repair. Consistent with these results, in vitro assays demonstrated that EXOSC4 silencing reduced classical parameters tumor aggressiveness, while EXOSC4 overexpression increased malignancy. Furthermore, in vivo studies confirmed the pro-tumorigenic potential of EXOSC4 by inducing tumor growth in murine models. In conclusion, our results reveal a critical role of the RNA-Exosome machinery, particularly the EXOSC4 component in MASLD-CHC progression. These results suggest that EXOSC4 may serve as a potential biomarker and/or therapeutic target for this pathology.

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P20

JOINT3349

Setmelanotide in the Management of Pediatric Obesity Due to Genetic Disorders: Clinical Response and Quality of Life Assessment

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Background
Setmelanotide, a melanocortin-4 receptor (MC4R) agonist, has been approved for treating obesity caused by genetic disorders affecting the leptin-melanocortin pathway. This single-center case series evaluates six pediatric patients who began treatment between March and December 2024.
Methods
Baseline assessments included anthropometric measurements, laboratory tests, and adapted questionnaires for ages below and above 12 years. The questionnaires included hunger symptoms and impact of hyperphagia from patient and caregiver perspectives. Two patients with Bardet-Biedl Syndrome (BBS) had completed six months of follow-up at the time of submission, allowing comparisons between baseline and six-month evaluations.
Results
The study included six children (two males, four females) aged 5 to 15 years. At baseline, the median BMI-for-age z-score was +3.25 (range: 2.84–5.8), and the median body fat percentage was 35.43% (range: 24.5–42.5%). Genetic diagnoses included four patients with BBS (one compound heterozygosity for BBS1 and one for BBS2, heterozygosity for BBS4 and BBS19, and homozygosity for BBS9), one patient with a homozygous pro-opiomelanocortin (POMC) deficiency, and another with compound heterozygosity for leptin receptor (LEPR) deficiency. 50% of the patients had prediabetes, and 50% had hypertriglyceridemia at baseline. Hunger scores for patients <12 years ranged from 9–13 out of 15, while older patients scored between 5–10 out of 12. The hyperphagia impact scores ranged from 13–21 out of 24 in younger patients and 10–21 out of 24 in older ones. The highest-rated symptom was "persistent hunger after eating," and hyperphagia most affected "leisure and free time" and "relationships with family and friends." Family members reported the greatest impact on "mood and emotions" and "relationships". After six months, two BBS patients showed improvements in anthropometric and quality-of-life measures. A 6-year-old patient's hunger score decreased from 9 to 8, hyperphagia impact from 13 to 9, family impact from 11 to 8, and BMI reduced by -2.02 kg/m^2. A 13-year-old patient's hunger score dropped from 6 to 4, hyperphagia impact from 10 to 7, family impact from 15 to 14, and BMI decreased by -5.11 kg/m^2.
Conclusions
Preliminary results suggest setmelanotide improves BMI, hunger scores, and hyperphagia's impact on patients and families. Further analysis when the follow-up for the other patients has been completed will provide more insight into the consistency and magnitude of these changes. While results are promising, ongoing evaluation may help assess the durability of setmelanotide's effects and its long-term impact on obesity management and quality of life.

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P652

JOINT3276

Adverse waist-for-height ratio trajectories in childhood are associated with cardiometabolic and cardiovascular risk by age 10

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Introduction
Waist-for-height ratio reflects central adiposity, a key predictor of cardiometabolic health. This study examines how adverse waist-for-height trajectories in childhood are associated with increased cardiometabolic and cardiovascular risk by age 10.
Methods
Analysis was conducted within the COPSAC2010 cohort, comprising 700 mother-child pairs with detailed phenotyping across 14 visits. We used latent class analysis to identify child waist-for-height ratio trajectories from 1 week to 10 years. Cardiometabolic risk (CMR) was derived from composite z-scores of HDL, triglycerides, glucose, blood pressure (height-adjusted), and HOMA-IR, while cardiovascular disease (CVD) risk was calculated using NMR blood metabolomics and Cox models from the UK Biobank. Scores were z-scored within the cohort for interpretation. Models were adjusted for demographics, lifestyle factors, physical activity, sleep, diet, and relevant clinical measures.
Results
We identified three distinct waist-for-height ratio trajectories from 1 week to 10 years: a stable "Reference group" (66%), a "Rising-then-falling" group (18%), and a "Slow-rising" group (15%). Compared to the reference group, the "Slow-rising" group (15%) had significantly higher CMR ($\alpha = 0.79$, $P < 0.0001$) and CVD scores ($\alpha = 0.53$, $P < 0.0001$), reflecting worse cardiometabolic risk. This group also showed elevated levels of C-peptide ($\alpha = 106$, $P < 0.0001$), HOMA-IR ($\alpha = 0.15$, $P < 0.0001$), GlycA ($\alpha = 0.04$, $P < 0.0001$), and hs-CRP ($\alpha = 0.60$, $P < 0.0001$), alongside lower HDL ($\alpha = -0.17$, $P < 0.001$). Compared to the reference group, the "Rising-then-falling" group (18%) had significantly lower HbA1c levels ($\alpha = -0.90$, $P = 0.003$) and slightly higher ApoB levels ($\alpha = 0.03$, $P = 0.032$). Adjusting for waist-for-height ratio cross-sectionally at 10 years explained most of the variance in risk, rendering previous associations for the "Slow-rising" group nonsignificant, however findings for the "Rising-then-falling" remained significant.
Conclusion
Childhood waist-for-height ratio trajectories are strongly linked to cardiometabolic and cardiovascular risk by age 10. These findings emphasise the need for early monitoring and intervention to address central adiposity patterns and reduce the risk of long-term adverse health outcomes.

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P653

JOINT2202

Efficacy of treatment with combination dapagliflozin and metformin vs metformin alone in overweight and obese women with polycystic ovary syndrome: a randomized controlled trial

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Background
Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by insulin resistance and hyperandrogenemia, particularly in overweight and obese women. Dapagliflozin and other sodium-glucose cotransporter-2 (SGLT2) inhibitors may offer additional benefits to metformin, which is commonly used to improve metabolic parameters in patients with PCOS. This study compares the efficacy of metformin alone vs dapagliflozin plus metformin in reducing hyperandrogenism and insulin resistance in overweight and obese women with PCOS.
Methods
Sixty-four overweight or obese non-diabetic women between 18 and 40 years old diagnosed with polycystic ovary syndrome (PCOS) as per Rotterdam criteria were enrolled. Patients were randomly allocated to receive either a combination of dapaglifozin plus metformin (DAPA + MET) or metformin (MET) alone treatment. The DAPA + MET group received dapagliflozin 10 mg once daily plus metformin 1000 mg twice daily, while the MET group received metformin 1000 mg twice daily for six months. Changes in hormonal profile, anthropometric parameters, glucose and lipid homeostasis, and adverse events (AEs) were evaluated.
Results
At baseline, both groups had similar demographic, clinical and metabolic characteristics. Over 24 weeks, both groups showed significant reductions in body mass index (BMI), fasting insulin, fasting plasma glucose (FPG), homeostatic model assessment for insulin resistance (HOMA-IR), and androgenic markers like free androgen index (FAI) and serum testosterone levels ($p < 0.05$ within groups). The DAPA + MET group demonstrated greater reductions in BMI (-1. 62 vs. -0. 42 kg/m^2), fasting insulin (-1. 38 vs. -0. 74), HOMA-IR (-0. 51 vs. -0. 31), serum testosterone (-0. 12 vs. -0. 06), and FAI (-1. 21 vs. -0. 62) compared to metformin alone. However, the differences between groups were not statistically significant. Changes in lipid profiles were also comparable between groups. Adverse events such as urinary tract infections (UTI) and vaginal irritation were reported more frequently in the DAPA + MET group ($P = 0.043$).
Conclusion
Both DAPA + MET and MET were effective in improving insulin resistance, hyperandrogenemia, and metabolic parameters in overweight and obese women with PCOS. While the combination therapy demonstrated greater improvements in weight loss and insulin sensitivity, the differences were not statistically significant. However, the increased incidence of UTIs and vaginal irritation should be considered when prescribing dapagliflozin in this population. Further long-term studies with larger sample sizes are needed to confirm the potential added benefits of dapagliflozin in managing PCOS.

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P654

JOINT148

Enzymatic approach to neonatal hyperbilirubinemia

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Background
The ultra -old problem of neonatal hyperbilirubinemia has been solved by complex settings of exchange transfusion and phototherapy and beside time/cost and ward consuming issues; treatment is not optimum. Till now it has not been clarified whether low grade hyperbilirubinemia is harmful or beneficial regarding the antioxidant nature of unconjugated bilirubin. Besides Albumin binding, transportation to the liver, uptake, conjugation and secretion into bile has not been fully investigated for therapeutic intervention. Conjugation within the circulation omits these steps and will be faster than natural absorption, conjugation and release. We proposed that peripheral conjugation with a canine glucose transferase short cut all these steps without the need for the energy rich uridyl-glucuronic-transferase which is relatively deficient in neonates in premature babies.
Methods
After successful preclinical study, two enzymes i. e. human glucuronic transferase and canine glucose transferase were used at in 12 patients in three clinical phases. Type I Crigler Najjar models were not available so moribund neonates with life expectancy of less than three months were used for toxicity studies.
Results
The human enzyme was unable to conjugate bilirubin in human serum because of the lack of uridyl-diphosphate. Addition of uridyl-diphosphate completed the task within minutes. Conjugation with glucose under canine glucose transferase was easy, without the need for uridyl-diphosphate and resulted in water soluble monoconjugates. The reaction was completed within seconds without complex needed agents or by products *In vitro*. *In vitro* studies of hundreds of blood samples were extremely successful with glucose transferase. The details are out of the scope of this presentation. A single injection caused a reduction of harmless Bilirubin of 8mg/dl down to zero in a timely curve in 12 human neonates.
Conclusion
Treatment of neonatal hyperbilirubinemia with canine glucose transferase at picogram concentrations is safe and can be accomplished as treatment and prophylaxis.

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P656

JOINT405

Growth trajectories of height and body composition in pre-pubertal and early pubertal stages across obesity transition groups: a longitudinal study

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Background
Childhood obesity, particularly its transitions between normal weight and obesity, remains poorly understood regarding its impact on growth and body composition during pre-pubertal and early pubertal stages. Investigating these dynamics is crucial for dispelling misconceptions about obesity's relationship with height and guiding effective early interventions.
Objective
To longitudinally analyze changes in body measurements and compositions during the pre-pubertal and early pubertal stages, comparing groups with differing obesity transitions.
Methods
Anthropometric and body composition data were collected at ages 7 and 12 from 5, 353 children categorized into four groups: obese (obese at both ages; $n = 215$), obese-to-normal (obese at age 7, non-obese at age 12; $n = 134$), normal-to-obese (non-obese at age 7, obese at age 12; $n = 373$), and control (non-obese at both ages; $n = 4,631$). Measurements included height, weight, body fat mass (BFM), skeletal muscle mass (SMM), body mass index (BMI), body fat mass index (BFMI), skeletal muscle mass index (SMMI), and waist-to-hip ratio (WHR). Growth differences were analyzed using a Difference-in-Difference (DID) estimator.
Results
The obese group exhibited significantly higher weight, BFM, SMM, BMI, BFMI, and SMMI at both ages compared to the control group. When comparing growth trajectories, the obese group showed greater increases in weight, BFM, SMM, BMI, BFMI, and WHR, but not height, relative to the obese-to-normal and control groups. Similarly, the normal-to-obese group displayed increased body composition metrics, excluding height, compared to controls.
Conclusions
Children remaining obese during pre-puberty and early puberty exhibit greater increases in body composition metrics, excluding height, compared to those transitioning to normal weight or remaining non-obese.

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P657

JOINT580

A comprohensive cohort analysis of 113 paediatric non-syndromic monogenic obesity

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Introduction
Clinical features of nonsyndromic monogenic obesity are predominantly derived from case-based publications due to rarity of the condition. Here, we aimed to establish the frequency of specific ethiologies among a nationwide cohort of monogenic obesity and describe clinical features and associated manifestations of each specific etiologies.
Methods
Cross-sectional data were collected from 22 paediatric endocrinology centers across Turkiye, including patients with biallelic LP/P variants in *LEP, LEPR, POMC, PCSK1, MC4R, SIM1, ADCY3, CEP19* and monoallelic LP/P variants in *MC4R*. Clinical data and anthropometric measurements prior to specific treatment were analyzed. Statistical analyses were performed for groups with ≥ 5 cases.
Results
A total of 113 patients (49% female) were evaluated. The most common mutations were monoallelic *MC4R*($n = 41$) and biallelic *LEPR*($n = 38$), followed by *POMC*($n = 10$), biallelic *MC4R*($n = 10$), *LEP*($n = 5$), *PCSK1*($n = 3$), *CEP19*($n = 3$), *ADYC3*($n = 2$), and *SIM1*($n = 1$) mutations (Table). Significant differences were identified in weight-SDS, BMI-SDS, bone age-SDS, and HOMA-IR values ($P = 0.008$, <0.0001, 0.0075, and 0.02 respectively) among different ethiologies. *LEP* mutations were associated with the highest BMI-SDS, while *LEPR* and biallelic *MC4R* cases had the worst metaboilic profile. Advanced bone age-SDS was observed in *LEPR* and monoallelic *MC4R* cases. The age of obesity-onset was predominantly <1 year in biallelic *LEP, LEPR, MC4R, ADCY3, CEP19* and *SIM1* mutations and 1-5 years in *POMC* and *PCSK1* mutations. Endocrine dysfunctions were common in *LEPR, POMC* and *PCSK1* cases. Psychiatric disorders and intellectual disability were observed in 11.5% and 8.3% of patients, respectively.
Conclusion
This paediatric cohort details the clinical characteristics of non-syndromic monogenic obesity and demonstrates that LEPR mutations are as common as monoallelic MC4R mutations in Turkiye. LEPR and biallelic MC4R mutations had the worst metabolic profile. LEPR and monoallelic MC4R cases exhibited significantly advanced bone age-SDS without increased height-SDS.

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P657

	LEP($n = 5$)	LEPR($n = 38$)	Biallelic MC4R($n = 10$)	Monoallelic MC4R($n = 41$)	POMC($n = 10$)	PCSK1($n = 3$)	CEP19($n = 3$)	ADYC3($n = 2$)	SIM1($n = 1$)
Age, mean±SDS	2, 1±1, 7	9, 1±5, 3	9, 5±4, 6	11, 7±4, 7	9, 5±5, 9	11, 2±4, 6	13, 1±0, 8	4, 1±1, 4	9, 1
Height-SDS, mean±SD	0, 7±0, 6	0, 9±1, 6	1, 4±1, 8	1, 2±1, 6	1, 7±1, 9	-1, 3±0, 6	0, 4±0, 7	1, 8±0, 1	2, 6
Weight-SDS, mean±SD	6, 4±1, 5	5, 4±2, 4	5, 8±1, 5	4, 0±1, 4	4, 1±1, 9	2, 8±1, 8	6, 0±1, 0	6, 7±1, 8	4, 2
BMI-SDS, mean±SD	6, 5±1, 4	4, 6±1, 2	4, 8±1, 0	3, 2±0, 9	3, 5±1, 5	3, 2±1, 3	4, 5±0, 3	5, 0±0, 7	3, 6
BA-SDS, mean±SD(n)	-0, 5±0, 5(3)	2, 1±2, 3(25)	0, 5±2, 1(5)	1, 8±1, 7(27)	-0, 4±2, 3(10)	0, 3±1, 1(2)		4, 8(1)	1, 4
Obesity-onset, n									
<1 y	5	33	9	13	6		3	2	
1-5 y		4	1	15	4	3			1
>5 y		1		13					
Hyperphagia, n	5/5	30/38	10/10	30/41	8/10	2/3	3/3	1/2	1/1
Homa-IR, mean±SD(n)	1, 6±1, 2(5)	6, 1±4, 2(38)	8, 2±7, 8(8)	4, 5±3, 8(40)	5, 7±5, 3(10)	3, 7(1)		3, 8±1, 8	2, 5
T2DM, n		6/38	1/10	5/41		1/3	3/3		
Adrenal insufficiency, n				1/41	10/10	2/3			
GH deficiency, n		3/38			1/10	1/3			
Central hypothyroidism, n		9/38		1/41	6/10	2/3			1/1
Hypogonadism, n	0/1	4/13(31)	0/4	0/32	1/6(17)				
Intellectual disability, n		2/38		2/41	3/10	1/3	1/3		
Psychiatric disorders, n		3/38	1/10	4/41		1/3	3/3	1/2	

P658

JOINT1127

Assessing how the edmonton obesity staging system for pediatrics (EOSS-P) in childhood relates to mental health outcomes 7 years later: findings from the quality cohort

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Introduction
The EOSS-P (Edmonton Obesity Staging System for Pediatrics) is a comprehensive tool that defines obesity severity beyond traditional

anthropometric measures (weight or body mass index). It assesses obesity burden across four domains: metabolic, mechanical, mental health, and milieu. We previously demonstrated that EOSS-P scores at 8-10 years were associated with adverse cardiometabolic health outcomes at 15-17 years. Given strong evidence between living with excess weight and poorer mental health outcomes, we aimed to study associations between EOSS-P staging at 8-10 years and mental health outcomes at 15-17 years.
Methods
Data were obtained from the QUALITY cohort, a prospective study of Quebec children with a parental history of obesity. This analysis focused on the children with obesity at ages 8-10 and 15-17 years ($n = 72$). EOSS-P was staged at 8-10 years, ranging from Stage 0 (no abnormalities across domains) to Stage 3 (significant impairment across domains). Participants reported on mental health symptoms at 15-17 years old using two validated questionnaires, the Composite International Diagnostic Interview for anxiety (CIDI-A) and for depression (CIDI-D). We estimated the associations between the EOSS-P stage at 8-10 years and mental health at 15-17 years using multivariable linear regression models adjusted for age and sex. Multiple imputation and inverse probability of censoring weighting addressed missing data and selection bias due to loss to follow-up, respectively. We log-transformed CIDI-A and expressed results in sympercents.
Results
At 8-10 yrs, 0. 6% of the sample belonged to EOSS-P Stage 0, 33. 0% to Stage 1, 40. 0% to Stage 2, and 26. 0% to Stage 3. Compared to Stage 1, belonging to Stage 2 at 8-10 years was associated with an increase in CIDI-D of 2. 39 points [CI: -0. 65; 5. 32] but no meaningful association with CIDI-A at 15-17 years. Belonging to Stage 3 at 8-10 years was associated with an increase in CIDI-D of 2. 04 points [CI: -1. 97; 5. 87] and a 17. 92% [CI: -24. 20%; 79. 33%] increase in CIDI-A at 15-17 years compared to belonging to Stage 1.
Conclusion
A higher EOSS-P stage at age 8-10 years showed a trend towards less favourable mental health at age 15-17 years, independent of baseline mental health staging within the EOSS-P. Notably, although modest, the increase in depressive and anxiety symptoms in late adolescence suggests a potentially clinically meaningful association, despite the small sample size. Results need to be confirmed in a larger sample.

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P660

JOINT846

Benefits of ambulatory blood pressure monitoring over office blood pressure in children and adolescents with severe obesity: findings from the bern obesity in childhood and adolescence biorepository

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Background
Prevalence of hypertension (HTN) among children and adolescents with severe obesity is up to five times higher compared to their normal-weight peers. Youth hypertension is a strong predictor of cardiovascular (CV) morbidity and premature mortality. Ambulatory blood pressure monitoring (ABPM) has proven superior to office blood pressure (oBP) for diagnosis and CV risk prediction in adults. Growing evidence supports its use in the paediatric population. However, data on ABPM in children and adolescents with severe obesity and associations with measures of mass and body composition remain sparse.
Methods
Data on anthropometry (percent of the 95th body mass index percentile according to CDC [%BMIp95], waist-to-height ratio [WHtR], impedance-related percent of body fat [%BF] and muscle mass [%MM]) as predictors, and on oBP and 24-hour ABPM as outcomes (normal BP, ambulatory HTN, white coat HTN [WCH] and masked HTN [MH], non-dipping) according to ESH guidelines were drawn from the Bern Obesity in Childhood and Adolescence Biorepository. Descriptive statistics and adjusted logistic regression analyses were applied.
Results
A total of 351 individuals, 52. 4% males, had a mean (SD) age of 12. 2 (2. 6) years and a %BMIp95 of 124 (17. 9). WHtR ($n = 316$) was 0. 58 (0. 06), %BF and %MM ($n = 241$) was 41. 9% (6. 4) and 31. 7% (3. 7), respectively. Based on oBP measurements ($n = 302$), 8% had Grade 1 HTN, 9% had Grade 2 HTN. Based on ABPM ($n = 351$), 15% had ambulatory HTN and 44% were non-dippers. In 302 participants with oBP and ABPM, ABPM detected WCH in 36 of 52 individuals with abnormal oBP, and MH in 28 of 251 individuals with normal oBP, overall disproving 21% of oBP findings. An increase in 1-unit %BMIp95 and 0. 01-unit WHtR was associated with ambulatory HTN (OR 1. 02 [1. 01-1. 04] and 1. 07 [1. 01-1. 13], respectively). An increase in 1-unit %BF was associated with non-dipping (1. 05 [1. 01-1. 10]), whereas a 1-unit increase in %MM was protective from non-dipping (0. 91 [0. 84-0. 98]).
Conclusion
Our results provide evidence for the benefits of ABPM in children and adolescents with severe obesity for discriminating BP subtypes and for risk stratification, and we show that body composition measures provide distinct information on blood pressure outcomes.

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P661

JOINT2565

Weight loss at 18 months of setmelanotide in 2-5-year-old patients with rare mc4r pathway diseases

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Background
Rare variants in melanocortin-4 receptor (MC4R) pathway genes may impair MC4R signalling, leading to hyperphagia and early-onset, severe obesity. In a Phase 3, open-label trial, the MC4R agonist setmelanotide reduced weight and hunger in patients aged 2 to 5 years with proopiomelanocortin (POMC) deficiency, leptin receptor (LEPR) deficiency, or Bardet-Biedl syndrome (BBS) at 1 year (primary time point). Here, we report sustained improvements in weight outcomes at 18 months of setmelanotide.
Methods
The VENTURE trial (NCT04966741) evaluated 52 weeks of setmelanotide treatment in patients aged 2 to 5 years with hyperphagia and obesity due to biallelic *POMC* or *LEPR* variants or genetically confirmed BBS. This analysis assessed body mass index (BMI), BMI z-score, and percent of the BMI 95th percentile (%BMI95) from baseline to Month 18 of a long-term extension study.
Results
Eight patients (POMC/lEPR, $n = 5$; BBS, $n = 3$) completed 18 months of setmelanotide. All patients had severe obesity at baseline (BMI z-score range, 2. 4 to 7. 3) and had clinically meaningful reductions in weight at Month 18. The mean

percent change from baseline in BMI was −21. 5% at Month 12, −22. 3% at Month 15, and −23. 3% at Month 18. The mean change from baseline in BMI z-score was −1. 9 at Month 12, −2. 0 at Month 15, and −2. 1 at Month 18. The mean change from baseline in %BMI95 in percentage points was −37. 0 at Month 12, −38. 5 at Month 15, and −41. 3 at Month 18. Skin hyperpigmentation (87. 5%; all treatment related) and nasopharyngitis (62. 5%; all not treatment related) were the most common reported adverse events.

Conclusion

In the first trial of setmelanotide in patients 2 to 5 years of age, robust reductions in age-appropriate weight measures were seen in all patients at 18 months of treatment, with no new safety concerns. No approved therapies for patients 2 to 5 years old with obesity in the studied populations currently exist, despite the need for early intervention with targeted therapy in these patients.

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P662

JOINT1016

Exosomal miRNA profile and its association with insulin resistance in obese children and NAFLD patients

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Objective

Recent studies suggest that microRNAs (miRNAs) may serve as novel biomarkers for predicting insulin resistance-related conditions, such as obesity, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD), in both adults and children. This study aimed to compare serum exosomal miRNA levels among obese children, children with NAFLD, and healthy controls in a Korean pediatric population. Additionally, the study sought to analyze the association between these miRNAs and markers of insulin resistance.

Methods

A total of 30 prepubertal children were included in this study, with 10 children in each group: obesity ($n = 10$), NAFLD ($n = 10$), and healthy controls ($n = 10$). Each group consisted of 5 males and 5 females. Serum exosomal miRNA was analyzed using next-generation sequencing (NGS). Statistical analyses were performed to compare miRNA expression levels between the groups and to assess correlations with clinical parameters and insulin resistance markers, including the triglyceride-glucose index (TyG), TyG index adjusted for ALT (TyG_ALT), and homeostatic model assessment of insulin resistance (HOMA-IR).

Results

All participants were prepubertal, with average ages of 8. 7 years in the NAFLD group, 8. 6 years in the obesity group, and 8. 3 years in the control group, with no significant age differences between the groups. MicroRNAs 34a-5p, 122-5p, 885-5p, and 885-3p were found to be significantly upregulated in the NAFLD group compared to both the obesity and control groups. These miRNAs were positively correlated with AST and uric acid levels. Additionally, miRNAs 122-5p, 885-5p, and 885-3p showed positive correlations with ALT and the TyG_ALT index. In contrast, miRNAs 570-3p and 32-3p were downregulated in the NAFLD group compared to both the obesity and control groups and negatively correlated with AST, ALT, and the TyG_ALT index.

Conclusion

Specific miRNAs, particularly 34a-5p, 122-5p, 885-5p, 885-3p, 570-3p, and 32-3p, exhibit differential expression in children with NAFLD compared to obese and healthy controls. These miRNAs are closely associated with liver function and insulin resistance markers, highlighting their potential as biomarkers for NAFLD and related metabolic disturbances in pediatric patients.

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P664

JOINT1896

Hepatic triglyceride export in acromegaly and the effects of treatment - a preliminary study

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Overview

High growth hormone (GH) concentrations are associated with low intrahepatic lipids (IHL). Lately, our study group reported a GH mediated stimulation of hepatic triglyceride (TG) export in healthy males as possible antisteatotic mechanism. However, the impact of long-term GH excess in acromegaly on hepatic TG export is yet unknown.

Methods

For this preliminary analysis, GH/IGF-I axis activity and hepatic TG secretion were investigated in 8 patients with active acromegaly (4 female, median 52 [IQR: 44-55] years, BMI 28. 1 [26. 5-31. 9] kg/m2). Hepatic TG secretion was assessed via an intralipid infusion protocol and IHL were measured using magnetic resonance spectroscopy. In 5 Patients, measurements were repeated after successful treatment. Data before treatment were compared to an unmatched group of 9 male volunteers (23 [22-27] years, BMI 21. 2 [20. 2-25] kg/m2) with low IHL.

Results

IHL content was comparable between patients with acromegaly and controls (1. 2 [1. 1-1. 4] vs. 0. 9 [0. 8-1. 4] %, $P = 0. 556$). Hepatic TG secretion was not increased in active acromegaly (patients vs controls: 577 [483-738] vs 436 [401-785] mg/h, $P = 0. 336$). Successful treatment of acromegaly did not significantly reduce hepatic TG secretion (577 [483-738] vs 475 [393-634] mg/h, $P = 0. 242$). Data for IHL was present for 6 patients before and 3 patients after treatment initiation (1. 2 [1. 1-1. 4] vs. 0. 9 [0. 7-1. 3] %).

Conclusion

According to this preliminary analysis, low IHL in acromegaly is not associated with a substantial increase in hepatic TG secretion. These findings are in contrary to previous investigations of healthy individuals during short-term GH/IGF-I axis modulation. Further studies will need to clarify possible adaptations in hepatic lipid metabolism after long-term GH excess.

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P665

JOINT1341

Phase II study to assess the efficacy and safety of pasireotide in patients with post-bariatric hypoglycaemia: PASIPHY study design

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Introduction

Post-bariatric hypoglycaemia (PBH) complicates up to 38% and 12% of gastric bypass and vertical sleeve gastrectomy surgeries, respectively. PBH, characterised by postprandial hyperinsulinaemic hypoglycaemic episodes in association with neuroglycopenic symptoms, is caused by rapid gastric emptying and excessive secretion of glucagon-like peptide 1 (GLP-1) and insulin. There are no approved medical therapies; affected patients suffer extreme disability. Pasireotide, a somatostatin receptor ligand, binds with high affinity to somatostatin receptor subtype 5, inhibiting GLP-1 and insulin secretion and slowing gastric emptying. PASIPHY, a Phase II dose-finding study (NCT05928390), will assess pasireotide efficacy and safety in patients with PBH.

Methods
~72 patients with PBH (age ≥18 years; bariatric surgery ≥6 months prior) will enrol across ~25 sites (Europe/USA). The study comprises a ≤3-week (W) screening, a 4W run-in and a 12W randomised, double-blind, placebo-controlled treatment period. Patients with ≥4 postprandial hypoglycaemic events (self-monitored blood glucose [SMBG] <54 mg/dL [<3. 0 mmol/l], a neuroglycopenia event or a level 3 hypoglycaemic event) during the run-in period are randomly allocated to subcutaneous pasireotide at doses of 50, 100 or 200 μg 3 times a day (tid) or matching placebo (3:1 ratio). All patients initiate treatment with 50 μg pasireotide; dose increases occur on days 5 (to 100 μg) and 9 (to 200 μg). Those completing the 12W core phase can choose to receive pasireotide during a 36W open-label extension. All patients will start the extension on pasireotide 50 μg tid; dose can be adjusted for safety/efficacy reasons (up to 200 μg). The primary endpoint is change in blood glucose levels measured by peak:nadir glucose area under the curve during the mixed-meal tolerance test (MMTT) from baseline to W12 of treatment. Core-phase secondary endpoints (assessed at W4, W8 and W12, unless otherwise specified) include: change from baseline in rate of level 2 hypoglycaemic events; change from baseline in rate of level 3 hypoglycaemic events; duration of level 2 hypoglycaemic events; change from baseline in frequency of rescue therapy use; change from baseline to W12 in insulin, glucagon and GLP-1 secretion during MMTT; change from baseline to W12 in health-related quality of life; and incidence of adverse events throughout the study. These endpoints and others will be assessed throughout the extension.
Conclusion
PASIPHY will provide valuable data on pasireotide efficacy and safety, ascertain which dose has the best benefit:risk ratio, and determine whether it is a viable treatment option for patients with PBH.

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P666

JOINT651

Empagliflozin: sex-specific effects on mitochondrial function and cellular redox-balance in HFPEF and MASLD

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Background
Empagliflozin, a sodium-glucose co-transporter 2 (SGLT-2) inhibitor, has shown beneficial effects in obesity-related conditions such as heart failure with preserved ejection fraction (HFpEF) and metabolic dysfunction-associated steatotic liver disease (MASLD). However, the precise cellular mechanisms behind these effects are not fully understood, and there is limited knowledge about gender-specific differences in responsiveness to empagliflozin.
Methods
Male and female wistar rats were fed either standard chow **(CO)** or a high-fat/fructose **(HFD)** diet combined with L-NAME for 8 weeks to induce obesity and associated comorbidities like HFpEF and MASLD. Following this regimen, the rats received either empagliflozin **(EMPA)** or saline **(HFD)** for additional 8 weeks, with ad libitum access to either HFD or a low-fat/high-fructose diet. Echocardiography (ECG) was conducted at the end of treatment. Histological assessment for H. E., OilRed and CD3 was performed in hepatic tissue. Isolated cardiomyocytes were evaluated for mitochondrial redox state, while isolated cardiac and hepatic mitochondria were subjected to high-resolution respirometry to assess oxygen consumption (with pyruvate/malate, fatty acids, and succinate as substrates) and redox state with an Oroboros Oxygraph-2k.
Results
In the ECG analysis, the male HFD group exhibited a significantly reduced E/A-ratio with preserved ejection fraction (EF), indicating diastolic dysfunction and an HFpEF phenotype when compared to CO. Cardiac mitochondrial respiration in HFD was significantly lower than in CO but was fully restored by EMPA. EMPA treatment significantly increased the E/A-ratio, in line with a significantly restored mitochondrial redox balance. In female HFD rats, echocardiography similarly showed a significantly reduced E/A-ratio, consistent with diastolic impairment and preserved ejection fraction. Here, EMPA restored the E/A-ratio and mitochondrial respiration was significantly higher compared to HFD. Hepatic histological assessment in the male HFD group indicated increased lipid storage and inflammation with non-significant EMPA-effects. Regarding mitochondrial respiration, the male HFD group exhibited significantly higher respiration rates compared to CO. Mitochondrial O_2 consumption was significantly lower with EMPA compared to HFD in males with stronger effects in females.
Conclusions
Empagliflozin has distinct sex-specific effects in a diet-induced model of HFpEF and MASLD. It enhances cardiac and hepatic mitochondrial function in males while yielding different outcomes in females. Males experience a stronger impact from empagliflozin on cardiac mitochondrial respiration, while stronger effects on hepatic mitochondrial respiration could be detected in females. These findings underscore the importance of incorporating sex-based analyses in HFpEF and MASLD research, as responses to empagliflozin may vary significantly between sexes, potentially influencing treatment strategies.

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P667

JOINT1907

Diagnostic performance of triglyceride-glucose-based indices for identifying metabolic syndrome in paediatric populations

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Aim
Considering the difficulties in directly measuring insulin, various surrogate markers integrating glucose, lipid profiles, and anthropometric measures have been proposed. This study aims to evaluate the diagnostic performance of the Triglycerides-Glucose Index (TyG), along with TyG-BMI, TyG-waist circumference (WC), and TyG-waist-to-height ratio (WHtR) indices, in identifying metabolic syndrome (MetS) in pediatric populations, in comparison to traditional parameters.
Methods
We retrospectively studied 746 children and adolescents (372 F/374 M) divided into different groups using the BMI z-score. Insulin resistance (IR) surrogates was calculated as: HOMA-IR, TyG, TyG-BMI, TyG-WC, TyG- waist-to-height ratio (WHtR). MetS was defined as the presence of at least 3 of the following components: BMI z-score ≥2 and/or WC/H ratio ≥0. 5; fasting blood glucose > 100 mg/dl and/or pathological HOMA-IR according to pubertal stage; dyslipidemia; hypertension.
Results
Overall prevalence of MetS was 15. 01% (112/746). MetS occurred only in children with obesity and overweight ($P = 0.004$). The Area under the ROC curve of TyG, TyG-BMI, TyG-WC, TyG-WHtR were 0. 801 ($P < 0.001$), 0. 840 ($P < 0.001$), 0. 832 ($P < 0.001$) and TyG-WHtR 0. 816 ($P < 0.001$) respectively, which was similar than that of HOMA-IR 0. 866 ($P < 0.001$).
Conclusions
The TyG, TyG-BMI, TyG-WC, and TyG-WHtR indices have shown significant potential in predicting the development of MetS among children and adolescents with overweight or obesity. These indices offer a practical approach for identifying high-risk individuals within otherwise healthy populations. Considering the high cost of insulin sensitivity testing, the triglyceride-glucose product serves as an effective and cost-efficient surrogate marker for evaluating IR in clinical settings.

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P668

JOINT3676

The rising burden of childhood obesity: prevention could start at primary school

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Background
Physical activity (PA), dietary habits, and sleep hygiene are crucial for the prevention of childhood obesity (CO) early in life. Early prevention is foundamental to reduce the long-term health risks associated with CO, and schools can serve as an effective setting for promoting healthy behaviors. The "EpPOI: Education to Prevent CO" project aimed to investigate these factors through caregiver surveys, the Mediterranean Diet Quality Index for children and adolescents (Kid-Med), and the MOBAK assessment of functional movement skills (FMS).
Methods
Caregivers completed an online survey about their children's PA, sleep hygiene, and dietary habits. Adherence to the Mediterranean diet (MD) was assessed using the Kid-Med questionnaire. The FMS of 102 children aged 3–5 were evaluated with the MOBAK test, and caregivers rated their children's motor skills using a Likert-scale questionnaire.
Results
Diet 95 mothers completed the survey. Only 5. 3% of children achieved a Kid-Med score reflecting adequate MD adherence, despite over 50% of respondents reporting regular consumption of vegetables, fruits, legumes, and olive oil. However, 50. 5% of children consumed sweets daily, and 80% skipped breakfast. Parental perception of their child's PA significantly predicted MD adherence, with PA positively correlating with fruit ($P < 0.034$), vegetable ($P < 0.015$), and fish consumption ($P < 0.005$). **PA:** Despite 61. 1% of children regularly participating in sports activity, only 20. 5% achieved a satisfactory MOBAK total score (Score 3). Boys scored higher than girls in locomotion (Score 2) and total motor skills (Score 3) ($P < 0.026$, $P < 0.016$, respectively). A significant negative correlation was found between BMI and Score 3 ($P < 0.030$). Parents significantly overestimated their children's motor skills ($P = 0.0001$).
Conclusions
This study highlights the gap between caregivers' perceptions and the actual behaviors or abilities of pre-school children regarding lifestyle habits. Most children demonstrated low adherence to the MD, with poor dietary habits such as frequent sweet consumption and skipping breakfast. Although sports participation was common, motor skill proficiency was limited, particularly among children with higher BMI. Effective CO prevention requires an integrated approach combining adherence to healthy dietary patterns like the Mediterranean diet, enhanced parental awareness, and the promotion of physical activity. Schools, as accessible community structures, can play a pivotal role in fostering these behaviors early in life.
Keywords Physical activity, Mediterranean diet, functional movement skills, childhood obesity, childhood obesity prevention, school-based interventions.

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P669

JOINT3863

The dutch experience with anti-obesity drugs in young adults and adults with prader-willi syndrome

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Introduction
At the Dutch Center of Reference for Prader-Willi Syndrome (PWS) we see over 450 children and adults with PWS. One of the most challenging medical problems in PWS is obesity and its complications. In PWS, obesity is multifactorial and caused by both physical factors (low muscle mass, hypotonia, low basal metabolic rate, hormone deficiencies), medication and behavioral factors (hyperphagia). Anti-obesity drugs are thought to attenuate this hypothalamic hyperphagia. In this study, we report the effects of anti-obesity drugs in PWS.
Methods
Retrospective study among 201 young adults and adults with PWS attending the Dutch national reference center for PWS. All patients follow the same trajectory consisting of a medical questionnaire, structured interview, complete physical examination, biochemical measurements and, if needed, imaging. [1] After screening for medical problems, treatment is started. Since 2024, lifestyle coaching for people with intellectual disabilities has become available in the Netherlands and we have started to prescribe anti-obesity drugs to adults with PWS in our center. In case of obesity (BMI > 30), we offer two treatment options:
1. After routine PWS-specific food safety advice, lifestyle coaching for people with intellectual disabilities is started. After participating in this program for one year, anti-obesity drugs are started, reimbursed by the Dutch health insurance.
2. In some patients, caregivers want to start anti-obesity drugs on own costs because lifestyle is already considered optimal and routine PWS-specific food safety measures have already been taken. In that case, the lifestyle intervention program is skipped and anti-obesity drugs like GLP1-agonists (Liraglutide and Semaglutide) and Naltrexon/bupropion are prescribed.
Results
Since the start of this standard obesity approach, we have prescribed anti-obesity drugs to 28 adults with PWS aged 20-56 years. Average percentage of weight loss was 8. 7% (ranging from 0. 9 to 19. 5%) for Liraglutide, 9. 3% (ranging from 2. 9 to 23. 9%) for Semaglutide and 0. 2% (ranging from a weight gain of +3. 1% to a weight loss of 3. 4%) for Naltrexon/bupropion. The single patient on Dulaglutide lost 0. 7% of his weight. Few side effects were reported and no serious gastrointestinal problems were reported.
Conclusion
Anti-obesity drugs can have a beneficial effect on weight in people with PWS. However, the effect is heterogeneous and external control of food intake seems to be more important than the medication.
Reference
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P670

JOINT1088

Impact of a 4-week multidisciplinary prehabilitation program on tumor-related gene expression in patients with colon cancer: the ONCOFIT project

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Obesity is one of the key factors associated with colon cancer development independent from inherited genetic mutations. Furthermore, obesity-related unhealthy lifestyle behaviors (e. g., low physical activity and fitness or an unhealthy diet) significantly increase the risk of postoperative complications in patients undergoing surgery, the first-line treatment for colon cancer. These complications affect more than 50% of patients, leading to higher morbi-mortality rates, increased healthcare costs and a reduced quality of life. For that, lifestyle-based prehabilitation multimodal programs (PMP) (exercise, dietary behavior changes and psychological support) have been proposed to improve physiological reserve and postoperative recovery, and to reduce risk factors for cancer recurrence. However, the molecular mechanisms underlying these types of interventions remain unexplored. The aim of this study was to analyze the effects of a 4-week PMP on the expression of key tumor-related genes in patients undergoing resection of colon cancer. For this purpose, we analyzed mRNA expression of 93 genes (microfluidics-based qPCR array) involved in tumor environment, development and progression (e. g., tumor markers, inflammation, immune system, or energy metabolism) in tumor and non-tumoral adjacent tissues from patients with colon cancer ($n = 48$; including both men and women) randomly assigned to a PMP ($n = 23$) or a usual care ($n = 25$). Statistical associations with key clinical features of colon cancer were performed. The results revealed a significant beneficial regulation of the pattern of genes expression in patients undergoing PMP, which have been previously described to be altered in the context of this pathology.

These beneficial patterns include genes (i) involved in the regulation of intracellular calcium (*CALB2*), (ii) associated with inflammation and immune response regulation (*TGFB1*, *VASN*, *TNFa*, *IL6ST*, *IL6R*, *PTGS2*, and *SPP1*), (iii) potent growth factors promoting cell proliferation, survival, and differentiation (*IGF1* and *IGF2*), (iv) related to metastatic processes in the liver and lungs (*CXCL12*), and (v) involved in tumor suppression and apoptosis (*TP53* and *BCL2*), among others. Additionally, many of these genes were correlated with pivotal clinical and histopathological parameters, such as body weight or tumor volume. In conclusion, a 4-week PMP modulates the expression of relevant cancer-related genes in patients with colon cancer compared with those receiving usual care. These changes correlated with clinical parameters of the patients. Although further research is needed in this area, this transcriptional regulation may help explain the beneficial outcomes observed with the PMP in the ONCOFIT Project.

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P671

JOINT2229

Comparison of insulin resistance indices in obese children and adolescents based on a 10-year data

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Objective

The increasing prevalence of childhood obesity and the development of insulin resistance (IR) and type 2 diabetes mellitus (T2D) are major public health concerns. The aim of this study was to compare the HOMA, FGIR and QUICKI indices for measuring IR in obese children and adolescents according to oral glucose tolerance test (OGTT) Results

Methods

Patients attending the Pediatric Endocrinology Clinic with exogenous obesity and undergoing OGTT in the last 10 years were included in the study. Patients' data were obtained retrospectively from hospital records. The children were divided into two groups according to the presence or absence of IR. The HOMA, FGIR and QUICKI methods were analysed to confirm the OGTT findings of IR in these groups. Receiver operating characteristic curve (ROC) analysis was used to determine cut-off points and to calculate sensitivity and specificity for IR.

Results

A total of 899 obese children (568 girls and 331 boys, mean age 14. 06 ± 2. 06 years) were included in the study. IR was diagnosed in 76. 3%, impaired fasting glucose (IFG) in 11. 3%, impaired glucose tolerance (IGT) in 13. 9% and T2D in 5. 8% of the children. 708 cases were assessed for metabolic syndrome and 195 (27. 5%) children were diagnosed with MS. The rates of akantozis nigrikans (60. 5% & 17. 2%) and hepatic steatosis on ultrasound (50. 7% & 12. 8%) were higher in the IR group (p:0. 045 and p:0. 009). Triglycerides were higher in the IR group than in the non-IR group, while other cholesterol levels were similar ($P < 0.001$). Notably, the rates of IFG, IGT and T2D were not significantly different between groups ($p > 0.05$). The HOMA and QUICKI indices were higher in the IR group, while the FGIR values were similar ($P < 0.001$, $P < 0.001$ and p:0. 057, respectively). Among the incidences, the area under the curve (AUC) was higher for HOMA-IR (0. 711 for girls and 0. 7 for boys) compared to FGIR (0. 278 for girls and 0. 262 for boys) and QUICKI (0. 289 for girls and 0. 306 for boys). The HOMA-IR cut-off value was 4. 22 (70% sensitivity and 30% specificity) in pubertal girls and 4. 18 (70% sensitivity and 30% specificity) in pubertal boys.

Conclusions

HOMA is a more accurate measure of IR in children and adolescents than FGIR and QUICKI. For the diagnosis of IR, the HOMA threshold is 4. 22 in girls and 4. 18 in boys based on OGTT Results The OGTT remains important in the diagnosis of insulin resistance, pre-diabetes and T2D, despite being an invasive method.

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P672

JOINT2441

Western diet-induced effects on renal glucose and sodium transporters - a novel mechanism in pathophysiology of the metabolic syndrome

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Background

Western diet which is characterized by a high content of sugar and saturated fat is well known to be associated with obesity, insulin resistance, type 2 diabetes and cardiovascular disease. While chronic kidney disease has long been thought to be the consequence of metabolic disease, it has only recently become clear, that renal damage at an early stage plays a key role in pathophysiology and course of metabolic disease. Underlining the close correlation, SGLT-2 inhibitors and GLP-1 receptor agonists have been shown to improve both, metabolic disease and chronic kidney disease.

Aim

Here we aimed to test whether Western diet causes renal damage by affecting hemodynamically and metabolically important renal transporters in a murine model of diet-induced obesity. Additionally, we aimed to test whether potential harmful effects are reversible by switching the diet from a Western type to a more beneficial one.

Method

Male C57BL/6 mice were fed ad libitum a Western diet for 10 weeks and afterwards switched to either standard diet for eight more weeks or continued to be fed a Western diet. Mice fed standard diet for 18 weeks served as control group.

Results

Western diet feeding for 18 weeks was associated with excess weight gain and development of insulin resistance. Sodium glucose transporter 1 (SGLT1) mRNA expression was significantly higher in kidneys of mice fed a Western diet for 18 weeks than in standard diet fed mice and those switched from Western diet to standard diet after 10 weeks. Additionally, renal sodium glucose transporter 2 (SGLT2) levels were also found to be elevated in Western diet fed mice, showing an already significant difference after 10 weeks and even higher levels after 18 weeks. Importantly, renal SGLT-2 mRNA expressions were comparable in mice fed a Western diet for 18 weeks and in those switched from Western diet to standard diet. Complementary to the upregulation of SGLT2 a downregulation of renal epithelial sodium channel (ENaC) mRNA was observed, which could not be prevented by the dietary switch neither.

Conclusions

Our data show that Western diet causes partially irreversible alterations in renal glucose and sodium transporters that might play a crucial role in development and course of metabolic disease. Importantly, SGLT-2 overexpression occurs early and is not dependent on overt hyperglycemia.

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P674

JOINT275

Mesothelial cells act as critical mediator in hyperandrogenism-induced visceral obesity

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Androgen excess is a common endocrine disorder in women and drives a selective expansion of visceral adipose tissue (VAT). Mesothelial cell is only present in visceral but not subcutaneous adipose tissues. But its function is poorly understood. Single cell RNA sequencing (scRNA-seq) reveals a dramatic decrease in VAT mesothelial cell number upon androgen excess-induced obesity. This is in accompany of a malformation of extracellular matrix (ECM) in the VAT of female mice. Female mice with mesothelial cell-specific deletion of androgen receptor (*Ar*) are resistant to androgen excess-induced visceral obesity and ECM malformation. Depletion of mesothelial cells in VAT directly impairs ECM formation, accompanied by VAT gain and metabolic disorders even on a normal diet, highlighting the key function of mesothelial cells in VAT ECM formation. Furthermore, VAT organoids deficient of mesothelial cells exhibit compromised ECM formation and enhanced adipogenesis, which are reversed by mesothelial cell conditioned medium. Mechanistically, mesothelial cells abundantly secret proteoglycan Decorin (DCN), which is indispensable for ECM formation in VAT. Normalizing DCN expression in VAT rescues androgen excess-induced ECM malformation, visceral obesity and insulin resistance in female mice. These findings reveal the intermediatory function of mesothelial cell in aiding proper ECM formation and its implication in hyperandrogenism-induced visceral obesity.

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P675

JOINT3930

Sex-specific effects of different dietary compositions and NO-synthase inhibition on mitochondrial respiration and cellular redox state in HFPEF and MASLD

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Background
Obesity is closely linked to heart failure with preserved ejection fraction (HFpEF) and metabolic-dysfunction associated steatotic liver disease (MASLD). A model combining diet-induced obesity with L-NAME–induced hypertension may replicate HFpEF and MASLD conditions effectively. However, the optimal dietary composition and duration for inducing these diseases remain uncertain. This study evaluates the impact of various diets combined with L-NAME, a pan-nitric oxide synthase inhibitor, on HFpEF and MASLD characteristics in male and female Wistar rats.
Methods
Male and female Wistar rats were assigned to receive either standard chow (CO), standard chow with L-NAME, low-fat diet (LFD + L-NAME), or high-fat, high-fructose diet (HFD) with or without L-NAME. HFD groups had ad libitum access to HFD or LFD. Isolated cardiomyocytes were evaluated for mitochondrial redox state. Isolated cardiac and hepatic mitochondria were subjected to high-resolution respirometry to assess oxygen consumption and ROS emission.
Results
In male rats, the HFD group exhibited an oxidized cardiac mitochondrial redox state, indicative of increased metabolic demand compared to CO, while effects of LFD and L-NAME alone were less visible. Cardiac mitochondrial respiration was effectively impared in the HFD group. In contrast, hepatic mitochondrial respiration was significantly elevated in the HFD group compared to CO but only partially affected by LFD and L-NAME. In females, the mitochondrial redox state was more reduced across all conditions compared to CO, indicating lower mitochondrial demand or increased metabolic redundancy. Mitochondrial respiration was paradoxically elevated in all intervention groups compared to controls. Hepatic mitochondria from the HFD group exhibit significantly more oxygen compared to CO.
Conclusions
The combination of HFD and L-NAME induces HFpEF and MASLD characteristics with distinct sex-specific effects. This investigation is crucial for developing future therapeutic strategies and underscores the importance of analyzing sex-specific differences, which can significantly influence treatment outcomes in patients with HFpEF and MASLD.

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P676

JOINT3333

Cardiometabolic profile between metabolically healthy obese (MHO) vs metabolically unhealthy obese (MUO) adolescents

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Background
Pediatric and adolescent obesity is a worldwide pandemia. Since the majority of adolescents with obesity will be an adult with the same condition and its complications, a precocious identification of cardiovascular risk factors is mandatory. Our aims were to evaluate the frequency of MHO vs MUO in children and adolescents with obesity followed in our Pediatric Clinic and to compare the cardiometabolic profile.
Patients and Methods
We evaluated 149 patients (52% males) median age 13 years (range 5–18), 16% Tanner stage 1, 38% Tanner stages 2-4, and 46% Tanner stage 5. Data on body mass index (BMI), waist-to-height ratio (WHtR), and laboratory tests were collected. MHO phenotype includes HDL cholesterol (HDL-C) >40 mg/dl, fasting plasma glucose (FPG) <100 mg/dl, Systolic and Diastolic Blood Pressure (SBP and DBP) $< 90°$ percentile by gender, height and age, triglycerides ≤ 100 mg/dl or <130 mg/dl for aged <10 or >10 years, respectively. MUO phenotype included impaired of at least one of the above parameters. As marker of cardiovascular risk was SPISE, calculated using the formula: [600 × (HDL cholesterol^0. 185)/(triglycerides^0. 2) × (BMI^1. 338)].
Results
In the whole cohort, 40% of patients had elevated BP, 34% low HDL-C, 20% elevated triglycerides, and 9% elevated FPG. MUO phenotype was in 101 (68%) patients, with Tanner stages 2-5 more represented than Tanner stage 1 (78% vs 22%, $P = 0.016$). A high prevalence of elevated SBP/DBP was observed (59%, $P < 0.001$). MUO phenotype showed higher levels of BMI-SDS (2. 9 [2. 3;2. 9] vs 2. 6 [2. 5;3. 5], $P = 0.004$), WHtR (0. 59 [0. 55;0. 66] vs 0. 57 [0. 53;0. 62], $P = 0.029$), SDP (119 [113;126] vs 109 [103;115], $P < 0.001$) and DBP (68 [62;76] vs 62 [59;68], $P = 0.001$), FPG (92 mg/dl [88-96] vs 89 mg/dl [85-93], $P = 0.004$), Hb1Ac (5. 3 % [5. 0-5. 5] vs 5. 0 % [4. 8-5. 3], $P = 0.002$), and triglycerides (90 mg/dl [65-130] vs 65 [53-85], $P < 0.001$). Conversely, MUO exhibited lower HDL-C (41 mg/dl [37-47] vs 49 mg/dl [45-58], $P < 0.001$) and SPISE (4. 8 [3. 9-5. 8] vs 5. 6 [4. 9-6. 5], $P = 0.003$). After adjusting for pubertal status, WHtR, and hypertension, SPISE emerged as an independent predictor of MUO ($Or = 0.39$ [95%CI 0. 21-0. 75], $P = 0.004$). The area under the ROC curve of SPISE in predicting the MUO phenotype was 0. 65 (95%CI 0. 56-0. 74, $P = 0.003$).
Conclusions
The MUO phenotype showed a worse cardiometabolic profile than the MHO phenotype; SPISE appears to effectively capture the metabolic component of the increased cardiometabolic risk. Given the high prevalence of hypertension, routine BP monitoring is crucial in optimizing risk stratification of the MUO subset.

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P677

JOINT2732

Role of AMPK in preserving metabolic homeostasis in visceral adipose tissue and skeletal muscle in a PCOS rat model

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Introduction
Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder affecting women of reproductive age. Early manifestations of the syndrome emerge before puberty, often in conjunction with obesity, which, in the presence of hyperandrogenemia and/or hyperinsulinemia during adolescence, contributes to the full manifestation of PCOS in adulthood. To elucidate the contributions of prepubertal obesity and hyperandrogenemia to the development of metabolic disturbances in PCOS, we analysed lipid and glucose metabolism in the main insulin-responsive tissues (visceral and subcutaneous adipose tissue (VAT and SAT), skeletal muscle) in a well-established PCOS animal model.
Methods
Female Wistar rats were subjected to postnatal overfeeding via litter size reduction and treated with 5α-dihydrotestosterone (DHT) to induce PCOS-like features. Systemic insulin sensitivity was assessed alongside the expression of key markers of glucose and lipid metabolism, and energy sensing, like AMPK activation, in VAT, SAT, and skeletal muscle.
Results
Litter size reduction led to increase in body mass and visceral adiposity, while DHT treatment combined with overfeeding resulted in systemic insulin resistance and hyperinsulinemia. In VAT, both litter size reduction and DHT treatment contributed to adipocyte hypertrophy, along with a suppression of *de novo* lipogenesis (reduced gene expression of lipogenic enzymes) and lipolysis (decreased hormone-sensitive lipase), while insulin sensitivity was preserved due to AMPK activation. Conversely, SAT exhibited increased expression of

lipogenic and lipolytic markers and reduced AMPK activity, suggesting an impaired metabolic profile in this tissue as a result of effect of both factors, litter size reduction and DHT treatment. In skeletal muscle, insulin signalling was disrupted at key nodes (pIRS1-Ser307, AKT) in overfed animals, while DHT treatment reduced glucose transport (decreased GLUT4 expression), leading to diminished glucose uptake and systemic hyperinsulinemia. In this altered energy landscape, as result of effects of both factors, skeletal muscle preferentially utilised fatty acids for energy, indicated by enhanced fatty acid uptake and increased markers of lipolysis and α-oxidation. However, this shift induced oxidative stress and inflammation, and triggered AMPK activation as a compensatory mechanism that maintain metabolic homeostasis.

Conclusion

AMPK emerges as a critical metabolic regulator that acts as a protective mechanism in VAT and skeletal muscle to counteract metabolic stress and maintain tissue functionality. The differential regulation of AMPK in VAT and SAT highlights its tissue-specific role in PCOS-associated metabolic disturbances. Given its pivotal function, targeted activation of AMPK may represent a promising therapeutic strategy to improve metabolic health in women with PCOS.

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P678

JOINT2061

Piezo1 activation suppresses bone marrow adipogenesis for healthy skeleton through inhibition of a mechanoinflammatory autocrine loop

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With aging or upon osteoporosis, bone marrow adipogenesis is enhanced and inversely correlates with the loss of bone mass. Bone marrow adipocytes are derived from the multipotent bone marrow mesenchymal stem cells (BMMSCs), which can differentiate into either fat or bone. BMMSCs are mechano-sensitive cells, but how mechanical loading is implicated in the *in vivo* regulation of bone marrow adipogenesis and its impact on bone remodeling remains poorly understood. Here we identify the mechanosensitive cationic channel Piezo1 in BMMSCs as a key suppressor of bone marrow adipogenesis by preventing local inflammation, thereby enhancing osteoblast differentiation and bone formation. Mice with a specific Piezo1 invalidation in BMMSCs exhibit lower body weight, osteoporosis, and marrow adiposity, together with a resistance to the beneficial effects of exercise on bone health. Accordingly, Piezo1-deficient BMMSCs *In vitro* preferentially differentiate into adipocytes rather than osteoblasts. Mechanistically, Piezo1 invalidation enables c-Jun activation to increase Ccl2 production, while autocrine activation of CCR2 by Ccl2 induces the expression and secretion of lipocalin-2 (Lcn2) via NF-κB activation, thereby promoting BMMSCs adipogenesis. Conversely, pharmacological inhibition of Ccl2 signaling and shRNA-mediated knockdown or antibody-mediated blockage of Lcn2 inhibit adipogenesis but restore osteogenesis in Piezo1-deficient BMMSCs. Collectively, these findings demonstrate that Piezo1 activation in BMMSCs suppresses bone marrow adipogenesis to maintain skeleton strength by preventing the Ccl2-Lcn2 inflammatory autocrine loop, thus uncovering a previously unrecognized link between mechanotransduction, inflammation, and cell fate determination.

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P679

JOINT448

The visceral adipose-derived hormone ANNEXIN A8 alleviates obesity-induced chronic inflammation via modulating macrophage functions

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Obesity is a major risk factor for a panel of chronic diseases and thus is becoming a major challenge worldwide. In particular, abnormally high level of visceral adipose tissue (VAT) deposition, known as visceral obesity, is an independent risk factor for metabolic diseases. We found that *Annexin A8* (*Anxa8)* gene is selectively induced in VAT of obese mice. The transcription of ANXA8 is induced by hypoxia. Mice with adipocyte-selective deletion of *Anxa8* are more susceptible to diet-induced glucose intolerance and chronic inflammation. Simillarly, neutralization of circulating ANXA8 exacerbates diet-induced metabolic diseases. Conversely supplementation of recombinant ANXA8 protein protects mice against diet-induced glucose intolerance and chronic inflammation. Mechanistically ANXA8 directly modulates macrophage polarization via activation of AMPK pathway. In human serum ANXA8 concentration was positively correlated with VAT amount, and VAT/SAT ratio, but was less correlated with subcutaneous adipose tissue (SAT).

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P680

JOINT892

Recommendations for screening for polycystic ovarian syndrome (PCOS) in adolescents with obesity: are national and international management guidelines aligned?

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Introduction

Polycystic Ovarian Syndrome (PCOS) may affect up to 18% of adolescent girls and has significant implications on reproductive, metabolic and mental health. The diagnosis of adolescent PCOS is challenging due to differing criteria and manifestations. Adolescents with obesity are at higher risk of PCOS and should be screened accordingly. However, screening for obesity-associated comorbidities, including PCOS, have not been standardized. A scoping review was conducted to evaluate and compare the presence and extent of recommendations for PCOS screening and management in national and international guidelines for pediatric obesity, and to summarize recommendations from guidelines developed specific to adolescent PCOS.

Methods

A scoping review protocol was developed in accordance with the PRISMA extension for scoping reviews checklist. Databases searched included: PubMed, MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature and various guideline repositories. The inclusion criteria include (1) national or international guidelines, consensus or position statements written by government, professional bodies or expert panels, and (2) pertained to the clinical management of paediatric obesity or adolescent PCOS, and (3) published in English or with available English translations. The Appraisal of Guidelines for Research and Evaluation (AGREE)-II instrument was used for quality assessment of the included articles. Recommendations for the screening and management of PCOS in adolescents with obesity were made, with certainty of evidence ascribed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.

Results

Fourteen of 32 international childhood/adolescent obesity guidelines included some mention of PCOS screening and/or management, and 7 adolescent PCOS specific guidelines were summarized. Details of recommendations varied across the guidelines, even in the PCOS-specific guidelines. Based on the strength and quality of evidence presented, we summarize key recommendations for PCOS screening and management: (1) Perform a comprehensive menstrual history for overweight or obese patients, (2) Assess onset and progression of hirsutism, and onset and severity of cystic or inflammatory acne, (3) PCOS-specific investigations include serum free/total testosterone and sex hormone-binding globulin, (4) Routine pelvic ultrasound and serum anti-Mullerian hormone measurements are not recommended in adolescents, (5) Individualised PCOS management with weight management as a cornerstone, (6) Combined oral contraceptives and metformin may be useful for management.

Conclusion

Adolescent obesity and PCOS guidelines have been inconsistent with the recommendations on PCOS screening management. Given the significant morbidities associated with PCOS, appropriate screening and prompt management is essential and should be part of routine care in adolescents with obesity.

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P681

JOINT2951

Body fat percentage is associated with pubertal onset in boys and girls

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Background
Pubertal timing is influenced by a variety of factors, including body composition. While body mass index (BMI) is commonly used as a marker of adiposity, fat percentage (BF%) may be more strongly associated with pubertal onset in children. Notably, BF% increases with pubertal development, a trend most pronounced in girls. This study aims to evaluate the association between BF% and timing of pubertal onset.
Methods
In total, 1, 007 children and adolescents (59% girls) aged 12. 8 years (5. 9-23. 4) from The COPENHAGEN Puberty Study were included. Besides a clinical examination including pubertal staging, key anthropometric variables, such as BMI, skinfold measurements, and hip/waist ratio, were recorded. BF% was estimated using Slaughter's equation for skinfold thickness, and pubertal onset was defined by the age of thelarche in girls (>B2) and testis volume >3 ml (> G2) in boys. Sex and age-related SD scores for BF% were calculated using the GAMLSS methods to analyze the relationship between age- and sex adjusted BF% in relation to pubertal timing. Probit regression models were employed to estimate the age of pubertal onset according to differences in BF% quartiles.
Results
BF% and BMI correlated positively with age in girls (spearman rho $\rho = 0.46$, $P < 0.01$ and $\rho = 0.67$, $P < 0.01$, respectively). Similarly in boys, BMI correlated positively with age ($\rho = 0.66$, $P < 0.01$), whereas no correlation was seen for BF% and age in boys. Furthermore, girls generally had higher BF% and hip/waist ratio compared to boys; 19. 8% vs. 16. 9%, $P < 0.01$) and 1. 3 vs. 1. 1 in hip/waist ratio ($P < 0.01$). Significant lower age of pubertal onset was observed with the highest BF% in boys (mean age Q1: 12. 2 years vs. Q4: 11. 4 years, $P < 0.01$) and in girls (mean age Q1: 10. 0 years vs. Q4: 9. 8 years, $P < 0.01$) although less pronounced.
Conclusion
In healthy Danish children, a higher BF% was associated with an earlier age of pubertal onset. However, due to the cross-sectional design, causality cannot be determined. It is possible that increased BF% accelerates pubertal onset, or that earlier puberty leads to higher BF%. These findings highlight the important role of body composition in pubertal development and its timing.

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P682

JOINT3975

Effect of oral glucose administration on ghrelin levels in normal heigh children born small for gestational age being in the first decade of their life

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Introduction
Ghrelin is responsible for GH production and appetite stimulation. Ghrelin secretion is dependent on food intake, increases in the fasting state and decreases after meals. Ghrelin reduces energy expenditure and lipolysis and promotes weight gain. However, studies have shown that ghrelin levels are lower in obese individuals, whereas in leaner individuals they are higher than in controls. It seems that ghrelin may have a greater effect on postprandial satiety than on preprandial appetite stimulation. Some (but not all) small for gestational age (SGA) children who demonstrated catch-up phenomenon after birth, develop increasing obesity and elements of the metabolic syndrome. We therefore suspect an association between higher ghrelin levels and faster growth and weight gain in SGA children. The aim of the study was to assess fasting ghrelin levels and the degree of its reduction during oral glucose tolerance test (OGTT) in 5-9-year-old SGA children depending on BMI and the presence of metabolic syndrome components.
Material and Methods
91 prepubertal SGA children (34 boys and 57 girls) aged 4. 78-9. 75 years (6. 9 ± 1. 37 years) were qualified for the study. Height, body weight, waist circumference, and blood pressure were measured in each child. Fasting triglyceride and HDL-cholesterol levels were assessed. Glucose, insulin, and ghrelin levels were estimated fasting and during the (OGTT). Based on the obtained results, BMI SDS, waist-to-height ratio, and HOMA-IR were calculated.
Results
Ghrelin levels decreased significantly during OGTT [1859 (1356 – 3532) vs 1233 (953 – 1765), $P = 0.0000$]. In obese children (BMI SDS>2), fasting ghrelin levels were significantly lower than in nonobese children [1491 (1179 – 2917) vs 2197 (1539 – 3874), $P = 0.0021$], but decreased significantly more during the test [431 (163 -790) vs 693 (357 – 1798), $P = 0.0058$]. There was no difference in fasting ghrelin levels and ghrelin decrease during OGTT between groups with respect to the presence of visceral obesity, high triglyceride levels, low HDL cholesterol levels or tendency to high blood pressure. We found weak, negative correlations between fasting ghrelin levels and: BMISDS ($r = -0.25$), HOMA-IR ($r = -0.2$), insulin levels at 0' ($r = -0.21$) and 120' ($r = -0.24$) of the OGTT; as well as between ghrelin levels at 120' and insulin at 120' ($r = -0.2$).
Conclusion
Ghrelin levels in SGA children aged 5 to 9 years decreased significantly during OGTT, and this decrease was more profound in obese children. Further studies are needed to determine the impact of this finding on the improvement in growth rate and the development of metabolic disorders in SGA children.

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P683

JOINT2844

Cord blood exosomal miRNAS from small-for-gestational-age newborns associate with measures of subsequent catch-up growth and insulin resistance

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Introduction
Infants born small-for-gestational age [SGA, birth weight (BW) ≤-2 SD for gestational age (GA)] who experience marked catch-up growth are at risk for subsequent insulin resistance and body adiposity. The mechanisms underlying these associations are not fully delineated. Exosomes are extracellular vesicles mediating intercellular communication, and their cargo (including DNAs, RNAs and proteins) may contribute to altered crosstalk among tissues. We tested in SGA infants whether the profile of exosomal miRNAs at birth differs from that in AGA infants and, if so, whether differentially expressed miRNAs in SGA newborns associate with measures of catch-up growth and insulin resistance up to the postnatal ages of 4 and 12 months.
Subjects and Methods
miRNAs profile in cord blood-derived exosomes was assessed by high-throughput small-RNA sequencing in 10 SGA and 10 appropriate-for-gestational-age (AGA, birth weight between -1 SD and + 1 SD for GA) infants. Differentially expressed miRNAs with a $\log_2$ fold change ≥2. 4 or ≤-2. 4 were validated by RT-qPCR in 40 AGA and 35 SGA infants and correlated with anthropometric, body composition (by DXA) and endocrine-metabolic [glucose, insulin, HOMA-IR] parameters at the postnatal ages of 4 and 12 months. Target genes prediction for all differentially regulated miRNAs was obtained with the miRSystem and enrichment analysis was performed using DAVID software.
Results
Six exosomal miRNAs were found to be differentially expressed in SGA infants who subsequently developed spontaneous catch-up growth; miR-1-3p, miR-133a-3p and miR-206 were down-regulated (all P <0. 0001 vs AGA) whereas miR-372-3p, miR-519d-3p and miR-1299 were up-regulated (P between 0. 03 and <0. 0001 vs AGA). The target genes of these miRNAs relate to insulin, RAP1, TGF-

beta and neurotrophin signaling. Receiver operating characteristic (ROC) analysis disclosed that these miRNAs could distinguish SGA from AGA infants (0. 65< AUC<0. 99; P between 0. 03 and <0. 0001). The expression levels of these miRNAs associated with BMI and HOMA-IR at 4 and 12 months of age (P between 0. 01 and <0. 001). Up-regulated miRNAs in SGA newborns associated also with gains of total and abdominal fat during infancy (all P between 0. 05 and 0. 009).

Conclusion

The exosomal miRNA profile of SGA infants at birth was found to differ from that of AGA infants, and to associate with measures of catch-up growth, insulin resistance, and body adiposity into late infancy. Further follow-up will disclose to which extent these associations persist into childhood, puberty and adolescence.

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P684

JOINT256

Comparative analysis of GLP-1 receptor agonists, traditional glucose-lowering medications and traditional anti-obesity medications on skeletal outcomes in obese individuals with and without type 2 diabetes: a five-year propensity-score matched cohort study

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Background

The impact of newer anti-obesity medications on skeletal health remains incompletely understood, particularly in populations with varying metabolic profiles.

Methods

We conducted a five-year cohort study examining skeletal health outcomes in two distinct populations: obese individuals with type 2 diabetes (T2D) receiving semaglutide vs conventional glucose-lowering medications (sitagliptin, empagliflozin, glipizide), and obese individuals without T2D receiving semaglutide vs traditional anti-obesity medications (Contrave, phentermine, Qsymia). Primary outcomes included osteoporosis, osteoarthritis, gout, and bone density disorders. Risk assessment was performed using crude and multivariable-adjusted Cox proportional hazards models, with results presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Kaplan-Meier curves were constructed to visualize cumulative incidence, with statistical significance assessed via log-rank tests. To address multiple testing concerns across nine skeletal outcomes, we applied Bonferroni correction, setting the adjusted significance threshold (padj). E-values were calculated for significant associations to assess unmeasured confounding.

Results

In obese individuals with T2D, semaglutide demonstrated a protective effect against osteoporosis (HR 0. 61, 95% CI 0. 38-0. 97) and gout (HR 0. 63, 95% CI 0. 44-0. 90) compared to sitagliptin. The relationship was particularly robust for gout outcomes (E-value 2. 51). No significant differences were observed in knee osteoarthritis (HR 1. 05, 95% CI 0. 84-1. 30) or hip osteoarthritis (HR 0. 88, 95% CI 0. 65-1. 18) between treatment groups. Multiple sensitivity analyses yielded consistent Results

Conclusion

Our findings suggest differential effects of semaglutide on various skeletal health outcomes, with notable protective effects against osteoporosis and gout in obese patients with T2D. These results provide important insights for clinical decision-making in metabolic health management, particularly regarding bone health considerations in anti-obesity medication selection.

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P685

JOINT457

Sex differences in white adipose tissue adaptation and insulin sensitivity in a diet-induced obesity mouse model

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Background

Diet-induced obesity is an escalating health issue. Women have a higher prevalence of obesity than men, yet reproductive-age women have a lower incidence of metabolic diseases, including type 2 diabetes. This sex difference attenuates after menopause, suggesting protective roles of female sex hormones. However, the mechanisms by which sex hormones and high-fat, high-sucrose diet (HFD) influence white adipose tissue (WAT) adaptation, including adipokine secretion, remain to be explored.

Methods

Fifty-six C57BL/6NJcl mice [28 males (M) and 28 females (F)] were studied, with 14 per sex undergoing gonadectomy (G) and the rest receiving a sham operation (S) at 8 weeks old. After a one-week recovery, 7 mice from each group were switched to HFD for 12 weeks, while others remained on a standard chow diet (CD), resulting in 8 groups: MSC, MGC, FSC, FGC, MSH, MGH, FSH, and FGH. An intraperitoneal glucose tolerance test (IPGTT) was performed at 21 weeks old. At 22 weeks old, WAT was collected and underwent *ex vivo* insulin stimulation to assess Akt phosphorylation by Western blotting.

Results

HFD increased body weight (BW) in all groups ($P < 0.01$). Despite similar dietary calorie intake in HFD-fed groups, FSH had the least BW gain ($P < 0.01$). Fasting glucose levels were higher in males than females and were increased by HFD and gonadectomy (all $P < 0.01$). Fasting insulin levels, as well as the HOMA-IR, were significantly elevated by HFD feeding in most groups ($P < 0.01$), except sham-operated females (FSC vs. FSH, $p > 0.90$). IPGTT confirmed that HFD induced glucose intolerance ($P < 0.01$), though FSH showed better glucose tolerance than other HFD-fed groups. WAT weight increased with HFD ($P < 0.01$), being higher in males and gonadectomized mice (both $P < 0.01$). Serum leptin levels mirrored WAT mass, increasing with HFD ($P < 0.01$), being higher in males ($P = 0.02$), and elevated by gonadectomy ($P < 0.01$). Serum adiponectin levels showed a sex-specific pattern, increasing with HFD only in gonad-intact females (FSH > FSC, $P = 0.02$; FSH > MSH, $P = 0.02$), resulting in the highest adiponectin/leptin ratio among HFD-fed groups. Insulin-stimulated Akt phosphorylation in WAT explants was reduced in HFD-fed groups ($P < 0.01$), with a greater reduction in males ($P < 0.01$) than females ($P = 0.09$).

Conclusion

HFD impairs glucose homeostasis and insulin signaling in a sex-dependent manner. Gonad-intact females exhibit better metabolic adaptation under HFD, reflected by lower BW gain, better glucose tolerance, a higher adiponectin/leptin ratio, and a smaller reduction in Akt phosphorylation in WAT. These findings highlight the protective role of female gonadal hormones in metabolic adaptation to diet-induced obesity.

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P686

JOINT2833

Characteristics of postmenopausal women with PCOS

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Background

Polycystic ovary syndrome (PCOS) is not limited to younger ages but persists during menopause. However, only little is known about this important lifetime for PCOS women – especially in view of a number of risk factors for metabolic and cardiovascular disease manifestations. We aimed to characterize postmenopausal women by both actual hormonal/metabolic data and medical history questionnaires in the "BioPersMed cohort" (Biomarkers in Personalized Medicine) conducted at the University Hospital of Graz to evaluate the prevalence and specificities of PCOS after the menopause.

Methods

The BioPersMed cohort has $n = 1022$ participants over 45 years of age, is a longitudinal phenotyping study with regular visits, including large endocrine, metabolic and cardiovascular/functional diagnostic panels as well as oral glucose tolerance tests with concomitant insulin and C-peptide measurements (OGTT). PCOS questionnaires included all Rotterdam criteria, e. g. menstrual regularity before menopause, known PCO morphology, but also unfulfilled child wish and other data. PCOS women were BMI-matched to non-PCOS participants to investigate further interdependencies.

Results
Out of the BioPersMed participants, $n = 305$ women met the inclusion criteria, with a typical PCOS profile in $n = 51$ women (16. 7%), according to published prevalences. Only one of them was ever diagnosed with "PCOS" in the past. BMI was significantly higher in PCOS women; they had a higher prevalence for diabetes mellitus type 2 (T2DM). BMI-matched non-PCOS controls showed significantly lower androgens, but similar SHBG and parameters of glucose metabolism. Hypertension was more prevalent in PCOS-women and an unfulfilled child wish over time was significantly higher in PCOS women with 22. 2% vs. 2. 8%, $P = 0. 024$. Further analyses are on the way.
Conclusion
PCOS in the menopause is an important cardiovascular and metabolic risk factor in up to 20% of all women. While a retrospective diagnosis of certain features of PCOS might be questionable, postmenopausal women with PCOS could largely benefit from having an individual diagnosis and guidance. The medical community should increase their awareness for these women, as biomarker and functional data are increasingly available - especially in this large group of women, who rarely had the chance of a PCOS diagnosis at an earlier age with adequate therapy options, respectively.

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P687

JOINT686

Evolution and determinants of metabolic phenotypes from childhood into adulthood: data from the QUALITY cohort

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Introduction
The metabolic consequences of obesity in adulthood are well-documented. While some children living with obesity maintain a healthy metabolic profile, others develop complications persisting into adulthood. Conversely, healthy-weight children can also exhibit an unhealthy phenotype.
Objectives
To describe metabolic phenotype evolutions from childhood to early adulthood and identify modifiable childhood determinants of unhealthy evolutions.
Methods
The QUALITY cohort included 630 children aged 8–10 years at baseline(V1), all with at least one parent living with obesity. Participants were reassessed at 10–12 years(V2), 15–17 years(V3), and 24–26 years (V4). Biological markers, physical activity, body composition, and screen time were assessed at each visit. Metabolic phenotypes were categorized into four groups: normal-weight metabolically healthy (NWMH), normal-weight metabolically unhealthy (NWMU), metabolically healthy living with obesity (MHO), and metabolically unhealthy living with obesity (MUO), based on IDF criteria. Descriptive analyses and Markov modeling assessed phenotype evolution and transition probabilities at each visit. Multiple logistic regressions among metabolically healthy participants at V1 estimated associations between transition to metabolically unhealthy phenotypes at V4 and childhood determinants. Inverse Probability Weighting was applied to adjust for missing data.
Results
A total of 169 participants with phenotype data at all four visits were analyzed. The prevalence of unhealthy phenotypes (NWMU + MUO) increased from 31% at V1 to 57% at V4, with a 20% rise occurring between V2 and V3. MUO prevalence steadily increased, from 12% at V1 to 35% at V4. Markov modeling showed that NWMH and MUO were the most stable phenotypes, with a high probability (67% and 69%, respectively) of remaining stable to the next visit. Among metabolically healthy children at V1, regardless of baseline weight status, boys (OR = 3. 63, 95%CI:2. 0-6. 7) and those with a higher % body fat at V1 (OR = 1. 05, 95%CI:1. 02-1. 08) had higher odds of transitioning to an unhealthy phenotype at V4. Additionally, when examining changes in lifestyle habits from V1 to V2, every 10-minute increase in moderate-to-vigorous physical activity between V1 and V2 was associated with 29% (95%CI: 15-42%) lower odds of transitioning to an unhealthy phenotype at V4, after adjusting for baseline physical activity.
Conclusion
The proportion of unhealthy phenotypes nearly doubled over 16 years in this high-risk population, with puberty being a critical period for transition to an unhealthy phenotype. Early interventions, especially for boys, with an emphasis on reducing adiposity early in childhood and promoting sustained physical activity appear important to preventing the progression towards unhealthy phenotypes.

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P688

JOINT135

Clinical, genetic characteristics and long-term follow-up of sitosterolemia in children

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Background
Sitosterolemia is a rare lipid disorder characterized by the elevated of phytosterols and LDL cholesterol, caused by mutations in the ABCG5 and/or ABCG8 genes. To get a better understanding of the disease, we summarized the clinical manifestations, laboratory examination, gene mutations and treatment effect of 12 sitosterolemia children.
Methods
The clinical features, laboratory characteristics and gene mutations of 12 children with sitosterolemia were analysed, followed up for the longest period of more than 8 years.
Results
12 patients with sitosterolemia were diagnosed in our center. These patients were aged from 4 months to 8. 3 years at diagnosis. the median age was 1. 2 years old. All patients did gene testing. 10 patients found mutations in the ABCG5 gene, 1 patients had mutation in ABCG8, and no variations was found in 1 patient. Serum Sitosterol were completed in 9 patients, and all support the diagnosis of sitosterolemia. 9 patients were managed with low cholesterol and phytosterol di*et al*one. 3 patient treated with ezetimibe or/and cholestyramine. Long term follow-up showed a decrease in total cholesterol (TC) and low density-lipoprotein cholesterol (LDL-C) in all patients, 3 patients with xanthoma disappearing in 1-2 years treatment and the remaining 4 patients showing significant decrease.
Conclusions
Xanthoma is landmark present of sitosteronism children, most our patients have mutations in the ABCG5 gene. Genetic and plant sterol profiles are of great significance for sitosteronism diagnosis. Most patients can achieve good results through dietary control. Ezetimibe and cholestyramine are effective for sitosteronism children and with relative safety.

Keywords Sitosterolemia; Xanthoma; Hypercholesterolemia; *ABCG5*; *ABCG8*
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P690

JOINT553

CASP3-mediated PARP1 cleavage promotes hepatocyte apoptosis in non-alcoholic fatty liver disease

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Introduction
Non-alcoholic fatty liver disease (NAFLD) is characterized by excessive hepatic triglyceride (TG) accumulation and is commonly associated with obesity and metabolic syndrome. Due to the lack of effective pharmaceutical treatments, lifestyle interventions, such as dietary control and exercise, remain fundamental for NAFLD management. Studies have shown that obesity-related NAFLD is closely linked to mitochondrial stress and hepatocyte apoptosis, with excessive hepatocyte apoptosis being a critical factor in the progression to non-alcoholic steatohepatitis (NASH). Therefore, identifying targets and drugs that inhibit hepatocyte apoptosis may help alleviate obesity and slow the progression from

NAFL to NASH. Poly(ADP-ribose) polymerase 1 (PARP1) is a key regulator of cellular stress responses involved in various physiological and pathological processes. As a substrate of the caspase-3-dependent apoptotic pathway, its cleavage product cl-PARP1 (89 kDa) plays a significant role in apoptosis. However, the role of this mechanism in NAFLD remains poorly understood.
Methods
In this study, db/db mice were used as an animal model, and FFA-induced HepG2 cells were used for *In vitro* experiments. Western blot (WB), quantitative PCR (qPCR), immunohistochemistry (IHC), immunofluorescence, apoptosis staining, and plasmid transfection techniques were employed to investigate the role of the CASP3-PARP1 apoptotic pathway in NAFLD pathogenesis.
Results
In the db/db mouse model of fatty liver and FFA-induced HepG2 cells, CASP3 was activated, leading to increased cl-PARP1 (89 kDa), elevated Bax expression, and decreased Bcl2 expression. Additionally, enhanced TRITC-dUTP red fluorescence signals indicated aggravated hepatocyte apoptosis. In HepG2 cells, overexpression of CASP3 plasmid resulted in significantly increased cl-PARP1 (89 kDa), further confirming CASP3's role in PARP1 cleavage.
Conclusion
This study demonstrates that CASP3 is activated in fatty liver, promoting hepatocyte apoptosis through the cleavage of PARP1 to generate cl-PARP1 (89 kDa). Pharmacological inhibition of CASP3 and PARP1 may slow down hepatocyte apoptosis, representing a promising therapeutic strategy for NAFLD. Further investigation into the CASP3-PARP1 pathway could provide new drug targets and therapeutic approaches for NAFLD.
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P691

JOINT3798

Semaglutide as a promising treatment for hypothalamic obesity: a twelve-month case series on four females with craniopharyngioma

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Purpose
Patients with hypothalamic pathology often develop hypothalamic obesity, causing severe metabolic alterations resulting in increased morbidity and mortality. Treatments for hypothalamic obesity have not proven very effective, although the glucagon-like peptide-1 receptor agonist semaglutide has been shown to have positive effects. We examined semaglutide's effect on weight loss in a sample of patients with hypothalamic obesity.
Methods
Four female patients with hypothalamic obesity resulting from treatment of craniopharyngiomas were treated with semaglutide for twelve months. Whole Body Dual-energy x-ray absorptiometry scans were performed, and blood samples drawn at baseline, after six and twelve months. Semaglutide dosages were increased monthly along with tracking of body weight and eating behavior (Three Factor Eating Questionnaire, TFEQ-R18). Semi-structured interviews were conducted with the four patients to explore their quality-of-life following weight loss.
Results
BMI was reduced in all cases, with an average of 9. 8 kg/m^2 (range: 5. 8-13. 6 g/m^2) corresponding to a weight loss of 20. 9% (range: 10. 5-26. 2%) or 25. 7 kg (range: 15. 5-42. 0 kg). We found a comparable reduction in total fat mass (20. 8%, $P = 0.02$) and lean mass (17. 8%, $P = 0.04$). The patients all experienced an improved quality-of-life, including greater ease in physical activity, reduced pain and finding it easier to purchase clothing in their size. Unfavorable eating eating behaviors were reduced after 1 month of treatment (emotional eating –41 points, $P = 0.02$, uncontrolled eatin –23 points, $P = 0.11$). HbA1c and total cholesterol were significantly reduced ($P = 0.014$ for both), with stable values from 6 months on.
Conclusion
Semaglutide is a promising and safe treatment option for hypothalamic obesity, that improves eating behavior, reduces weight and improves metabolic markers.
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P692

JOINT3892

Long term effect of setmelanotide and semaglutide on a patient with severe obesity due to 16p11. 2 microdeletion, encompassing the SH2B1 gene

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SH2B Adaptor Protein 1 (SH2B1) is an important component in the leptin-melanocortin pathway. Microdeletions in chromosome 16p11. 2, encompassing the SH2B1 gene, as well as pathogenic SH2B1 variants, are found to be associated with severe, early-onset obesity, hyperphagia, developmental delay, and insulin resistance. One year of treatment with setmelanotide (IMCIVREE™, Rhythm Pharmaceuticals), a melanocortin-4 (MC4) receptor agonist, was associated with clinically meaningful reductions in weight-related parameters in patients with heterozygous SH2B1 variants or 16p11. 2 deletion in a previous study. We present the effect of setmelanotide treatment over 4 years in an adolescent patient with severe, early-onset obesity due to a heterozygous 16p11. 2 deletion, encompassing the SH2B1 gene. The patient (female, 12 years old) presented with hyperphagia and severe obesity due to 16p11. 2 microdeletion (BMI Z score 2. 51). She had a mild developmental delay, concentration and learning deficits and displayed aggressive behavior. At the age of 9 years, treatment with metformin was initiated due to prediabetes, which progressed to T2DM at the age of 12 years. Further screening for comorbidities revealed arterial hypertension, microalbuminuria, obstructive sleep apnea syndrome, dyslipidemia, and steatotic liver disease. Treatment with setmelanotide, in the context of participation in the trial (NCT03013543, NCT03651765), was started at the age of 12 $^{7/12}$ years. During setmelanotide treatment, BMI Z score change was -0. 19 and -0. 26 at months 3 and 12 compared to baseline, respectively. During this period, HbA1c levels decreased to normal and hunger was well controlled. After month 12, BMI levels increased gradually (max. BMI Z score change: 0. 5 at month 39 from baseline), which may be attributed in part to lack of physical activity and motivation. Likewise, HbA1c levels increased up to 7. 0% and glp-1 analogues (at first liraglutide, then semaglutide) were added. Combined treatment resulted in stabilization of BMI and improvement of glycemic control. When setmelanotide administration was stopped after 4 years according to study protocol, the patient experienced sudden excessive weight gain and pronounced hyperphagia. Reintroduction of setmelanotide resulted in weight loss and good hunger control. Central body weight regulation in young patients with monogenic obesity remains challenging. Combined administration of setmelanotide and semaglutide resulted in BMI, hunger and glucose control in an adolescent patient with severe obesity and type 2 diabetes mellitus, due to a 16p11. 2 microdeletion, encompassing the SH2B1 gene. An individualized therapeutic approach, including different pharmacological regiments in combination with lifestyle intervention and psychological support, should be considered in patients with monogenic obesity.
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P693

JOINT2439

A case report of nevus excision under setmelanotide treatment

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Introduction
Pro-opiomelanocortin (POMC) deficiency is a rare cause of monogenic obesity characterized by early-onset hyperphagia and severe obesity. Setmelanotide, a melanocortin-4 receptor (MC4R) agonist, is the only approved treatment for this condition. Known side effects include skin hyperpigmentation and the development of hyperpigmented nevi, due to MC1R off-target activation, raising concerns about potential skin cancer risk. Despite these known effects, no previous cases have documented the histological impact of Setmelanotide on the skin. We present the case of a pediatric patient treated with Setmelanotide who underwent surgical excision of a hyperpigmented nevus, with histological findings providing novel insights into the drug's dermatological effects. Additionally, we report the patient's weight-related outcomes during the first six months of treatment.

Methods
An 8-year-old patient with genetically confirmed POMC deficiency was treated with Setmelanotide starting from 0. 5 and up to 1 mg/d. During Setmelanotide treatment a multidisciplinary follow-up was conducted according to the Italian Medicines Agency (AIFA) monitoring register. Furthermore, weight, body mass index (BMI), and metabolic parameters were monitored over six months of therapy.
Results
During dermatological follow-up, skin hyperpigmentation and an atypical hyperpigmented nevus on the lower leg was observed (maximum diameter 0. 9 cm). The nevus was surgically excised and sent to histological analysis. Histological examination revealed a compound melanocytic nevus with junctional and dermal melanocytic proliferation, without evidence of malignant transformation. Immunohistochemistry showed MART1 and HMB45 positivity both in junctional and dermal components, weak focal p16 positivity, and preserved PRKAR1A expression. During Setmelanotide treatment the patient exhibited reduced appetite and improved hyperphagia, and BMI decreased from $+4.$ 2 SD (32. 6 Kg/m^2) to $+3.$ 8 SD (31. 3 Kg/m^2) in six months. Skin hyperpigmentation remained stable without further complications.
Discussion
This is the first reported case to document histological effects of Setmelanotide on the skin, broadening the understanding of its dermatological safety profile. Our findings support the safety and efficacy of Setmelanotide in managing patients affected by POMC deficiency and highlight the importance of regular dermatological monitoring in those receiving this treatment, particularly in the presence of hyperpigmented lesions, to exclude rare adverse events and ensure optimal management of the therapy. Further studies are warranted to assess long-term dermatological outcomes and the potential implications of off-target MC1R activation.

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P694

JOINT1186
Early life determinants of body composition in healthy term-born children at age 5 years

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Background
Childhood overweight and obesity are global public health threats, with several comorbidities and adverse health outcomes. As childhood overweight and obesity are likely to track into adulthood, there is a need to understand how body composition evolves from infancy to childhood and which early life determinants influence adiposity programming. Hence, the aim of this study was to investigate how body composition tracks from infancy to childhood and to identify which perinatal, infancy, childhood and nutritional factors are associated with different body composition trajectories.
Methods
We included 346 healthy term-born children of the Sophia Pluto study, a birth cohort study in The Netherlands. Body composition was measured at 1, 3 and 6 months by air displacement plethysmography (PEA POD) and at 5 years by Dual-energy X-ray Absorptiometry (DXA). Age- and sex-adjusted Standard Deviation Scores (SDS) were calculated for Fat Mass Index (FMI) and Fat Free Mass Index (FFMI). For both variables, group tertiles were determined with the categories " high", "moderate" and "low". Odds ratios (OR) were calculated using logistic regression models.
Results
At age 5 years, 4. 6% of children had overweight or obesity based on the WHO criteria. Children in the highest FMI SDS tertile at 5 years had a median FMI SDS of 1. 06 (interquartile range [0. 69;1. 51]). A high FMI SDS tracked from age 1, 3 and 6 months to 5 years ($Or = 1.$ 67 [$P = 0.$ 036], $Or = 2.$ 55 [$p < 0.$ 001] and $Or = 3.$ 29 [$p < 0.$ 001], respectively). High FFMI SDS also tracked from age 1, 3 and 6 months to 5 years ($Or = 2.$ 36 [$p < 0.$ 001], $Or = 2.$ 20 [$P = 0.$ 001] and $Or = 2.$ 45 [$p < 0.$ 001], respectively). Association analyses of perinatal, infancy, childhood and nutritional factors with body composition trajectories will be presented at the congress.
Conclusions
Infants with a high FMI or FFMI SDS in the first 6 months of life are likely to remain in the highest tertile up to age 5 years. These data further support the presence of a critical window of adiposity and FFM programming in early infancy.

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P695

JOINT2097
Transient infantile hypertriglyceridemia: the first case from the state of qatar

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Introduction
Transient Infantile Hypertriglyceridemia (HTGTI) is a rare autosomal recessive disorder caused by **GPD1** mutations. It is, characterized by transient hypertriglyceridemia, hepatomegaly, elevated liver enzymes, and hepatic steatosis. Its pathophysiology and long-term metabolic consequences remain poorly understood, with only 31 genetically confirmed cases reported worldwide.
Case Presentation
The patient was born at term and delivered by cesarean section due to abruptio placenta. He presented at the age of 5 months with acute vomiting following a flu-like illness. Laboratory tests revealed elevated liver enzymes, prompting further investigation despite symptom resolution. Follow-up biochemical tests consistently showed hypertriglyceridemia and elevated liver enzymes. Abdominal ultrasound initially revealed hepatosplenomegaly with abnormal liver echotexture. A follow-up ultrasound demonstrated hepatomegaly with increased parenchymal echogenicity, suggestive of parenchymal disease with fatty changes. Genetic testing (WES) identified a homozygous likely pathogenic **GPD1** variant, confirming autosomal recessive HTGTI with both parents being carriers. In the family history a 6-year-old cousin had presented at 4 months with vomiting and bronchiolitis. During hospitalization, abnormal liver function tests and hepatomegaly were noted, though jaundice was absent. Investigation showed dyslipidemia and transaminitis. Initial genetic testing was inconclusive. However, a liver biopsy showed marked steatosis and fibrosis, including porto-portal bridging. whole exome sequencing identified a **GPD1** variant of uncertain significance (VUS), later reclassified as pathogenic. The biopsy showed no features of glycogen storage or metabolic disease, emphasizing the need for genetic, biochemical, and clinical correlation.
Management and Follow-Up
Management included a low-fat diet restricting long-chain triglycerides with medium-chain fatty acid supplementation. Regular monitoring of growth, development, and triglyceride levels was essential. Genetic counseling was provided to discuss the 25% recurrence risk in future pregnancies.
Conclusion
This is the first case report of HTGTI from the state of Qatar. The mechanism/s of the transient hypertriglyceridemia remains unclear and the long-term implications are also unknown. The power of WES helped with the genetic diagnosis and in terms of dietary management. Further research is needed to define its long-term metabolic consequences and optimize treatment strategies.

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P696

JOINT888
Real-world outcomes of liraglutide treatment in children with obesity: beyond weight loss

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Background
Liraglutide is a glucagon-like peptide-1 receptor agonist used for pharmacological treatment of children with obesity.
Objective
To evaluate the effects of liraglutide treatment on anthropometric measures, body composition, and metabolic parameters in children with obesity.
Methods
This cohort study analyzed real-world clinical data from children with obesity in Slovenia who were treated with liraglutide between June 2022 and December 2024. The primary outcome measures included changes in anthropometric measurements, body composition, and metabolic parameters over six months.
Results
31 patients (13 males) had completed six months of liraglutide treatment. The average age at treatment initiation was 15. 56 $\pm$ 1. 59 years. The main outcome measures are presented in Table 1. The average loss of body mass was -5. 34 $\pm$ 6. 41% (-5. 66 $\pm$ 7. 28 kg) and the average reduction of BMI was 6. 10 $\pm$ 5. 64%. Children were assigned to 4 categories according to the percentage of body mass

Table 1: Anthropometric measurements, body composition and metabolic values before and after 6 months of treatment with liraglutide

	Month 0 Average ± SD	Month 6 Average ± SD	p value
Body mass	115. 09 ± 23. 65 kg	109. 43 ± 26. 26 kg	0. 38
Body mass SDS	+3. 97	+3. 57	0. 11
BMI	39. 46 ± 5. 84 kg/m^2	37. 15 ± 6. 55 kg/m^2	0. 15
BMI SDS	+3. 50	+3. 22	0. 05
Waist-to-height ratio	0. 73 ± 0. 09 (n = 18)	0. 69 ± 0. 07 (n = 21)	0. 09
Bioimpedance – body fat	46. 41 ± 5. 42% (n = 22)	42. 48 ± 5. 66% (n = 17)	0. 04
Bioimpedance – skeletal muscle mass	33. 56 ± 6. 99 kg (n = 22)	34. 45 ± 8. 46 (n = 17)	0. 72
Densitometry – body fat	47. 61 ± 4. 44% (n = 15)	43. 98 ± 5. 30% (n = 21)	0. 03
Densitometry – lean muscle mass	57. 26 ± 13. 26 kg (n = 15)	59. 61 ± 12. 66 (n = 21)	0. 60
HOMA-IR	5. 35 ± 2. 95 (n = 25)	3. 76 ± 2. 50 (n = 27)	0. 13
TyG index	4. 48 ± 0. 21 (n = 24)	4. 40 ± 0. 23 (n = 28)	0. 19

reduction: 8 patients lost less than 5%, 7 patients lost 5-10%, 8 patients lost above 10% and 8 patients showed no reduction in body mass after 6 months of treatment.

Conclusions

Liraglutide treatment led to a significant reduction in body fat percentage while preserving skeletal muscle mass. However, metabolic parameters did not show significant improvement after six months.

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P697

JOINT1392

Prevalence of obstructive sleep apnea syndrome in patients with lipodystrophy: a retrospective analysis

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Objective

Lipodystrophies (LD) are a heterogeneous and rare group of disorders characterised by a general or partial loss of subcutaneous adipose tissue with a contrasting ectopic accumulation. Obstructive Sleep Apnea Syndrome (OSAS), characterized by upper airway collapse, is primarily associated with obesity as its most prevalent risk factor. Specifically, increased fat deposition in the neck contributes significantly to the pathogenesis of OSAS. Despite the well-established link between fat distribution and OSAS, data on the prevalence of OSAS in patients with LD remain scarce. This study aims to address this gap by systematically assessing the prevalence of OSAS in LD patients and investigating its associated clinical and metabolic determinants.

Materials and Methods

This single-center, retrospective, descriptive study included 163 LD patients who were followed up at the Ege University Endocrinology outpatient clinic. Inclusion criteria encompassed being genetically confirmed, aged 18 years or older, non-pregnant, HIV-negative, and free from uncontrolled asthma, chronic obstructive pulmonary disease, or New York Heart Association class III-IV heart failure. Patients with a history of head and neck radiotherapy were excluded. Among the screened cohort, 28 LD patients who had undergone polysomnography were included in the study. Retrospective data on anthropometric measurements, fat distribution abnormalities, cervical skinfold thickness, biochemical parameters, and polysomnography findings were extracted from electronic medical records.

Results

Among patients included in the study, 28. 6% (n = 8) were diagnosed with generalized LD, and 71. 4% (n = 20) with partial LD. The mean age of the patients was 42±13 years. Male patients accounted for 21. 4% (n = 6), while females constituted 78. 6% (n = 22). The mean score of the Epworth Sleepiness Scale was 9. 2±6. 0 (range: 1–22). OSAS (AHI>15) was diagnosed in 11 patients (55%) with partial LD, whereas no cases were identified among those with generalized LD.

Discussion

This study provides novel insights into the prevalence of OSAS in patients with LD, highlighting a substantial difference between generalized and partial LD phenotypes. While OSAS is classically linked to obesity, our results suggest that abnormal fat distribution in LD may be an independent risk factor.

Conclusion

We demonstrated the high frequency of OSAS in patients with partial LD. Our findings underscore the necessity of OSAS screening in partial LD patients, particularly those with severe metabolic complications, given its association with cardiometabolic diseases, cognitive dysfunction, and increased mortality risk. The significant prevalence of OSAS in partial LD highlights the need for a paradigm shift in screening strategies.

Keywords Lipodystrophy, obstructive sleep apnea syndrome, polysomnography

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P699

JOINT2805

The effect of GLP-1 administration on food intake in people with weight regain post-metabolic surgery

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Background

Metabolic surgery remains the most effective option for sustainable weight loss. Sleeve gastrectomy is one of the commonly performed procedures. However, the percentage of people who fail to lose weight after surgery or regain weight ranges between 20–30%. Depending on the definition, category and surgery type, this percentage can vary between 3. 9 to 71%. The mechanisms behind the divergent responses to metabolic surgery are not fully understood. We hypothesised that people who regain weight after initial successful weight loss with sleeve gastrectomy might exhibit a resistance to the anorectic effects of GLP-1, the post-prandial secretion of which is known to be markedly stimulated by metabolic surgery.

Subjects and Methods

Ten patients who lost more than 20% of their pre-operative weight and sustained it after Sleeve Gastrectomy ("good responders") and nine patients who lost more than 20% of their pre-operative weight at nadir but then regained weight ("regainers"), were enrolled in a single blinded study. The participants received two subcutaneous infusions at random order, one placebo infusion and one GLP-1(7-36) •NH_2 infusion for 4. 5 hours. An ad libitum meal study was performed 4 hours after the initiation of each infusion. Participants were asked to eat a large portion of a standardised meal until they were comfortably full. Food intake was the primary outcome.

Results

Both the good responders and regainers significantly reduced their food intake during the GLP-1 infusion compared to placebo (P = 0. 038 and P = 0. 047 respectively).

Conclusions

People who regain weight after initial successful weight loss after Sleeve Gastrectomy retain sensitivity to GLP-1 treatment similarly to the people who have achieved successful and sustainable weight loss. This finding suggests that adjunctive treatment with GLP-1 analogues may play a role in managing weight regain after metabolic surgery.

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P700

JOINT657

Development of a gas chromatography mass spectrometry method for urinary oestrogen profiling in pre- and postmenopausal women

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Oestrogen analysis presents a significant challenge due to the low concentrations of these hormones, particularly oestradiol, the most potent oestrogen. Oestrogens

plays important roles in fertility, bone health, and various endocrine disorders. Traditional methods for measuring oestrogens, such as immunoassays, are unreliable at low concentrations and prone to high cross-reactivity, leading to inaccurate results and potential misdiagnoses. Mass spectrometry (MS) is as a more selective and sensitive alternative for oestrogen analysis. Unlike immunoassays, MS offers reduced cross-reactivity, enhancing the reliability of hormone measurements. However, quantifying oestrogens remains challenging due to their low concentrations and poor ionization, even when using highly sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) techniques. These methods often require large sample volumes, particularly when measuring in populations such as post-menopausal women, men, and children. Gas chromatography-mass spectrometry (GC-MS) is a viable alternative employing post extraction derivatisation which improves ionizability allowing quantitation of poorly ionising, low concentration oestrogens. Additionally, use of urine permits sample concentration without unacceptable matrix effects associated with serum. Therefore, we developed a GC-MS method for urinary oestrogen profiling for the detection of eleven oestrogens, including oestradiol, oestrone, and their hydroxy and methoxy derivatives. Twenty-four-hour urine samples were collected from 51 healthy females (26 pre-menopausal (age 20-49) and 25 post-menopausal (age 50-76). Steroids were extracted from 2mL of 24-hour urine, deconjugated and derivatised into methyloxime-trimethylsilyl ethers. The oestrogens were measured on a Shimadzu GC-MS-QP2020NX relative to an internal standard and a calibration series to ensure accuracy. Our GC-MS method quantified oestrogens in both pre- and postmenopausal women. The highest concentration oestrogens were oestradiol, median (5^{th}-95^{th} percentile) in all (6, 2-34) pre-menopausal (14, 2-34), post-menopausal (4, 1-18), oestriol all, (3, 0. 5-20), pre (6, 1-21) post (2, 0. 7-6), oestrone all (3, 0. 5-30), pre (5 (1-33), post (1, 0. 2-20) and 2-methoxy-oestrone all (8, 3-20) pre (7, 3-20) post (8, 3-17)μg/24hr. All other oestrogens were detectable at median concentrations ranging from 0. 2-1. 7μg/24hr. There were significant differences (Mann-Whitney-U $P < 0.05$) in excretion of oestrone, oestradiol, and 2-hydroxyoestrone, when comparing pre and post-menopausal women. There were positive correlations between excretion of oestrone, oestriol and progesterone metabolites whereas excretion of oestradiol correlated with androgen metabolites. GC-MS urinary oestrogen profiling is essential for detecting low oestrogen concentrations, particularly in post-menopausal women and those undergoing treatments such as tamoxifen. Our method demonstrates the sensitivity needed for assessing treatment efficacy in challenging clinical applications.

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P701

JOINT3815

Cumulative effects of genetic variants detected in a patient with early-onset non-syndromic childhood obesity

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Background

The presence of monogenic mutations should be suspected in children with early onset non-syndromic obesity and hyperphagia. The SIM1 (Single-minded homolog 1) mutations are a well-known cause of monogenic obesity with an autosomal dominant inheritance. A variant of the SIM1 gene is associated with other obesity-related genetic mutations in a male patient with early-onset obesity.

Case Description

A 9-years-old boy, with a BMI of 30, 2 kg/m2 (2, 37 SDS), started to gain weight at 19 months of life, with progressive hyperphagia. He was born of full-term an uneventful pregnancy with an appropriate birth weight, to non-consanguineous parents. His mother presents severe obesity. He had no significant neonatal history. At the first evaluation, at the age of 3 years old, his height was 99 cm (+0, 69 SDS vs target height -1, 35 SDS), weight was 22 Kg (+3, 12 SDS) and BMI of 22, 3 Kg/m2 (+2, 23 SDS). Physical examination not revealed dysmorphic features. He presented a persistent polydipsia and water deprivation tests ruled out diabetes insipidus. Brain MRI was normal and additional endocrinological disease and hypothalamic disorders were excluded At the age of 6 years old, his height was 124, 7 cm (+0, 39 SDS), weight 42, 2 Kg (+2, 82 SDS) and BMI of 27, 4 Kg/m2 (+2, 27 SDS). Biochemical examinations documented an impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), associated with mild hepatic steatosis at ultrasound. In addition, he presents behavior disorder with a delay in speech development. CGH array documented a de novo 546Kb microduplication in 16p11.2 (OMIM #614671). Next Generation Sequency (panel based on 80 genes), performed at the age of 9, revealed mainly a novel and frameshift variant, c.290dup p.(Asp98Argfs*29), detected in heterozygosity in the SIM1 gene, inherited from the father. NGS showed other heterozygosity variants classified as VOUS according to ACGM: c.437C>T p.(Ala146Val) in CREBBP gene; c.3041T>A p.(Val1014Glu) in PLXNA4 gene; c.915A>C p.(Leu305Phe) in SEMA3C gene.

Conclusion

SIM1 gene is implicated in the development of the paraventricular nucleus (PVN) that contains the melanocortin 4 receptor (MC4R), a key component of appetite regulation. CREBBP is implicated in mechanisms of neuroplasticity. SEMA3A, with its reactors also encoded by the PLXNA4 gene, is implicated in the development of hypothalamic neuronal circuits. Although the role of the SIM1 gene mutation is decisive, we suggest that the cumulative effects of the other identified variants could interact in determining a phenotype of severe obesity through abnormalities in the development and function of hypothalamic circuits.

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P702

JOINT2058

Metabolomic mechanisms involved in the impact of liver injury on elevated coronary heart disease risk

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Background

Coronary heart disease (CHD) is a common ischemic heart disease, with over 11.39 million patients in China and a mortality rate of 126.91 per 100, 000. Liver injury is a significant risk factor for CHD, but the mechanisms by which it affects CHD risk remain unclear. Fibrosis-4 index (FIB-4) is a common biomarker for liver fibrosis and injury, with established links to cardiovascular diseases. This study investigates whether FIB-4 is an independent risk factor for CHD and explores the metabolomic mechanisms through which FIB-4 influences CHD risk.

Methods

This study recruited 1, 668 healthy participants from central China, with 304 participants undergoing targeted metabolomics analysis. T-tests and rank sum tests compared baseline differences between participants with and without CHD by the end of the follow-up. Proportional Cox regression evaluated the relationship between FIB-4 and CHD, with adjustments for confounders in three models: Model 1 (gender); Model 2 (further adjusted for body mass index (BMI), estimated glomerular filtration rate (eGFR), systolic blood pressure (SBP), diastolic blood pressure (DBP), high-density lipoprotein cholesterol (HDL-C), alkaline phosphatase (ALP), triglycerides (TG), glucose, hemoglobin A1C (HbA1c)); Model 3 (further adjusted for hypertension, hyperlipidemia, diabetes). Spearman correlation identified metabolites associated with liver injury, and FDR correction was applied. A logistic regression model was fitted to identify metabolites independently associated with CHD.

Results

At follow-up, 858 participants had developed CHD, while 810 did not. CHD patients had notably higher levels of SBP, DBP, TG and glucose ($p < 0.05$), as well as higher FIB-4 values ($p < 0.001$). After controlling for multiple confounders, proportional Cox regression (Model 3) demonstrated that increased FIB-4 was significantly associated with higher CHD risk, remaining robust after adjusting for covariates (HR 1.250; 95% CI, 1.136-1.375). We identified 108 metabolites associated with liver injury, and through a logistic regression model adjusted for multiple confounders, 15 metabolites were independently associated with CHD. Among these, Guanosine Monophosphate (GMP, OR 0.213; 95% CI, 0.061-0.716), Tryptophanamide (OR 0.885; 95% CI, 0.795-0.986), Lithocholic Acid Acetate (LAA, OR 0.788; 95% CI, 0.646-0.966), Methylmalonic Acid (MMA, OR 0.349; 95% CI, 0.126-0.932), and Glycohyodeoxycholic Acid (GHDCA OR 1.741; 95% CI, 1.039-3.044) were concurrently correlated with liver injury.

Conclusion

Elevated FIB-4 is strongly linked to increased CHD risk. Metabolomics analysis reveals that GMP, Tryptophanamide, LAA, MMA, and GHDCA are associated with both FIB-4 and CHD, potentially implicating these metabolites in the process through which liver injury contributes to CHD development.

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P703

JOINT2982

Multi-omics characteristics of balanced diet combined with high-intensity interval training for weight loss in obese children

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Obeject
To explore the effect and potential mechanisms of balanced diet combined with high-intensity interval training (HIIT) in reducing fat mass and increasing muscle mass in overweight and obese children.
Methods
Totally 44 obese and 10 overweight children aged from 8 to 18 years old were recruited to participate in a 3-week weight loss summer camp, all the subjects received the same dietary regimen and HIIT. We compared the changes in physical parameters, body composition (DXA), biochemical parameters (including OGTT test) and liver CAP (Fibroscan) in all the subjects, additionally, serum metabolomic and lipidomic profiles, gut microbiomes were further investigated in 8 of them at the beginning and the end of the summer camp.
Results
The average weight of the participants decreased by 3.29kg, BMI by 1.16kg/m2, waist circumference by 3.1cm, liver CAP by 8.44, but the difference was not statistically significant. The total fat mass decreased from (27278.32 + 8133.78) to (24275.68 + 6871.31), while total lean mass increased from (32652.02 + 8495.73) to (35210.37 + 8465.29) ($p < 0.05$). ALT, uric acid, GGT, TC, LDL, Apolipoprotein A1/B, HOMA-IR were significantly improved after the summer camp ($p < 0.05$). Serum metabolisms revealed 27 differential metabolites, serum lipidomic revealed 21 differential lipids, gut microbiomes revealed 60 differential species ($p < 0.05$), enrichment analysis revealed that the differential metabolites, lipids and gut microbiotas were involved in sphingolipid metabolism, glycerophospholipid metabolism, glycosylphosphatidylinositol-anchor biosynthesis, cysteine and methionine metabolism and primary bile acid biosynthesis, which were involved in cell autophagy and associated with insulin resistance.
Conclusion
Three weeks of balanced diet and HIIT can significantly reduce the total fat mass, increase total lean mass, and improve the glucose and lipid metabolism indicators among obesity and overweight children. Mult-omics sequencing is helpful to find early metabolite changes and explore the potential mechanisms during weight loss in children.

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P704

JOINT1668

Mental health in 10 year old children with overweight

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Background
The interplay between mental health and overweight has gained significant attention in recent years. Obesity has been associated with psychiatric disorders such as ADHD, autism, depression, anxiety and their symptom severity, however the potential causal interplay, i.e., the direction of such association, remains elusive. In this study, we harness the longitudinal data of the COPSAC2010 birth cohort to investigate the potential causal interplay between overweight and mental health at 10 years.
Methods
Children of the COPSAC2010 ($n = 700$) cohort have been examined longitudinally in regards to anthropometrics and mental health in clinical visits at age 6 and 10. At age 6, mental health was measured with the Strength and Difficulties Questionnaire (SDQ), and at age 10, in the COPSYCH study, we thoroughly examined neuropsychiatric diagnoses, dimensional psychopathology(including SDQ), and performed cognitive assessments, of the children. We divided children into two groups: overweight at age 10 zBMI > 1.04 ($n = 110$), and non-overweight zBMI ≤ 1.04 ($n = 482$). We analyzed the relationship between overweight and mental health by means of logistic and linear regression, both cross-sectionally at age 10 and longitudinally.
Results
Cross-sectionally at age 10, we found a trend towards higher prevalence of ADHD combined presentation diagnosis (11% vs 5 %, OR 2.3[1.1;4.8], $P = 0.02$), a significantly higher load of psychopathological symptoms and problematic behavioral traits in the group of children with overweight. Children with overweight scored around four points lower in the General IQ (Est -4.25[-7.21;-1.30], $P = 0.005$). Longitudinally, we found a significantly increased OR 1.12 (1.06;1.18): $P < 0.001$ for overweight at 10 years in relation to each point rise in SDQ total difficulties score at 6 years, independently of 6 years BMI. In contrast we saw no association between overweight at 6 years and the total difficulties score at 10 years, adjusted for total difficulties score at 6 years ($P = 0.29$).
Conclusion
We found an association between mental health and overweight in children at 10 years: i)a higher risk of ADHD combined presentation, ii)higher total problem scores in psychopathology questionnaires and, iii) less efficient cognitive functioning. Results from our prospective data suggested that behavioral problems at 6 years precedes overweight at 10 years. The results from this study should be considered when a child with adiposity is examined, and the treatment is planned. A perspective for future recommendation could be a routine neurocognitive and psychological assessment in overweight/obese children, before planning and initiation of a treatment plan.

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P705

JOINT3021

Role of ligand- and genetic variant dependent melanocortin 4 receptor (MC4R) bias signaling for the individual risk to develop obesity

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Introduction
The melanocortin 4 receptor (MC4R), a G protein-coupled receptor (GPCR), is a critical regulator of body weight within the hypothalamus and is embedded in the leptin-melanocortin signaling pathway. Heterozygous *MC4R* gene mutations have been identified as potent genetic risk factors for the development of obesity. Additionally, the MC4R agonist setmelanotide has recently been approved as a pharmacological treatment option for patients with certain rare monogenic forms of obesity. In recent years it has been described that MC4R related differential (biased) signaling is playing an important role for body weight regulation and the downstream effect of MC4R ligands. However, the interplay between *MC4R* genetic variants and different endogenous and external MC4R ligands remains elusive.
Methods
We analyzed *In vitro* the signaling of 20 heterozygous *MC4R* mutations, which have been identified in a cohort of children with obesity, in regards to Gs, Gq/11, ERK, G12/13 and b-arrestin2 recruitment and after stimulation with different MC4R ligands (α-MSH, β-MSH, setmelanotide) in HEK293 cells. Additionally, *MC4R* mutations were further characterized by analysis of our previously solved the cryo-electron microscopic (cyro-EM) structures.
Results
We observed a ligand and genetic variant dependent differential (bias) signaling of the MC4R. The "protective" *MC4R* variant V103I was associated with an increase of Gq signaling after stimulation with α-MSH. Contrary to the complete loss of function variants like Y80C, D90N and S127L (deficit in all analyzed pathways), *MC4R* variants as S77L or T178M led to a reduction of non-Gs signaling cascades while Gs signaling was not altered. These signaling profiles were ligand dependent, which was partially related to MC4R conformation changes, which were analyzed based on cryo-EM structure data.
Conclusion
Our findings emphasize the critical role of differential (bias) signaling for MC4R function. Structural data- combined with *In vitro* functional data allowed to gain further insights into the structural regulation of the MC4R, which can be relevant to optimized MC4R agonists as a treatment option for patients with certain forms of obesity.

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P706

JOINT352

Sex Hormone-binding globulin prevent carbon tetrachloride-induced liver fibrosis development

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Sex hormone-binding globulin (SHBG) plasma levels are reduced in subjects suffering MASLD and MASH. We have previously shown both *In vitro* and *in vivo*, that SHBG protects against MASLD development by reducing hepatic fat accumulation via inhibiting hepatic lipogenesis. In the present work, we are interested in exploring if SHBG could protect also against development of liver fibrosis. For this purpose, *in vivo* studies were performed using wild-type and the human *SHBG* transgenic mice developing liver fibrosis induced by carbon tetrachloride (CCl_4). Our results clearly showed that SHBG overexpression reduced the CCl_4 induced liver fibrosis in both male and female mice. Histological examination showed that *SHBG* transgenic mice had reduced NAS score and reduced collagen accumulation. Human SHBG transgenic mice treated with CCl_4 had reduced Col1A1 mRNA and protein levels when compared with wild-type CCl_4 treated mice. Mechanistically, we found that *SHBG* transgenic mice showed increased hepatic protein levels of several metalloproteases when compared with wild-type CCl_4 treated mice. Taking together, we found for the first time that SHBG could protect against liver fibrosis by inhibiting Col1A1 mRNA and protein levels and by reducing collagen through an increase in MMPs activity.

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P707

JOINT3339

The beta-2-adrenoreceptor agonist fenoterol increases resting enery expenditure without activation of brown adipose tissue in humans

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Background
Brown adipose tissue (BAT) may directly dissipate energy from lipids and carbohydrates into heat and its activity is associated with a favorable metabolic phenotype in human adults. In rodents, BAT is activated by the sympathetic nervous system and its transmitter norepinephrine via the α3-adrenoreceptor (α3-AR). In humans stimulation of the α3-AR even with high doses of the selective agonist Mirabegon leads to a rather weak activation of BAT as compared to a cold stimulus. *In vitro* studies in cell lines from human BAT and one human study have pointed towards the α2-AR as a possible activator of human BAT. Here, we studied the effect of the potent and selective α2-AR agonist fenoterol on human energy expenditure (EE) and BAT activity.
Methods
Healthy normal weight volunteers were initially screened for cold-induced thermogeneis. Twelve individuals with cold-induced thermogenesis of >5% of resting energy expenditure were included. They received the following interventions over two hours in random order: A) standardized mild cold stimulus; B) intravenous infusion of the selective α2-agonist Fenoterol. EE was measured continously with indirect calorimetry, skin and core temperature were recorded and BAT activity was quantified in the supraclavicular BAT depot by 18F-FDG-PET/CT after each intervention.
Results
Resting EE at baseline was 1516±347 kcal/24h before cold-exposure and 1502±281 kcal/24h before Fenoterol. Cold exposure resulted in a mean increase in EE of 195 kcal/24h ($P = 0.044$ vs. baseline) and Fenoterol infusion increased EE by 358 kcal/24h ($P < 0.0001$). The mean standardized uptake value (SUVmean) of supraclavicular BAT was 3.06 (IQR 2.19;3.64) g/ml after cold exposure but only 1.66 g/ml [1.63;1.70] after Fenoterol infusion. Correspondingly, the active BAT volume was 90 (26;190) ml vs. 3 (1;16) ml. Supraclavicular temperature increased promptly in response to cold, but not after fenoterol. Fenoterol immediately and strongly increased levels of circulating fatty acids and glycerol, while triglyceride levels remained stable. A slower lipolytic response occurred during cold stimulation. In both interventions the lipolytic response paralleled the kinetics of EE during the respective visit. Only fenoterol increased serum-glucose, insulin, and lactate. In another cohort of healthy individuals, expression of the α3-AR but not of the α2-AR was correlated to the level of UCP1, the hallmark of brown adipocytes.
Conclusion
We found no evidence that α2-ARs play a major role in activation of human BAT. A reason for the observed fenoterol-induced increase in REE could be futile metabolic cycles e.g. lipid cycling in skeletal muscle or white adipose tissue.

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P708

JOINT1049

Sex hormones and high-fat, high-sucrose diets: unraveling their interaction on brown adipose tissue morphology and gene expression

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Background
Overweight and obesity are escalating global health challenges, with food containing high fat and sugar being one of the causes. The discovery of functional brown adipose tissue (BAT), an organ of non-shivering thermogenesis, in adults offers new opportunities for obesity therapies. Emerging evidence suggests that sex hormones influence BAT structure and function, but the exact mechanisms remain to be fully elucidated.
Methods
Fifty-six mice [28 males (M), 28 females (F)] were used, with 14 per sex undergoing gonadectomy (G) at 8 weeks old, and the rest receiving a sham operation (S). After a one-week recovery, 7 mice from each group were switched to a high-fat, high-sucrose diet (HFD) for 12 weeks, while the others continued on standard chow diet (CD), resulting in a total of 8 groups: MSC, MGC, FSC, FGC, MSH, MGH, FSH, and FGH. At the end (age 22 weeks), interscapular BAT was collected. BAT morphology was analyzed using ImageJ with the Adiposoft extension. mRNA expression levels were quantified by qPCR.
Results
HFD increased BAT weight, reduced nuclear density, and increased droplet size in BAT across all groups. While *Ucp1* expression (a thermogenic gene) showed no sex differences among CD-fed groups, HFD-fed females expressed more *Ucp1* than males (FSH>MSH, $P = 0.04$). Gonadectomy influenced *Ucp1* expression in a sex-dependent manner in the HFD-fed group, increasing it in males (MGH>MSH, $P < 0.01$) but having minimal effect in females. *Ppargc1a*, a transcriptional coactivator of *Ucp*1, and lipolytic genes *Atgl* and *Hsl* followed similar trends to *Ucp1*, showing little changes with HFD but significant alterations with gonadectomy in a sex-dependent fashion. For fatty acid uptake, *Lpl* expression was not significantly affected by HFD alone ($P = 0.31$) but was significantly reduced when combined with gonadectomy in both sexes ($P < 0.01$). HFD decreased *Pck1* (a gluconeogenic gene) expression across all groups ($P < 0.01$). Additionally, HFD suppressed *Cfd* (adipsin, an anti-thermogenic adipokine) expression in all groups ($P < 0.01$), and gonadectomy reduced *Cfd* levels in females regardless of diet condition ($P < 0.01$).
Conclusion
HFD and sex hormones, along with their interaction, influence BAT morphology, metabolism, and substrate uptake. Gonadectomy shows a stronger effect than HFD on thermogenic and lipolytic activities. These findings reveal complex hormonal-dietary effects, providing insights into HFD-induced obesity and potential therapeutic strategies.

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P709

JOINT2286

Anthropometric and metabolic assessment in adults with down syndrome: the need for novel indices and customized criteria

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Objective
This study aimed to evaluate the metabolic profile of adults with Down syndrome (DS) using novel anthropometric and metabolic indices, highlighting the limitations of conventional obesity assessment methods, such as BMI, in this population compared to healthy controls.
Methods
A cross-sectional study was conducted with 22 adults with DS and 28 age- and sex-matched healthy controls. Anthropometric measurements, including BMI, waist circumference (WC), hip circumference, and waist-to-height ratio (WHtR), were recorded along with novel indices like the Body Adiposity Index (BAI), A Body Shape Index (ABSI), and Visceral Adiposity Index (VAI). Body composition was assessed via bioelectrical impedance. Metabolic parameters, including fasting plasma glucose, HbA1c, lipid profiles, and HOMA-IR, were measured. CBC-derived inflammation indices neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-hemoglobin ratio (MHR), neutrophil-to- hemoglobin ratio (NHR), lymphocyte-to-HDL ratio (LHR), platelet -to-hemoglobin ratio (PHR), systemic ımmune-ınflammation ındex (SII), aggregate ındex of systemic ınflammation (AISI), systemic ınflammatory responseındex(SIRI) were analyzed. Metabolic syndrome (MetS) was defined per IDF 2005 criteria. Statistical analyses included group comparisons and correlations between indices and metabolic markers.
Results
Individuals with DS exhibited higher WHtR ($p < 0.001$) and shorter stature ($p < 0.001$) than controls, despite similar BMI levels. The MetS prevalence was lower in the DS group (9.09%) than in controls (21.4%; $P = 0.001$), even with higher abdominal obesity rates. Lipid and glucose profiles were better in DS individuals with abdominal obesity compared to controls, but differences were not statistically significant. WHtR correlated with fasting glucose, HbA1c, and blood pressure in DS, whereas BMI showed limited correlations with metabolic markers. The VAI values were similar between groups ($P = 0.96$), while the BAI ($p < 0.001$) and ABSI ($P = 0.001$) were significantly higher in the DS group. Within DS, BAI was higher in women than men ($P = 0.001$), while VAI and ABSI did not differ by gender. Among CBC-derived indices, only PLR was significantly elevated in the DS group ($P = 0.038$). VAI correlated with WC, TG, TG/HDL ratio, and inversely with HDL cholesterol, while BAI correlated with systolic and diastolic blood pressure, HbA1c, and WC.
Conclusion
This study highlights the distinct metabolic and inflammatory profiles of individuals with DS, emphasizing the limitations of BMI and the utility of novel metabolic and anthropometric indices. These findings underscore the need for population-specific assessments and tailored methods to improve metabolic risk evaluations in DS.

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P710

JOINT3666

Frequency of monogenic variants in a cohort of individuals with severe, early-onset obesity from a single large tertiary paediatric centre

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Introduction
Obesity is a complex, chronic disease characterised by excess adiposity which tracks throughout the lifecourse. Monogenic obesity presents in childhood with severe, early-onset obesity and hyperphagia, and its prevalence may be underestimated due to limited access to genetic testing. We describe genetic results from a large cohort of children and young people (CYP) living with severe obesity under the care of our tertiary paediatric weight management clinic.
Methods
131 CYP with severe obesity (body mass index (BMI) >99.6th centile for age) had genetic testing performed using the Rare Obesity Advanced Diagnosis™ 79-gene targeted panel (including the MC4R pathway variants) between March 2022 and November 2024. Variants were classified as pathogenic or potentially relevant variants according to American College of Medical Genetics criteria; further subdivided into suspected pathogenic, variants of unknown significance and suspected benign.

Pathogenic Variants (frequency)	Potentially Relevant Variants (frequency)			Gene with polymorphic risk variant (frequency)
	Suspected Pathogenic	Variant of Unknown Significance	Suspected Benign	
MC4R heterozygous(5)	KSR2(2)	KIDINS220(2)	ALMS1(3)	PCSK1 heterozygous (16)
SIM1 heterozygous(4)	SEMA3A(2)	PCSK1(2)	NCOA1(3)	
RAI1 heterozygous(1)	TUB(2)	SEMA3A(2)	KSR2(2)	
VPS13B heterozygous(1)	BBS9(2)	CREBBP(1)	PCSK1(2)	
SEMA3G heterozygous(1)	VPS13B(2)	GNAS(1)	POMC(2)	
Chromosomal rearrangement 16p11.2 deletion(1)	KIDINS220(1)	KSR2(1)	RAI1(2)	
	BBS7(1)	MAGEL2(1)	EP300(1)	
	SEMA4 (1)	PLXNA3(1)	HTR2C(1)	
	TTC8(1)	RPS6KA3(1)	NRP1(1)	
	POMC(1)	DNMT3A(1)	SIM1(1)	
	SDCCAG8(1)	MC4R(1)	PLXNA2(1)	
		PHF6(1)	BBS12(1)	
		EP300(1)	NROB2(1)	
		PCNT(1)		
		IFT172(1)		
		PLXNA1(1)		
		MKKS(1)		
		VPS13B(1)		
		BBS5(1)		
		CEP290(1)		
		PLXNA4(1)		
		TRIM32(1)		
		BBIP1(1)		

Results
69/131 patients were female. Age ranged from 1.5-17.5 years with onset of obesity between 3-11 years of age. Median BMI was 32.2kg/m^2 (range 22.1-55.0) and median BMI-SDS was 3.72 (range 2.10-6.46). 9.2% (12/131) of CYP were found to have pathogenic variants and suspected pathogenic variants were found in 10.7% (14/131). 16.8% (22/131) had variants of unknown significance, 14.5% (19/131) had suspected benign variants (some CYP had more than one variant) and one had a deletion in the 16p11.2 chromosomal region. *MC4R* (heterozygous) was the most frequent pathogenic variant (3.8%; 5/131), followed by heterozygous *SIM1* (3%; 4/131).
Conclusion
In this clinical population of CYP living with severe obesity, almost 10% had pathogenic variants associated with obesity and a further 10% had suspected pathogenic variants. The majority of the above variants were in genes encoding proteins in the leptin-melanocortin pathway which is crucial in the regulation of appetite and energy expenditure. Increased provision of genetic testing may facilitate a deeper understanding of the monogenic causes of obesity and enable the development of further targeted, personalised therapies to improve long-term outcomes.

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P711

JOINT2220

Clinical significance of urine NAG and blood Cys-C in early renal damage assessment of children with simple obesity

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Objective
To investigate the correlation between urinary n-acetyl-α-D-glucosaminase(-NAG)and serum cystatin C(Cys-C)levels and physical measurements, glucose and lipid metabolism, liver and kidney function and other indicators in children with simple obesity. To further explore the clinical significance of urinary NAG and serum Cys-C levels in the assessment of early renal damage in children with simple obesity.
Methods
302 children with simple obesity were selected , (110 cases in the mild to moderate obesity group and 192 cases in the severe obesity group)and 53 children of similar age were selected as the normal control group. Clinical data of the two groups, were collected to compare the differences in clinical data between the obese group and the normal control group, and to analyze the correlation between blood Cys-C, urine NAG and renal function. In addition, 302 children with simple obesity were divided into albuminuria group and normal albuminuria group according to urnie albumin creatine raio (UACR) ratio. The differences of general clinical data and laboratory parameters among albuminuria group and normal albuminuria group were compared. Multivariate Logistic regression analysis was used to find out the predictors of kidney damage, and ROC curve was used to verify them.

Results
1. There were statistically significant differences in eGFR, mALB and uNAG in the mild to moderate obesity group, the severe obesity group and the normal control group($P<0.01$).
2. Cys-C, uNAG, eGFR, BUN and UA in obesity 0-2 years, 2-5 years and ≥ 5 years course groups were higher than those in control group, with significant statistical difference ($P < 0.01$).
3. ROC curve: the combined detection of uNAG and Cys-C had the largest area under the curve (AUC = 0.8167), and the specificity and sensitivity were higher (75% and 85.7%).
Conclusions
1. The levels of uNAG and Cys-C in children with simple obesity are higher than those in normal children, suggesting that early kidney damage may occur in children with simple obesity.
2. uNAG is an independent factor of early kidney injury in children with simple obesity. The combined detection of uNAG and serum Cys-C is superior to the single detection of uNAG.

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P712

JOINT358

Association between 25-hydroxyvitamin-D and insulin resistance in korean adolescents: findings from the 2008-2014 KNHANES

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Background
We aimed to evaluate the relationship between vitamin D status and insulin resistance (IR) according to obesity status using non-insulin-based indices in adolescents.
Methods
This cross-sectional study included data from 3, 838 adolescents (aged 12 to 18) who participated in the Korea National Health and Nutrition Examination Survey from 2008 to 2014. The subjects were divided into two groups, normal weight and overweight & obese. Blood vitamin D levels were assessed in two groups based on a threshold of 20 ng/mL of 25-hydroxyvitamin D [25(OH)D], and vitamin D deficiency was defined as <20 ng/mL. As non-insulin-based IR indices, we used triglyceride-glucose index (TyG), triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C), TyG index with body mass index (TyG-BMI), and metabolic score for IR (METS-IR).
Results
The prevalence of vitamin D deficiency in adolescents was 78.5%. Mean vitamin D levels were higher in boys, those who did strength training, and those with waist circumference below the 90th percentile. In normal weight individuals, TyG-BMI and METS-IR were significantly higher in those with vitamin D deficiency than in those with adequate vitamin D levels. This trend was also observed in individuals with the overweight and obese group, where a significant difference was found in TyG-BMI index. Even after adjusting for covariates, the association between vitamin D and IR as assessed by the METS-IR index persisted in the normal weight group.
Conclusions
Vitamin D deficiency is significantly associated with higher insulin resistance in adolescents, as measured by non-insulin-based indices. This association appears to be particularly strong in overweight and obese individuals.

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P713

JOINT3365

Investigate the role of insulin in regulating the local expression of aromatase in the growth plate

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Objective
Body Mass Index (BMI) and bone age (BA) are key indicators for assessing an individual's growth and development. Children with obesity may appear to have taller height but fail to achieve optimal adult height due to the accelerated maturation of the epiphyseal growth plates, resulting in premature bone age and termination of growth. In this study, we assessed the impact of obesity-induced hyperinsulinemia on linear growth trajectories and the underlying mechanisms involved, using a high-fat diet-induced obesity rat model.
Methods
Twelve healthy 1-week-old Sprague-Dawley rats, weighing between 60-80g, were randomized into two groups: a control group and an obese group, receiving a standard diet and high-fat diet, respectively. After 6 weeks of induction, weekly body weights and body lengths were assessed. At the end of the study, all rats were euthanized, and blood samples were collected for further analysis. Hematological parameters such as serum insulin levels were assessed using ELISA. Tibia and humerus bones were collected to assess the bone length. Growth plates were separated for histological, immunohistochemical, PCR and Western blot analyses.
Results
Serum insulin levels were significantly higher in the obese group compared to the control group ($P < 0.01$). Compared with the control group, the obese group exhibited significantly increased growth plate length ($P < 0.01$), particularly in the proliferative and hypertrophic zones. Immunohistochemical staining further revealed that elevated levels of aromatase and insulin receptor (IR) expression in growth plates were predominantly observed in the hypertrophic zone. The relative mRNA expression levels of both aromatase and insulin receptors in the growth plates of obese rats were significantly elevated compared to the control group ($P < 0.01$). Western blot analysis demonstrated significantly increased expression of both CYP19A1 and IR in the growth plates of obese rats ($P < 0.01$).
Conclusion
Advanced bone age observed in obese children could potentially be attributed to the insulin signaling pathway-mediated regulation of aromatase expression in the growth plate.

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P714

JOINT2488

Muscle respiratory capacity correlates with insulin sensitivity independent of adiposity and metabolic flexibility

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Introduction
Impaired metabolic flexibility (MetFlex) is a key pathophysiological mechanism underlying metabolic dysregulation in obesity. It is characterised by a reduced ability to adapt metabolism in response to substrate availability. This study examined the relationship between insulin sensitivity and MetFlex in normal-weight and women with obesity and explored their association with mitochondrial respiratory function in skeletal muscle.
Methods
A pilot study included 21 normal-weight women (age 32 ± 5, BMI 21.4 ± 1.5) and 15 women with obesity (age 36 ± 7, BMI 34.3 ± 3.6). Anthropometric and biochemical parameters as well as insulin sensitivity (hyperinsulinemic-euglycemic clamp, HEC), glucose tolerance (oral glucose tolerance test, OGTT), metabolic flexibility (indirect calorimetry during HEC, OGTT) and cardiorespiratory fitness (exercise test) were assessed. Skeletal muscle biopsies were obtained for mitochondrial respiration analysis (O2K, Oroboros).
Results
All women were eumenorrheic and none had thyroid dysfunction. Women with obesity exhibited higher triglyceride levels (1.2 ± 0.5 vs. 0.7 ± 0.4 mmol/l, $P = 0.0142$), lower cardiorespiratory fitness (23 ± 4.5 vs 40.8 ± 5.4 $ml^{-1}kg^{-1}min^{-1}$, $p = <0.0001$), and reduced insulin sensitivity ($5, 5 \pm 2, 0$ vs $11, 0 \pm 2$, 1 mg. $kg^{-1}min^{-1}$, $P = 0, 001$) compared to normal-weight women. Contrary to our hypothesis, MetFlex, assessed as change in respiratory quotient (ΔRQ) during HEC or glucose tolerance tests, did not differ between groups. In women with obesity, mitochondrial respiratory capacity, ATP production and fatty acid oxidation were reduced, with impaired mitochondrial membrane integrity. In all participants, respiratory capacity, ATP production and fatty acid oxidation correlated with insulin sensitivity and cardiorespiratory fitness, but not with MetFlex.
Conclusion
Our findings suggest that impaired insulin sensitivity in obese women may precede detectable changes in MetFlex. Insulin sensitivity is strongly associated with mitochondrial integrity and muscle respiratory capacity, independent of adiposity and metabolic flexibility.

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P715

JOINT1915

Educational cartoon in the podiacar PROject: an approach to combat paediatric obesity

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Aims
Pediatric obesity is an escalating global health concern with profound physical and psychological impacts, both in the short and long term. The EU-funded initiative, "Fight against Pediatric Obesity: from a Predictive Tool for Type 2 Diabetes and Cardiovascular Disease Risk to Healthy Educational Programs" (PODiaCar), seeks to address childhood obesity through a comprehensive, multidimensional strategy. A key component of this project is the development of educational cartoons aimed at encouraging healthy lifestyle behaviors among children.
Methods
The interdisciplinary PODiaCar team collaborated with Officine Creative at the University of Pavia, Italy, to create the cartoon. Essential messages about nutrition and lifestyle were derived from an extensive literature review and refined with expert insights to ensure they were engaging, age-appropriate, and free from stigmatization. The storyline and characters were carefully designed, using clear language and visually appealing graphics to effectively capture children's attention and facilitate learning.
Results
The outcome of this effort is "Grandma Wilma's Tales, " an engaging animated story centered around Grandma Wilma and her grandson Charlie, who is initially reluctant to adopt healthier eating habits. The first episode introduces Vitto and his dog Buzz, illustrating the negative effects of poor diet and inactivity while highlighting the advantages of a balanced lifestyle. By using a positive and relatable approach, the cartoon helps children connect with the characters and internalize key messages about nutrition and physical activity.
Conclusions
This educational cartoon fosters awareness of the importance of a balanced diet and regular physical activity while ensuring a non-stigmatizing approach. By creating an engaging and relatable learning environment, the series motivates children to embrace healthier daily habits.

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P716

JOINT2275

Combination therapy of semaglutide and methylphenidate leads to significant weight loss in prader-willi syndrome patients

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Prader-Willi syndrome (PWS) is a neurodevelopmental disorder with impaired hypothalamic function due to abnormal DNA methylation within the region of 15q11.2-q13. The available pharmacological options reported for the treatment of hyperphagia and obesity in PWS include Phentermine, Topiramate, Glucagon-like peptide 1 receptor agonist (Exenatide, Liraglutide), Naltrexone- Bupropion and Setmelanotide. However, most of these have been ineffective and some have been withdrawn due to adverse effects. Achieving weight loss in PWS patients is extremely difficult. We report our experience of using a combination therapy of Semaglutide and Methylphenidate in 5 children with PWS to achieve a significant weight loss and improvement in food-seeking behaviors. Five genetically confirmed PWS patients (ages 7, 8, 10, 16, 17 years) were recruited. All had preexisting comorbidities such as T2DM (2), obstructive sleep apnea (5), fatty liver (5). In all 5, other treatment modalities for hyperphagia and obesity like growth hormone, low-calorie diets and laparoscopic sleeve gastrectomy (in one of them) were tried and failed. Hence, they were selected for this combination therapy. The treatment protocol involved using Methylphenidate as an appetite suppressant (starting at 18mg titrated to 36mg, 54mg, 72mg and 108mg) along with Semaglutide (0.5mg titrated to 1mg, 1.5mg and finally 2.4mg). The titrations were made every 3 weeks based on the tolerability. The laboratory parameters, Ghrelin, Leptin, Dykens hyperphagia score, ultrasonography of abdomen, total body composition by DXA, baseline echocardiography was performed for all. This protocol was initiated in 5 children after hospitalization then discharged on combination therapy. Along with therapy they were on low calorie diets. They lost between 6 to 11.5% of weight after 4 to 12 months of starting treatment. In addition, there was complete resolution of T2DM in one of them, improvements in hyperphagia score, sleep apnea and total body composition. It is recommended a moderate weight loss of 5–10% as the goal for medically supervised weight loss. Ghrelin and Leptin were obtained in 2 of them. Ghrelin was 1125pg/ml pre therapy and 1254pg/ml after 1 month in the first. Leptin was 53ng/ml and 36 ng/ml post initiation. The other patient's Ghrelin was 2627pg/ml pre and 696pg/ml after 7 months. Leptin was 24ng/ml pre and 40ng/ml after 7 months. The anorectic potency of the combination of Semaglutide and Methylphenidate can be utilized in PWS. Significant weight loss can have game-changing effects on complications such as T2DM and severe obstructive sleep apnea. However, this combination therapy warrants further clinical trials.

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P717

JOINT127

Body mass index trajectories from early childhood to late adolescence: an analysis of the leicester respiratory cohorts

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Introduction
Childhood obesity has become a prevalent global health concern, affecting 25% of 10-year-olds in Leicestershire, UK. Understanding the development of obesity is crucial for identifying key predictors and groups at risk. In this study, we aimed to find distinct developmental trajectories of body mass index (BMI) and explore potential risk factors in a large, population-based pediatric cohort.
Methods
We used data from the Leicester Respiratory Cohorts (LRC), recruited in 1990 and 1998 as random samples of all 1-4 year old children living in Leicestershire UK. We calculated BMI using height and weight measurements from routine health care visits, study visits, and questionnaires, excluding extreme values with a z-score $<$-5 or $>$5, based on UK growth charts. Participants with at least 3 BMI values between 0-18 years were included. We used B-Splines to find a parsimonious pattern of BMI over age in the single class model. We then used Group Based Trajectory Modelling to identify the presence of distinct BMI trajectories, selecting the best model based on Bayesian Information Criterion, class size, average posterior probabilities, entropy, and biological plausibility. We employed multinomial logistic regression to identify factors associated with each BMI trajectory.
Results
Out of the 10, 350 children in the LRC, we included 5523 eligible children (52% boys). The best single class BMI pattern were quadratic B-Splines with two knots at 0.6 years and 9.7 years. We found 5 BMI development trajectories: normal (n = 2699, 49%), below normal (n = 1494, 27%), early overweight resolving (n = 576, 10%), school-age onset obesity (n = 217, 4%), and adolescent onset overweight (n = 537, 10%). Compared to boys, girls were more likely to be in the below normal (OR: 1.65, CI95%: 1.45-1.87), school-age onset obesity (1.48, 1.12-1.95), and adolescent onset overweight (1.48, 1.23-1.78) trajectories. Children of Asian ethnicity, compared to European, had higher odds of being in the below normal (2.75, 2.39-3.17), school-age onset obesity (1.68, 1.23-2.28), and adolescent onset overweight (1.41, 1.14-1.75) trajectories, but lower odds of being in the early overweight resolving (0.68, 0.53-0.87) trajectory. Children in the lowest tertile of socioeconomic status were more likely to be in the below

normal (1.65, 1.39-1.95) and school-age onset obesity (1.80, 1.21-2.68) trajectories, compared to children in the highest tertile.
Conclusion
We identified five distinct BMI developmental trajectories and found that female sex, Asian ethnicity, and low socio-economic status were associated with specific trajectories. Targeted interventions should focus on these high-risk groups to prevent obesity and related health issues.
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P718

JOINT1530
Effectiveness of simulation-based learning in enhancing confidence and clinical competence in managing lipid-related diseases: a mixed-methods study
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Background
The growing prevalence of lipid-related diseases poses a significant challenge to global health, underscoring the need for innovative educational strategies to upskill healthcare professionals in managing these conditions. Simulation via Instant Messaging for Bedside Application (SIMBA) is a novel simulation-based learning (SBL) model that has effectively enhanced healthcare professionals' confidence in managing diverse medical scenarios. By simulating real-world clinical situations, SIMBA provides an interactive platform for participants to develop and refine essential clinical skills.
Objectives
1. Evaluate the effectiveness of the SIMBA model in improving participants' confidence in managing lipid-related diseases.
2. Assess the clinical performance of healthcare professionals during simulations of lipid-related disease scenarios.
3. Determine the applicability of the SIMBA model as an educational tool for lipid disease training.
Methods
This mixed-methods study collected and analysed both qualitative and quantitative data. It was conducted in the UK from June to November 2024. The SIMBA model facilitated SBL sessions on five topics: Familial Hypercholesterolemia, Secondary Prevention of Cardiovascular Disease through Lipid Control, Chylomicronemia Syndrome, Acute Triglyceridemia, and Alström Syndrome. Healthcare professionals interested in lipid disorders were invited to participate, and those who completed both pre- and post-SIMBA surveys were included in the analysis. Statistical analysis was performed in STATA version 17.0. Changes in confidence to manage lipid-related pathology were measured using pre- and post-SIMBA surveys. Participant interactions during simulations were evaluated using an adapted Global Rating Scale approved by subject matter experts.
Results
Thirty participants completed both surveys and were included in the analysis. Confidence levels improved significantly after the sessions (pre-simulation vs post-simulation: 24.3% vs 94.7%; $P < 0.01$). Median scores out of 5 for core clinical competencies were as follows: history-taking (4.0), examination (3.9), investigation (3.8), result interpretation (2.5), clinical judgment (3.7), and management (3.4). 93.3% of participants deemed the sessions applicable to their clinical practice, with 73.4% rating them as excellent. Additionally, over 90% found the content impactful professionally and personally, facilitating effective knowledge translation into patient care.
Conclusion
The SIMBA model significantly enhanced healthcare professionals' confidence and clinical competencies in managing lipid-related diseases. Notably, gaps in interpreting diagnostic test results were identified, highlighting the need for targeted educational interventions. The SBL approach was well-received and considered highly applicable to clinical practice. Further studies are warranted to explore the model's long-term impacts and broader applicability to lipid disease management and education.
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P719

JOINT1692
AIP deficiency in zebrafish causes loss of intestinal epithelial differentiation via disrupted wnt signaling
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Background
Heterozygous mutations in the chaperone Aryl Hydrocarbon Receptor Interacting Protein (AIP) are implicated in approximately 10% of familial isolated pituitary adenomas, while homozygous mutations result in embryonic lethality in mice, *Drosophila* and *C. elegans* models. To date, five human patients with complete loss of AIP function have been identified, exhibiting, among other features, failure to thrive and severe diarrhoea requiring parenteral nutrition.
Methods
In this study, we generated an *aip* loss-of-function zebrafish model using CRISPR-Cas9 gene editing to investigate the molecular and physiological consequences of AIP deficiency. Survival rates were monitored daily, and intestinal morphology was assessed via haematoxylin and eosin (H&E) staining. Cellular proliferation was evaluated through PCNA immunohistochemistry, while stem cell populations were characterized using *in situ* hybridization for specific mRNA markers. Cell morphology was assessed via immunofluorescence. Gene expression of WNT signalling pathway was analysed through RNA sequencing (RNA-seq) and quantitative PCR (RT-qPCR) performed. Food ingestion capacity was evaluated using a feeding assay.
Results
aip mutant zebrafish exhibited growth retardation from 6 days post-fertilization (dpf). Although they demonstrated the ability to capture food, mutants displayed impaired digestion and absorption, possibly due to a failure of intestinal epithelial differentiation at 5 dpf. By 4 dpf, overactivation of WNT signalling and increased cellular proliferation were observed in mutants, accompanied by a marked deficiency in intestinal stem cells and disrupted cell elongation. By 7 dpf, *aip* knockout fish exhibited a notable increase in bi-nucleated cells within the intestinal epithelium, along with a significant reduction in the number of Goblet cells.
Conclusion
These findings suggest that loss of *aip* results in intestinal stem cell depletion, impaired cellular differentiation, and defects in cell elongation, partly mediated through dysregulation of the WNT signalling pathway.
Keywords *aip*, zebrafish, wnt, proliferation, stem cells.
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P720

JOINT522
Development of a novel thyroid hormone profiling method using liquid chromatography tandem mass spectrometry
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Introduction
Thyroid hormones (TH) are critical for numerous biological processes including development, growth, and metabolism. The thyroid gland primarily secretes thyroxine (T4) and a small amount of triiodothyronine (T3), with T3 being predominantly produced through the deiodination of T4 in peripheral tissues. Deiodinase enzymes both activate T4 to T3 and facilitate the deactivation/clearance of T3 into various metabolites, including rT3, 3, 5-T2, 3, 3'-T2, 3'5'-T2, 3-T1, 3'-T1, and T0.

Methods and Results
We developed a liquid chromatography tandem mass spectrometry (LC-MS/MS) method capable of analysing nine thyroid hormone metabolites (THM). Quantitation was achieved by comparison to reference standards following addition of internal standards (T3, rT3, 3-T1, and T4, all labelled with $^{13}C6$). Serum, calibrator, or quality control (QC) samples were treated with 1.25% NH4OH/acetonitrile (1:1) and centrifuged. The THM were then extracted using an Evolute Express AX 30mg solid phase extraction (SPE) plate, with the final elution using formic acid in methanol. After evaporation, samples were reconstituted in a methanol-water mixture before LC-MS/MS analysis using a Waters Acquity system with a Xevo-MS detector and a Luna Omega 1.6µm Polar C_{18} column. Full chromatographic separation of nine THM was achieved within a 7-minute run time. The method demonstrated recovery rates ranging from 96-107%. Application of the method to male serum enabled the quantification of all nine THM (T0, 3-T1, 3'-T1, 3, 5-T2, 3, 3'-T2, 3', 5'-T2, T3, rT3, T4).
Conclusions
This high-throughput LC-MS/MS method, provides a comprehensive tool for thyroid hormone profiling that will significantly advance THM research. Method validation is ongoing and will facilitate THM profiling in healthy and disease populations. This method has the potential to enhance understanding of TH metabolism in multiple contexts, supporting clinical diagnosis and management.

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P721

JOINT201

Relation of a-synuclein level to glucotoxicity, lipotoxicity and cerebral neurodegeneration in children with obesity

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Background
Children with obesity exhibit subtle neurocognitive deficits, the mechanism of which remains unknown. α-synuclein plays a fundamental role in neurodegeneration. Moreover, its role in glucose and lipids metabolism is emerging.
Objectives
This study aims to assess whether α-synuclein is correlated with the degree of neurodegeneration in children with obesity in comparison to healthy controls and correlate it to various neurocognitive and metabolic parameters.
Subjects/Methods
Forty children with obesity and 40 matched-healthy controls were assessed for anthropometric measurements and blood-pressure. Cognitive evaluation was performed using Stanford–Binet scale and Barkley Deficits in Executive Functioning (EF) Scale-Children and Adolescents. α-synuclein, fasting lipids and glucose were measured with calculation of the homeostatic model of insulin-resistance.
Results
Children with obesity had significantly higher α-synuclein ($P < 0.001$) and total EF percentile ($P = 0.001$) than controls. α-synuclein was negatively correlated to total IQ ($P = 0.001$), and positively correlated with total EF percentile ($P = 0.001$) and EF symptom count percentile ($P < 0.001$) in children with obesity. Multivariate-regression revealed that α-synuclein was independently related to diastolic blood-pressure percentile ($P = 0.013$), waist/hip ratio SDS ($P = 0.007$), total EF percentile ($P = 0.033$) and EF symptom count percentile ($P < 0.001$) in children with obesity.
Conclusion
α-synuclein could have a mechanistic role in neurocognitive deficit among children with obesity.

Keywords Alpha-synuclein, obese children, neurodegeneration.
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P722

JOINT2291

Beneficial effects of oleocanthal-rich olive oil on platelet functionality and other metabolic parameters of type II diabetic patients

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Background
A common phenomenon observed in type 2 diabetes mellitus is the postprandial dysmetabolism, which may act as a daily stressor of the already dysfunctional diabetic platelets.
Methods
Ex-vivo experiments have been performed on isolated platelet-rich plasma of 16 healthy volunteers. Antiplatelet activity, of 7 most common bioactive phenolic compounds of olive oil, was assessed in isolated platelet-rich plasma (PRP) by optical transmittance aggregometry, using ADP and TRAP as aggregating factors. According to the ex-vivo results, the clinical study followed and had a randomized, crossover design. Ten T2DM patients consumed five isocaloric meals containing 120g white bread combined with: (i)39g butter, (ii)39g butter and 400mg ibuprofen, (iii)40mL OO (phenolic content < 10mg/Kg), (iv)40mL OO with 250mg/Kg oleocanthal and (v)40mL OO with 500mg/Kg oleocanthal. Glycemia markers and lipid profile was measured in serum pre and postprandially, while the ex-vivo ADP- and TRAP-induced platelet aggregation were also calculated. TBARS and GPX3 were measured in plasma and TBARS and GPX1 in red blood cells(RBC), protein carbonyls(PC) in plasma pre- and post-prandially.
Results
Ex-vivo experiments showed that oleocanthal had better antiplatelet activity(APA) against ADP compared to TRAP while oleacein had milder APA than oleocanthal for all active agents. Regarding the clinical study, the glycemic and lipidemic response was similar between meals. However, a sustained (90-240 min) dose-dependent reduction in platelets' sensitivity to both ADP (50–100%) and TRAP (20–50%) was observed after the oleocanthal meals. in comparison to other meals. The APA of the OO containing 500mg/Kg oleocanthal was comparable to that of the ibuprofen meal. OO meals induced an increase of TBARS measured in both plasma and RBC. The Incremental area under the curve (iAUC) of TBARS in plasma was lower in oleocanthal enriched OO compared to OO. The kinetic activity of GPX3 after BU-IBU consumption was similar with that of OO meals, while the iAUCs of OO meals were greater compared to BU. Regarding GPX1, the kinetic activity was similar after all meals, showing a postprandial increase till t = 120min. The correlation analysis showed that the iAUC of the EC50 for ADP had an inverse correlation with iAUC of TBARS (r- = -0.311, $P = 0.036$). Moreover, positive was the correlation between iAUC of TBARS and iAUC of PC ($r = 0.385$, $P = 0.008$) while negative was the correlation between iAUC of RBC TBARS and LDL (r- = -0.348, $P = 0.019$).
Conclusions
The consumption of meals containing oleocanthal-rich OO can reduce platelet activity and has antioxidant properties, during the postprandial period, irrespective of postprandial hyperglycemia and lipidemia.

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P723

JOINT3311

Oxyntomodulin as a biomarker for metabolic dysregulation and obesity: pathophysiological insights and screening potential

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Background
Oxyntomodulin (OXM), an endogenous peptide derived from preproglucagon, plays a crucial role in energy homeostasis by modulating appetite regulation and glucose metabolism through dual activation of the glucagon-like peptide-1 receptor (GLP-1R) and glucagon receptor (GCGR). Despite its known anorexigenic and metabolic effects, its role in obesity pathophysiology remains underexplored. The present study investigates OXM dynamics in obesity and its potential utility as a biomarker for metabolic dysfunction and obesity-related risk stratification.
Methods
A total of 261 participants were stratified into three groups based on body mass index (BMI): normal-weight controls (CG, $n = 39$), overweight individuals (O1, $n = 88$), and obese individuals (O2, $n = 134$). Comprehensive metabolic profiling was conducted, including an oral glucose tolerance test (OGTT), insulin and C-peptide levels, body composition analysis via DXA/BIA, and serum OXM

quantification using enzyme-linked immunosorbent assay (ELISA). Correlation analyses assessed associations between OXM levels and key metabolic parameters.
Results
Serum OXM levels significantly differed across groups ($p < 0.0001$, ANOVA). The obese group (O2) exhibited significantly higher OXM levels compared to both the overweight (O1, $p < 0.0001$) and control (CG, $p < 0.0001$) groups. While a trend toward increased OXM was observed in overweight individuals (01) compared to controls (CG), this difference did not reach statistical significance ($P = 0.2258$). In the obese cohort, OXM levels correlated positively with fasting insulin ($r = 0.52$, $p < 0.0001$), C-peptide ($r = 0.60$, $p < 0.0001$), and visceral adipose tissue ($r = 0.33$, $p < 0.0001$), suggesting an adaptive response to metabolic stress. However, the increase in OXM was not associated with improved glycemic control, as indicated by a weak positive correlation with HbA1c ($r = 0.25$, $P = 0.0049$).
Conclusion
The findings support the hypothesis that elevated OXM in obesity represents a compensatory response to metabolic dysregulation rather than an effective homeostatic mechanism. The significant differences in OXM between groups, along with its correlation with key metabolic indicators, suggest its potential as a screening biomarker for obesity-related metabolic risk. Further research is warranted to evaluate its predictive value in clinical settings and its potential utility in personalized therapeutic strategies, particularly in the context of OXM-based pharmacotherapies.

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P724

JOINT3587

Weighing the benefits: maternal and fetal health post-bariatric surgery

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Introduction
50-80% of individuals undergoing bariatric surgery (BS) are women of reproductive age. Pregnancies following BS are associated with a higher risk of intrauterine growth restriction (IUGR) and low birth weight (LBW), but lower incidence of macrosomia, preeclampsia, and gestational diabetes (GD).
Methods
Our observational, retrospective study compared maternal-fetal outcomes of women who became pregnant after BS with matched controls based on age and BMI, using data from deliveries at our center between June 2019 and September 2024.
Results
Each group included 51 women, with an average BMI of 30.3 kg/m^2 and an average age of 36 years. Gastric sleeve (68.6%) was the most common procedure in the BS group and resulted in an average 33% weight loss pre-pregnancy. Despite a high rate of nutritional deficiencies (52.9% folic acid, 41.2% iron and 9.8% vitamin B12) and anemia (21.6%), there were no differences in weight gain during pregnancy (12% vs. 14% post-BS, $P = 0.535$), with an average weight gain of 10 kg in both groups. The mean gestational age was also similar between groups (272 days vs. 273 days post-BS, $P = 0.779$), as was the prevalence of preterm births, dystocia, and cesarean sections. There were no significant differences in pre-pregnancy diagnoses of diabetes or hypertension, nor in the need for medically assisted reproduction. Maternal outcomes also showed less frequent need of pharmacological treatment for GD in the post-BS group (RR 0.337, CI 0.13–0.87), while gestational hypertension, preeclampsia, and macrosomia were more prevalent in controls in a not statistically significant way. Neonatal outcomes indicated similar rates of LBW and malformations between groups. However, post-BS newborns had lower birth weights (3051g vs. 3231g, $P = 0.162$) and higher IUGR risk (RR 2.11, CI 1.71–2.60).
Conclusion
Post-BS pregnancies showed reduced prevalences of hypertensive disorders, macrosomia and need for GD treatment but increased risks of IUGR, emphasizing the need for specialized prenatal care.

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P725

JOINT449

Rhein induces adipose browning via inhibition of glucocorticoid receptor

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The existing anti-obese therapies mainly target to cut down the energy intake, which is often associated with neuro-endocrine side effects[2]. On the other hand, therapies to safely augment energy expenditure are lacking. Compelling evidence have shown that activation of adipose browning is sufficient to confer protection against a panel of metabolic disorders including obesity, diabetes and cardiovascular diseases. Here we found that rhein, the major component in the traditional Chinese medicine Rhubarb, robustly increased energy expenditure and adipose tissue browning in obese mice. Further analysis showed that Rhein-induced energy expenditure was mainly orchestrated through SIRT1 in adipocytes, as adipocyte-selective deletion of Sirt1 gene almost completely mitigated Rhein-induced effect on enhancing adipose energy expenditure. By pull-down assay, ARGLU1, a transcriptional co-regulator of glucocorticoid receptor, was identified as a protein that directly binds with rhein in adipocytes. Rhein-induced adipocyte browning was abolished *In vitro* upon overexpression of ARGLU1. Furthermore, in mice receiving glucocorticoid, supplementation of rhein rescued glucocorticoid-induced obesity, insulin resistance, and most importantly impairment of adipose browning. In conclusion, here we unravel the new mechanism underlying the anti-obese effect of rhein, which is achieved through modulating the activity of glucocorticoid receptor.

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P726

JOINT1167

Effects of maternal pre-pregnancy body mass index and gestational weight gain on body composition and blood sugar in three-year-old offspring

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Introduction
Maternal pre-pregnancy Body Mass Index (BMI) and gestational weight gain (GWG) are associated with outcomes for the mother and her offspring. A high maternal pre-pregnancy BMI is associated with increased risk of childhood obesity and excessive GWG is associated with higher neonatal body fat and birth weight as well as metabolic outcomes as Hemoglobin A1c (HbA1c). We aimed to explore the association between maternal pre-pregnancy BMI and offspring BMI z-scores at three years of age. We also explored the associations between GWG and 1) offspring body fat percentage (BF%) measured using Dual-energy X-ray Absorptiometry (DXA) and 2) offspring HbA1c at three years of age.
Methods
FitKids is a follow-up study on three-year-old offspring from pregnant women, who participated in a randomized controlled trial, FitMum, conducted at North Zealand Hospital, DK, from 2018-2021. 68 children (39 boys) with a mean age of 3.3 (SD 0.2) years participated in FitKids. BMI z-scores were calculated for all children, 53 children were DXA-scanned and 38 provided blood samples. Maternal pre-pregnancy BMI was calculated. Estimates of GWG for a standardized pregnancy period were predicted using a model based on longitudinally observed body weights during pregnancy and at admission for delivery. Associations between maternal GWG and offspring BF% and HbA1c were analyzed using linear regression analyses. The same applied for the association between maternal pre-pregnancy BMI and offspring BMI z-score at age three. All models were unadjusted.
Results
Mean pre-pregnancy BMI was 26.4 kg/m^2 (SD 5, 7) and mean GWG was 15.2 kg (SD 6.0). Mean offspring BF% was 25.8% (SD 3.4) and mean offspring HbA1C was 33.7 (SD 2.5). We found an association between maternal pre-pregnancy BMI and offspring BMI z-score at age three (slope 0.046, $P = 0.028$). There was

neither an association between maternal GWG and offspring BF% at three years of age (slope 0.075, $P = 0.394$) nor an association between maternal GWG and offspring HbA1c (slope 0.027, $P = 0.179$.

Conclusion

A higher maternal pre-pregnancy BMI was associated with a higher BMI z-score at three years of age. Maternal GWG did not affect offspring BF% or HbA1c at three years of age.

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P727

JOINT717

Serum and liver lipidome following empagliflozin administration for six months in a fast food diet mouse model

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Empagliflozin is a sodium-glucose co-transporter inhibitor approved for the treatment of type 2 diabetes mellitus. The aim of this study was the 6-month effect of empagliflozin on serum and liver lipidome in C57BL/6J mice (EMPA group) fed on fast food diet (FFD) compared with a group fed on FFD without empagliflozin (FFD group) and another control group fed on a chow diet (CD group). Following untargeted lipidomics analysis, FFD and EMPA groups displayed similar serum lipid profiles, characterized by elevated levels in most of the identified lipids, particularly glycerophospholipids, compared to the CD group. Conversely, hepatic lipid profiles varied more significantly between the groups. For example, phosphatidylcholine (PC), phosphatidylinositol (PI), and phosphatidylglycerol demonstrated mixed trends in the FFD and EMPA groups compared with the CD group. FFD appears to have a more substantial impact on lipidomic profiles compared with the preventive empagliflozin effect (CV ANOVA = 3.43×10^{-6} FFD vs. CD; 7.67×10^{-7} EMPA vs. CD; 2.00×10^{-2} EMPA vs. FFD). Interestingly, several glycerophospholipids, including PC 34:1, PC 35:1, PC 36:3, PC 38:4, PI 34:2 and PI 38:3, increased in both serum and hepatic tissues of the FFD and EMPA groups compared to the CD group. In conclusion, EMPA had largely similar lipidomic profile compared with FFD. However, both EMPA and FFD groups showed distinct lipidomic profiles compared to the CD group.

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P728

JOINT3120

Single point insulin sensitivity estimator (SPISE) for cardiovascular risk assessment in pediatric central nervous system cancer survivors (PCNSCSs): a practical approach for early detection

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Background

The long-term cancer survivors has increased, but the effects of therapies require attention. PCNSCSs are at risk for insulin resistance (IR) and cardiovascular (CV) complications. IR can be detected by a simple and reproducible method called SPISE.

Methods

We assessed SPISE in 57 PCNSCSs (27 males), median age 12 years (5-18), followed for at least two years post-treatment. Diagnoses included astrocytic (37%), embryonal (23%), sellar (14%), ependymal (14%), and germ cell (12%) tumors. Treatment involved radiotherapy (88% of patients, 37% craniospinal), chemotherapy (75%), and surgery (74%). We analyzed body mass index (BMI), waist/height ratio (WHtR), laboratory exams, and DXA. BMI $>$ 1 SDS defined overweight (40% of patients), BMI $>$ 2 SDS obesity (12%), WHtR $\geq$ 0.5 CV risk. SPISE was calculated as: 600 $\times$ HDL cholesterol^0.185/triglycerides^0.2 $\times$ BMI^1.338, fat/lean mass (FLR) by DXA.

Results

A WHtR $\geq$ 0.5 was found in 53% of PCNSCSs. Patients with WHtR $\geq$ 0.5 had higher BMI SDS values (1.33 [0.83; 2.02] vs. -0.04 [-0.71; 0.5], $p < 0.001$) and lower SPISE values (6.98 [5.15-8.50] vs. 10.60 [8.75-11.28], $p < 0.001$). SPISE was associated with WHtR $\geq$ 0.5 (Or = 0.626, 95% CI [0.462-0.848], $P = 0.003$), with an AUC of 0.81 ($p < 0.001$) for predicting WHtR $\geq$ 0.5. The optimal SPISE cut-off was 8.63 (sensitivity = 78%, specificity = 79%). PCNSCSs with SPISE $\leq$ 8.63 (51%) had higher FLR values (0.77 [0.57; 0.93] vs. 0.58 [0.36; 0.72], $P = 0.002$) and higher WHtR (0.52 [0.49; 0.57] vs. 0.47 [0.42; 0.49], p $<$. 001). Those with WHtR $\geq$ 0.5 had higher FLR values (0.86 [0.63; 0.94] vs. 0.54 [0.36; 0.74], $P = 0.001$), with FLR associated with WHtR $\geq$ 0.5 (Or = 61.9, 95% CI [4.73-811.0], $P = 0.002$). ROC curve analysis identified FLR $>$ 0.86 as a threshold for altered body composition (AUC = 0.77, $P = 0.001$, sensitivity = 53%, specificity = 93%). SPISE was associated with FLR $>$ 0.86 (Or = 0.56, 95% CI [0.42-0.75], $p < 0.001$), and its AUC for predicting FLR $>$ 0.86 was 0.82 ($p < 0.001$).

Conclusions

SPISE association with higher WHtR and FLR, indicates its valuable and non-invasive tool for identifying CV risk. SPISE requires few universally available laboratory data, and could be a useful tool for longitudinal studies in PCNSCSs. Furthermore, it may help to optimize resource allocation by prioritizing DXA for patients with low SPISE and high WHtR.

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P729

JOINT960

Real-world results of genetic testing and performance of clinical criteria for familial hypercholesterolemia in a targeted young adult population

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Background

Familial hypercholesterolemia (FH) is a common inherited disorder that significantly contributes to atherosclerotic cardiovascular disease (ASCVD). In Asia, limited access to genetic testing often necessitates the use of clinical criteria, such as the Simon-Broome (SB) or Dutch Lipid Clinic Network (DLCN) criteria, to identify FH. Younger adults, who typically have fewer metabolic comorbidities, are more likely to be diagnosed with FH. However, the accuracy of these criteria compared to genetic testing in younger adults remains unclear. This study assessed the performance of SB and DLCN criteria against genetic testing for FH in individuals under 25 years.

Methods

Between May 2021 and June 2024, 40 individuals under 25 years who underwent genetic testing for FH at a single institution were included. Retrospective data collection covered demographic (age, gender), anthropometric (BMI), clinical (physical stigmata of FH, family history of premature ASCVD), and biochemical (lipid profiles) parameters. Genetic testing results were classified as "positive" (pathogenic/likely pathogenic variants) or "negative" (VUS, benign, likely benign, no mutation). The diagnostic performance of SB, DLCN, total cholesterol (TChol), and LDL-C criteria was evaluated using receiver operating characteristic (ROC) curve analysis.

Results

Nineteen individuals (47.5%) tested positive for FH, with all carrying heterozygous mutations; 17 had LDLR gene variants. There were an additional 7 individuals with variants of uncertain significance (VUS). No significant differences were observed in age, gender, BMI, or comorbidities between test-positive and test-negative groups. While a higher proportion of test-positive individuals had a family history of premature ASCVD (36.8% vs 14.3%), this was not statistically significant ($P = 0.100$). Test-positive individuals had significantly higher median TChol (8.30 mmol/l vs 7.55 mmol/l, $P = 0.012$) and LDL-C (6.53 mmol/l vs 5.43 mmol/l, $P = 0.002$). ROC analysis showed AUCs of 0.866 for DLCN, 0.818 for SB, 0.791 for LDL-C, and 0.733 for TChol. DLCN $>$5 points achieved 94.7% sensitivity and 71.4% specificity, whilst raising the cut-off to $>$7 points improved specificity to 76.2% without changing sensitivity. SB "possible FH" had 89.5% sensitivity but lower specificity (57.1%). An LDL-C cutoff of $>$5.45 mmol/l provided the same sensitivity and specificity as SB.

Discussion
In our cohort of young adults, traditional FH criteria performed well but offered limited advantages over lipid levels alone. The low prevalence of physical signs and family history in this age group reduces the utility of SB and DLCN criteria. LDL-C thresholds alone may serve as a simpler and effective tool for FH detection in young Asian populations.

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P730

JOINT2737

Distinct response of the human plasma lipidome to cold and fenoterol

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Background/Objective
Brown adipose tissue (BAT) plays a crucial role in thermoregulation. Upon cold exposure, the sympathetic nervous system releases norepinephrine, which activates β-adrenergic receptors (β-AR) on brown adipocytes. This activation stimulates lipolysis, leading to the release of free fatty acids that serve both as activators of uncoupling protein 1 (UCP1) and as substrates for mitochondrial oxidation, thereby generating heat. Recent research has indicated that β_2-AR stimulation could activate human BAT. Here, we analysed the changes in lipidome in response to cold-exposure and β_2-adrenergic stimulation with the selective agonist fenoterol.
Methods
We performed a cross-over, randomized trial in twelve healthy volunteers (seven men and five women). We determined resting energy expenditure (REE) using indirect calorimetry once before and after a mild cold stimulus and in a further visit before and after a continuous fenoterol injection (145 µg). Both interventions were performed over 2 hours. Blood sampling to obtain serum for later metabolome analysis by gas chromatography-mass spectrometry (GC-MS) was performed at every visit.
Results
Our study demonstrates that both fenoterol and mild cold exposure significantly increased REE in humans: before fenoterol 1502±281 kcal/24h, after fenoterol 1860±305 kcal/24h ($P < 0.0001$); before cold 1516±347 kcal/24, after cold 1712±270 kcal/24h ($P = 0.02$). Both interventions led to a distinct change in plasma lipid levels. Specifically, fenoterol infusion induced a marked increase in free fatty acid (FA) levels; with FA 18:3 ($_{log2}$FC = 1.21, $P = 4 \times 10^{-8}$), FA 20:3 ($_{log2}$FC = 0.76, $P = 1.2 \times 10^{-7}$), FA 14:0 ($_{log2}$FC = 0.82, $P = 5.6 \times 10^{-7}$), FA 20:2 ($_{log2}$FC = 0.73, $P = 7.3 \times 10^{-7}$) and FA 12:0 ($_{log2}$FC = 0.78, $P = 8 \times 10^{-7}$). In contrast, cold exposure led to a more nuanced increase in FA levels; with FA 18:3 ($_{log2}$FC = 0.46, $P = 0.007$), FA 14:0 ($_{log2}$FC = 0.34, $P = 0.008$) and FA 22:6 ($_{log2}$FC = 0.44, $P = 0.009$). In contrast to fenoterol, the most regulated lipids after cold exposure were lysophosphatidylcholines which were reduced; LPC 18:2 (log2FC = -0.29, $P = 7.7 \times 10^{-5}$), LPC 18:1 ($_{log2}$FC = -0.18, $P = 2.1 \times 10^{-4}$) and LPC 18:3 ($_{log2}$FC = -0.15, $P = 2.8 \times 10^{-4}$).
Conclusion
Both cold exposure and stimulation of the β_2-AR increase lipolysis and REE in humans. Our findings indicate that enhanced lipolysis is a key mechanism driving β_2-AR-stimulated thermogenesis. However, the distinct lipidomic profile points towards different molecular mechanisms in response to cold.

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P731

JOINT2480

Evaluation of the relationship between IGF-1 and systemic immune-inflammatory markers and metabolic comorbidities in patients with obesity

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Background
Obese individuals can exhibit normal or high IGF-1 levels. The relationship between IGF-1 levels and body mass index (BMI) is not clear. Inflammatory changes and various metabolic features in obese patients may explain this difference. The clinical features of obese patients with low IGF-1 levels are important. It was suggested that obese people with low IGF-1 levels may have more adiposity, inflammation, and metabolic problems like dyslipidemia and hyperuricemia. Obese individuals are known to exhibit a chronic low-level inflammation state. Systemic immune-inflammatory markers are new markers that indicate chronic subclinical inflammation in various diseases. The neutrophil/lymphocyte ratio (NLR), the platelet/lymphocyte ratio (PLR), the lymphocyte/monocyte ratio (LMR), the systemic immune-inflammation index (SII), the systemic inflammatory response index (SIRI), and the systemic inflammation aggregate index (SIAI) are some of these indicators. Obese individuals have demonstrated high levels of SII, NLR, and PLR. This study aimed to evaluate the relationship between IGF-1 levels and systemic immune-inflammatory markers with metabolic comorbidities in patients with obesity.
Methods
We examined 210 obese subjects with a BMI $\geq$ 35 kg/m^2. For each age and gender, a standard IGF-1 standard deviation score (SDS) was used to figure out what the IGF-1 levels meant (low IGF-1 group: ≤ -2.0 SDS and standard IGF-1 group: -2.0 and $+2.0$ SDS). We recorded demographic characteristics, BMI, blood pressure, hypertension, diabetes, hyperuricemia status, NLR, PLR, LMR, SII, SIRI, and SIAI values.
Results
In this study, 7.62% of the subjects had low IGF-1 levels. NLR and SII were significantly higher in the standard IGF-1 group compared to low IGF group. Low IGF-1 levels do not correlate with systemic inflammatory markers. SII was found to be correlated with systolic blood pressure, ALT, and insulin levels. SIAI was correlated with systolic blood pressure. Rate of hypertension was higher in the low IGF 1 group. Low IGF-1 levels were not associated with diabetes and hyperuricemia.
Conclusion
This study is the first to demonstrate the relationship between IGF-1 and immune-inflammatory markers in obese patients. These results suggest that low IGF-1 levels may not be associated with increased inflammation and metabolic disorders in obese patients. Some of these markers were low in the low IGF-1 group, which may explain why metabolic complications were less common in this group.

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P732

JOINT1640

The french prader-willi registry: an essential tool for clinic and research on prader-willi syndrome

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Introduction
Since 2023, the French Reference Centre has developed a new tool for the national registry for children diagnosed with Prader-Willi Syndrome (PWS), based on the "old database" on Access® created in 2005 for children. This new registry was designed as a prospective follow-up of children from birth to 18 years. Physicians first filled the neonate medical sheet and collect signed informed consent from parents. After a multidisciplinary discussion of the neonate situation the patient is included in the data base after approval by the coordinator of the national centre for PWS. This procedure has been set-up after the first clinical trial with oxytocin (OXT) in neonates with PWS in 2017 and is now part of routine care. The procedure allows to have all newborns included in the registry and optimizes the access to compassionate use of OXT for neonates with PWS obtained in 2021 in France. In order to have the best chance to have complete and high quality data we chose to keep patients included in the "old data base" born since 2010 and not before.
Methods
The first step was to collect data from birth to 4 years on medical aspects comprising pregnancy, birth, development, diagnosis, comorbidities, treatments, clinical, radiological and biological results, socio-demographic and family characteristics, in the 408 patients born since 2010. The second step started in 2024 and aimed to add 4 visits to collect data until 18 years including a transition visit. This national registry aims to promote multidisciplinary analyses on current practices in the national network of the reference centre and to take decisions on training, research, treatment and finally improve the registry and patient follow up.

Results
From birth to 4 years, 1994 visits were recorded for 408 patients. Data were collected in 22 French expert centres of the reference centre. After 4 years, visits will be added in the same format at different age-ranges: 7-9 years, 11-13 years, 14-16 years and 16.5-18 years. Specific data linked to the patient's age have been added, especially pubertal data from age 11 and the transition phase before adult follow-up from age 16.5.
Conclusion
This new registry including prospective follow-up of children will allow to improve and facilitate data collection from centres who followed children with PWS and to study the disease trajectories from birth to 18 years. It will also allow to document the effects of treatments in these trajectories.

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P733

JOINT1945

A case of familial monogenic obesity: the role of MC4R mutation in childhood obesity

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Background
Obesity is a multifactorial disease with increasing prevalence in childhood. Severe early-onset obesity, especially with hyperphagia and rapid weight gain, may indicate monogenic causes, such as MC4R-related.This form often leads to metabolic complications and resistance to conventional treatment. Early genetic diagnosis is essential for guiding management and identifying potential therapeutic targets.
Case report
We describe two male siblings, born at term and appropriate for gestational age to non-consanguineous parents, who developed severe early-onset obesity. The first sibling was evaluated at 1.4y due to hyperphagia, excessive weight gain, and accelerated growth from 6 months of age. He had no medication use or neuropsychomotor delay. At initial assessment, his weight and height-for-age, and BMI (z-scores) were 33 kg (+3), 88.5 cm (+3.1), and 42.3 (+9.5), respectively. He exhibited acanthosis nigricans on the neck, axillae, and groin, with normal genital examination. Laboratory evaluation revealed elevated triglycerides, reduced HDL, while insulin, calcium profile, and thyroid function were normal. A monogenic etiology was suspected, and a genetic panel with 16 genes related to monogenic obesity was carried out. The results revealed a compound heterozygous *MC4R* variant (c.896C>A; p.Pro299His/c.240C>A;p.Tyr80*). The younger sibling with similar symptoms around 1y. At 1.4y, his weight, height-for-age, and BMI (Zs) were 20.8 (+6.1), 83 (+0.8), and 30.2 (+7.5), respectively. Genetic testing confirmed the same variant. The father had mild obesity (BMI =32.8), and the mother was overweight (BMI =29). Both parents and their younger brother underwent *MC4R* gene sequencing and it was detected the variant c.240C>A in the father and the variant c.896C>A in the mother and in the younger sibling, all of them in heterozygous. Lifestyle modifications and caloric restriction were attempted, without success. After loss to follow-up, the patients currently have weight and BMI (z-scores) of 88.6 kg/56.25 (+11.1) and 45.9 kg/39.5 (+10.1) at 4.5y and 3.4y, respectively.
Conclusion
MC4R-related obesity is the most common monogenic obesity and can present in homozygous heterozygous, or compound heterozygous states, with phenotypes ranging from overweight to severe obesity. This variability highlights the need for early genetic investigation in rapidly progressing obesity, as identifying a monogenic cause aids prognosis, optimizes management, and supports family counseling.

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P734

JOINT2746

Association of childhood BMI with height growth pattern and adult stature: mendelian randomization study

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Objective
Observational studies have reported that childhood body mass index (BMI) affects height growth patterns without significantly effecting adult stature. The causal relationship remain unclear. Mendelian randomization (MR)—a genetic instrumental variable approach leveraging Mendel's second law to minimize confounding—was employed to assess causality between childhood BMI and height growth patterns, including pre-pubertal growth (age $\leq$10 years), total pubertal height growth, late pubertal height growth, and adult stature, (standing and sitting height).
Methods
Adhering to the STROBE-MR guidelines. Whole genome-wide association study (GWAS) data were extracted from the MRC-IEU GWAS database (https://gwas.mrcieu.ac.uk). Causal estimates were derived using inverse variance weighting (IVW) as the primary method, supplemented by MR–Egger regression, weighted median, weighted mode, and simple mode analyses. Sensitivity analyses included Cochran's Q test for heterogeneity, MR–Egger's intercept and the MR-PRESSO test for pleiotropy assessment, and leave-one-out SNPs exclusion to evaluate robustness.
Results
MR analyses revealed childhood BMI exhibited a positive causal effect on pre-pubertal height growth ($\beta=0.11$, 95%CI [0.08, 0.13], $P=1.13\times10^{-13}$). But inversely negative correlated with total pubertal height growth (males: $\beta=-0.40$, 95%CI: [-0.61, -0.18], $P=2.64\times10^{-4}$; females: $\beta=-0.61$, 95%CI: [-0.85, -0.36]; $P=9.49\times10^{-7}$), late pubertal height growth (males:$\beta=-0.52$, 95%CI: [-0.75, -0.28], $P=2.46\times10^{-5}$; females: $\beta=-0.45$; 95%CI: [-0.68, -0.21], $P=2.02\times10^{-4}$). No significant link between childhood BMI and adult standing or sitting height. Sensitivity analysis revealed absence of horizontal pleiotropy (MR-Egger intercept $P>0.05$) and outlier SNPs (MR-PRESSO $P>0.05$), with leave-one-out' tests demonstrating results stablity.
Conclusion
This study demonstrates dual-phase effects: positively influencing early childhood height acceleration but suppressing pubertal growth trajectories. These transient effects resolve by adulthood, with no measurable impact on final stature. Findings underscore BMI's role as a modulator of developmental tempo rather than a determinant of adult height.
Keywords Mendelian randomization, Childhood BMI, Height growth pattern, Adult stature

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P735

JOINT2688

Non-high-density lipoprotein cholesterol for screening dyslipidemia in overweight Korean children

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Objectives
Non-high-density lipoprotein (HDL) cholesterol is an alternative method to assess dyslipidemia and is not required fasting. We aimed to assess the usefulness of non-HDL cholesterol for screening dyslipidemia in overweight Korean children.
Subjects and Methods
Total 751 overweight children and adolescents aged 2 to 20 years (268 boys and 483 girls). They were sampled lipid profile without fasting. Dyslipidemia was defined by having one of the followings; total cholesterol $\geq$200 mg/dL, triglyceride $\geq$100 mg/dL or $\geq$130 mg/dL depending on age, low-density lipoprotein (LDL) cholesterol $\geq$130 mg/dL, or HDL cholesterol $<$40 mg/dL. Non-HDL cholesterol $\geq$145 mg/dL was used to detect dyslipidemia. After then, we compared the sensitivity of non-HDL cholesterol to those from the Korean National Health and Nutrition Examination Surveys which was taken at fasting state.
Results
The overall prevalence of dyslipidemia was 52.6%. The prevalence of non-HDL cholesterol level $\geq$145 mg/dL were 18.7% and 17.0% in boys and girls, respectively. Dyslipidemia was found in 94.0% and 85.4% of overweight boys and girls with high non-HDL level, respectively. High non-HDL cholesterol level especially detected high measured LDL-cholesterol level with a sensitivity of 100%, and a specificity of 92.0%, and a sensitivity of 97.8%, and a specificity of 91.3%, in boys and girls ($P<0.001$ and $P<0.001$, respectively). The Sensitivity of detecting high LDL-cholesterol level was higher in using randomly sampled non-HDL cholesterol compared to using fasting non-HDL cholesterol in boys and girls (11.6% vs. 7.3%, $P=0.024$ and 9.1% vs. 8.2%, $P=0.253$, respectively).

Conclusions
Non-HDL cholesterol at random samples appeared to be useful in screening dyslipidemia in overweight children and adolescents. It was easily calculated from random sample not required fasting.

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P736

JOINT736

Mediating role of prepubertal adiposity in the association between breastfeeding and central precocious puberty: a nationwide cohort study

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Background
Previous studies have investigated the possible relationship between breastfeeding and pubertal timing in girls, but evidence in boys is limited and the underlying mechanisms remain to be elucidated. We aimed to examine the effect of breastfeeding during the first 4–6 months of life on central precocious puberty (CPP) in boys and girls, and whether this relationship was mediated by prepubertal adiposity using nationwide cohort in South Korea.
Methods
Children who underwent regular health check-up from National Health Screening Program for Infant and Children at 4–6 months (Exam I) and 66–71 months (Exam Vll) were included. Primary feeding practices were collected from primary caregiver-reported questionnaire during Exam I. Multivariable Cox proportional hazard regression was used to estimated adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for CPP after adjusting for preterm birth, multiple birth, low birth weight, overweight or obesity status in prepubertal age, maternal age at childbirth, gestational diabetes or hypertension, cesarean section, socioeconomic status and residence. Additionally, we performed mediation analysis to investigate the mediating effect of prepubertal adiposity on association between breastfeeding and CPP.
Results
Among a total of 322, 731 children (135, 232 boys and 187, 499 girls), 148, 402 (46.0%) were exclusively breastfed, 112, 738 (34.9%) were formula-fed, and 61, 591 (19.5%) were mixed-fed. In both boys and girls, formula-fed children had the largest risk of CPP (aHR 1.152 [95% CI 1.100–1.207] in boys, aHR 1.583 [95% CI 1.225-2.045] in girls), followed by mixed-fed children (aHR 1.130 [95% CI 1.068–1.195] in boys, aHR 1.440 [95% CI 1.063–1.950] in girls), compared to exclusive breastfed children. Mediation analysis revealed that lack of breastfeeding during early infancy was associated with an increased likelihood of developing prepubertal adiposity, which subsequently elevated the risk of CPP in both sexes.
Conclusion
Breastfeeding during the first 4–6 months of life was associated with a lower risk of CPP in both boys and girls. Prepubertal adiposity significantly medicated the relationship between feeding practices and CPP, highlighting the critical role of early-life nutrition in pubertal timing.

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P737

JOINT606

Pairing obesity medication with health behaviour and lifestyle therapy: a single center experience

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Background
About 30% of children in Europe are living with overweight or obesity. As a chronic and relapsing disease obesity should be treated as early and effective as possible. Health behaviour and lifestyle therapy (HBLT) is the first-line treatment and while effective at changing behavior, produces fairly modest weight loss for most youth with obesity. In addition to established pharmacotherapy, more effective obesity medication (OM) has recently been approved for the treatment of obesity in adolescents as adjunct to HBLT. Pairing HBLT and ongoing OM is a new challenge when striving for a comprehensive and chronic care model in pediatric obesity. This study evaluates the adherence to recommended treatment with HBLT in adolescents receiving OM.
Methods
In this explorative study, adolescents (aged $\geq$11 years) living with obesity and receiving OM were retrospectively analyzed. HBLT before and during OM (specifically liraglutide) was evaluated descriptively. HBLT was defined as intensive multidisciplinary HBLT according to national guidelines, dietary counseling, psychologic counseling, or any kind of HBLT. Moreover, change in anthropometric and cardiometabolic outcomes during OM treatment was evaluated.
Results
In this study, 37 patients with a mean age of 14.7 years were included in the study. Mean treatment duration was 10.3 months. 92% received HBLT before start of liraglutide treatment, while 62% had HBLT during liraglutide treatment. In 43% dose escalation was delayed and 41% discontinued treatment. Gastrointestinal adverse events were reported in 54% and ultimately led to discontinuation of treatment in 38%. Percentage change in BMI from baseline to end of treatment or last follow-up for patients who continued treatment was -2.7% (-0.9 kg/m^2). BMI reduction was greatest in patients who continued OM (-6.24%), whereas patients who discontinued gained 0.13% BMI on average. 28% reduced their BMI by 5%. OM was further associated with improvements in cardiometabolic risk factors.
Conclusion
Liraglutide is highly effective in real world pediatric obesity management. Adherence and coping with side effects are the main barriers to effective treatment. Concomitant HBLT to OM seems essential to strengthen patients' engagement and sustainability. Pairment of OM and HBLT should be a priority in national disease management plans.

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P738

JOINT2342

Perceived self-efficacy in the management of childhood overweight and obesity: a study of hungarian paediatricians

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Background
Childhood obesity represents a critical public health challenge in Hungary, with projections indicating that 45% of children aged 7-19 will be classified as overweight or obese by 2035. Although regulatory measures targeting obesogenic factors are essential, the active involvement of pediatricians in managing childhood obesity is equally important. Physician engagement in weight-related discussions is associated with improved weight management outcomes; however, barriers such as communication uncertainty, time constraints, and a lack of structured protocols can limit these efforts. Self-efficacy—physicians' confidence in their ability to manage obesity-related concerns—plays a critical role in shaping their engagement. Low self-efficacy has been linked to lower adherence to clinical guidelines and diminished engagement in behavioral counseling. Furthermore, implicit weight bias may negatively affect healthcare interactions and outcomes. This study aims to evaluate the perceived self-efficacy of Hungarian pediatricians in addressing childhood overweight and obesity.
Methods
A cross-sectional online survey was administered to 75 pediatricians from three distinct convenience samples. The 10-item Perceived Self-Efficacy Scale was used to assess self-efficacy levels. Correlations between self-efficacy scores and various factors, including years since graduation, workplace setting, and collaboration with healthcare professionals, were analyzed using Pearson's correlation and one-way ANOVA.
Results
A modest yet statistically significant positive correlation was observed between perceived self-efficacy and years since graduation ($r = 0.249$, $P = 0.031$). No

significant difference was found in perceived self-efficacy between workplace types (primary vs. secondary/tertiary care), F(1, 73) = 1.425, $P = 0.236$. However, significant positive associations were identified between perceived self-efficacy and interprofessional collaboration: pediatricians who consulted district nurses during infant obesity screenings ($r = 0.248$, $P = 0.040$) and those who collaborated with school doctors after evaluating overweight children ($r = 0.271$, $P = 0.019$) demonstrated higher self-efficacy.
Conclusion
The perceived self-efficacy of Hungarian pediatricians in managing childhood obesity is positively correlated with clinical experience and collaboration with other healthcare providers. These findings underscore the importance of self-efficacy in fostering physician engagement in obesity management and suggest that promoting professional collaboration and addressing communication barriers could enhance pediatricians' confidence and efficacy in treating childhood obesity.

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P739

JOINT1398

Muscle ultrasound (US) characterization in patients with lipodystrophy and potential metabolic correlates

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Background
Lipodystrophies are a group of rare disorders characterised by loss of subcutaneous adipose tissue with alterations in its function and distribution. From a clinical viewpoint, an early onset of severe insulin resistance, cardiovascular diseases and neuromuscular abnormalities have been documented. To date, neuromuscular manifestations of lipodystrophy are under-investigated. The aim of this study was to investigate muscle ultrasound (US) alterations in a cohort of patients with lipodystrophy and their association with metabolic characteristics. This report presents preliminary results after the initial patients' recruitment.
Methods
This is a monocentric prospective cohort study. Patients underwent muscle US (bilateral brachial biceps and rectus femoris) with the evaluation of the following variables for each muscle group: thickness, cross-sectional area (CSA), US-pattern and echogenicity assessed using Heckmatt scale (1, normal muscle; 2, increase in muscle echogenicity with normal bone echo; 3, moderate increase in muscle echogenicity with decreased bone echo; 4, severe increase in muscle echogenicity with shadowing obscuring the underlying bone echo). For each patient, clinical, metabolic and muscle functional parameters, and cutaneous Advanced Glycation End products (AGEs) were also evaluated.
Results
Five patients with familial partial lipodystrophy (FPLD) (3 patients with type 1 FPLD and 2 patients with LMNA-associated type 2 FPLD) and one patient with congenital generalized lipodystrophy (CGL) were currently included (M/F 1/5; median age 54, IQR 45-62 years; BMI 22, IQR 21-27). Muscle hypotrophy was found only in the patient with CGL, while a condition of normo/pseudohypertrophy was detected in the remaining patients. According to the Heckmatt scale, all patients presented an increased muscle echogenicity (3 patients with score 2 and 3 patients with score 3). Two main different US-patterns have been recognized: A) homogenously increased echogenicity of the entire muscle with partial loss of architectural features, compatible with muscle fibrosis and steatosis (4 patients); B) focal areas of markedly increased echogenicity, oftentimes obscuring bone echo, that could suggest fibrosis with associated inflammation (2 patients). Patients with higher muscle echogenicity (Heckmatt score 3) had higher BMI, fat mass, HbA1c, triglycerides levels and AGEs than subjects with lower muscle echogenicity (Heckmatt score 2). Further, US-pattern B was associated with higher AGEs, suggesting that muscle inflammatory US pattern could reflect systemic inflammation.
Conclusions
Lipodystrophy is associated with specific muscle US alterations that reflects a condition of muscle fibrosis/steatosis, sometimes accompanied by inflammation. These alterations could reflect metabolic dysregulation and systemic inflammation, thus representing an indirect marker of increased cardiovascular risk.

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P740

JOINT1741

Association between body composition, lipid profile, inflammatory markers and fatty acid composition in healthy women: a cross-sectional study

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Background
Oxidative stress and chronic inflammation are major contributors to obesity-related pathologies (cardiovascular, metabolic disorders, cancer). Platelets and composition of their phospholipid membrane play a crucial role in modulating chronic inflammatory. Alterations in platelet membrane fatty acids (FA) leads to increased production of pro-inflammatory or anti-inflammatory mediators.
Objective
Study aimed to investigate the association between body composition, lipids, inflammatory markers and FA composition in healthy women.
Material and Methods
Study included 101 healthy women, median age 36, 95 years. Body composition including fat mass (FM), lean mass (LM) was measured by dual-energy X-ray absorptiometry (iDXA, GE Lunar). Fat mass index (FMI) was calculated (FMkg/height^2). Women were divided into 3 groups based on FMI: fat deficit (FD)(FMI$<$5 kg/m^2), normal fat (NF)(FMI5-9kg/m^2), excess fat(EF)(FMI$>$ 9kg/m^2). Lipids, C-reactive protein (CRP) was measured. FA of platelets phospholipid membrane was analyzed using gas chromatography-mass spectrometry. Each FA was calculated from the total FA amount(100%), counting the percentage of total saturated FA (SFA) (myristic, palmitic, stearic), monounsaturated FA (MUFA) (palmitoleic, oleic, vaccenic, erucic), polyunsaturated FA (PUFA) (omega 3:α-linolenic, eicosapentaenoic, docosahexaenoic, omega 6:linoleic, arachidonic, gamma-linolenic). Statistical analysis included the Mann-Whitney U test and Spearman correlation. The study was approved by the local ethics Committee.
Results
Total FM was 28.82kg[IQR19.87–41.43], total LM was 44.30kg[IQR40.46–48.91]. Platelet membranes contained 78.12%SFA, 19.37%MUFA, 3.97%PUFA. Among SFA palmitic acid was the most prevalent (52.47%); oleic acid was the most common MUFA (7.24%;) and linoleic acid was the predominant PUFA(7.45%). A strong positive correlation was observed between FM and CRB (ρ=0.641, $P < 0.001$); a moderate correlation with triglycerides (ρ= 0.477, $P < 0.001$) and PUFA (ρ= 0.389, $P < 0.001$); a weak correlation with LDL-cholesterol (ρ=0.279, $P = 0.004$) and MUFA (ρ=0.211, $P = 0.036$). FM correlates negatively with HDL-cholesterol (ρ=-0.614, $P < 0.001$) and SFA (ρ=-0.253, $P = 0.012$). A total of 64 (58.7%) of women had EF, 37(33.9%) had NF, 7.3%(8) had a FD. Women with EF had higher LDL-cholesterol(3.30 mmol/l[IQR 2.61-3.67] vs. 2.78 mmol/l[IQR2.29-3.24], $P = 0.032$), triglycerides(1.08 mmol/l[IQR0.74-1.44] vs. 0.73 mmol/l[IQR0.55-0.99], $P = 0.001$), and CRP(1.73mg/l[IQR 0.87-4.75] vs. 0.51mg/l[IQR0.30-0.83], $P < 0.001$), and lower HDL-cholesterol(1.48 mmol/l[IQR 1.26 - 1.70] vs. 1.89 mmol/l[IQR1.72-2.16], $P < 0.001$) levels compared to those with NF. Women with EF had a lower SFAs (76.19%vs.83.43%, $P = 0.028$) and a higher PUFA (5.4%vs.3.1%, $P = 0.003$). MUFA did not differ statistically (20.57% vs. 14.91%, $P = 0.060$)
Conclusions
Women with excess fat exhibited a less favorable metabolic profile, higher LDL-cholesterol, triglycerides, and CRP, lower HDL-cholesterol compared to normal fat women. Total fat mass was positively correlated with CRB, triglycerides, and PUFA, inversely with HDL-cholesterol and MUFA. Women with excess fat had a lower percentage of SFA and a higher percentage of PUFA.

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P741

JOINT1709

Transforming lives: the impact of liver transplantation in treating glycogen storage disease type 1a – a case report

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Glycogen Storage Disease Type 1a (GSD type 1a) is a rare, autosomal recessive disorder characterized by defects in the glucose-6-phosphatase enzyme. Patients

with GSD type 1a can experience severe metabolic complications, including hypoglycemia, hyperlipidemia, hyperuricemia, hypertension, liver dysfunction, hepatomegaly, splenomegaly and hepatic adenomas. Additionally osteoporosis and growth retardation can occur. Liver transplantation has emerged as an effective therapeutic option in cases of metabolic complications. Here, we present a case to emphasize the potential benefits of liver transplantation in GSD type 1a. A 20-year-old male patient was referred to our outpatient clinic for evaluation of persistent hypoglycemia, hypertriglyceridemia, and osteoporosis following a femoral fracture in 2021. He had been diagnosed with GSD type 1a in infancy due to recurrent episodes of hypoglycemia. Despite being managed with amylopectin cornstarch, his metabolic control remained suboptimal. The patient experienced level 1 or 2 hypoglycemia once or twice a week, even with strict adherence to his diet. His triglyceride levels, despite a low triglyceride diet and the use of gemfibrozil 600 mg twice daily, ranged from 700 to 1600 mg/dl. Furthermore, his uric acid level remained elevated at 6.5 mg/dl despite being on daily allopurinol therapy (300 mg). He had ALT of 158 U/l, AST of 161 U/l, GGT of 168 U/l and ALP of 127 U/l. On physical examination, the patient had a height of 158 cm and a weight of 54 kg, with Tanner stage 3 pubic hair and stage 4 genitalia. Serial abdominal MRIs demonstrated multiple stable hepatic adenomas over a two-year period. His Bone Mineral Density (BMD) at L1-L4 was 0.420, with a Z-score of -6.0, confirming the presence of osteoporosis. In January 2024, the patient underwent a living donor liver transplantation as part of his metabolic management. Post-transplant he didn't experience further hypoglycemic episodes. His triglyceride levels decreased to a range of 100-200 mg/dl, and his uric acid level normalized to 6 mg/dl without the need for allopurinol. His liver function tests returned to normal ranges. The patient continues to receive weekly 20, 000 IU of Vitamin D and BMD monitoring is scheduled. Liver transplantation has proven to be an effective therapeutic intervention in patients with GSD type 1a, particularly in managing metabolic complications. In cases where metabolic control cannot be adequately achieved, early liver transplantation should be considered. Further research is necessary to explore and refine treatment strategies for rare metabolic disorders like GSD type 1a.

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P742

JOINT1151

Macrophage glucocorticoid and androgen metabolism influence muscle cell metabolism

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Background
Macrophages play a key role in muscle regeneration following injury, with androgens (testosterone [T] and dihydrotestosterone [DHT]) and glucocorticoids (cortisone [E] and cortisol [F]) influencing anabolic, anti-anabolic, and catabolic muscle metabolism. We have shown that inflammation dynamically regulates glucocorticoid and androgen metabolism in macrophages, and these processes may be dysregulated in inflammatory diseases.
Methods
Primary human macrophages from healthy donors were polarized with TNFα/IFNγ or left unpolarized before treatment with F precursor (E; 100 nmol/l) and DHT precursors (T & A4; 100 nmol/l). Treated macrophages or conditioned media were co-cultured with myotubes and myoblasts derived from healthy human quadriceps. Macrophage F and DHT metabolite synthesis was measured by LC-MS/MS. Myotube thickness (microscopy), muscle metabolism markers (qRT-PCR), cell migration (scratch assay), proliferation (BrdU), and protein synthesis (synthesis assay) were assessed.
Results
Inflammatory-activated macrophages exhibited a distinct regulation of steroid metabolism, increasing cortisol (F) activation from cortisone (E) and dihydrotestosterone (DHT) activation from testosterone (T) and androstenedione (A4). Conditioned media or co-culture with activated macrophages led to reduced myotube fiber size without altering metabolic gene expression. However, conditioned media with T significantly increased fiber thickness ($P < 0.001$). T treatment also decreased myoblast proliferation after 72 hours ($P = 0.0196$) without affecting cell viability. In contrast, conditioned media with E did not affect fiber thickness but significantly reduced myoblast proliferation at 72 hours ($P = 0.0009$). E treatment increased catabolic markers (Foxo1, Fbox32) and decreased the anabolic marker Igf-1. In comparison, T-conditioned media decreased catabolic Foxo1 and anti-anabolic Myostatin (Mstn) and increased the differentiation marker Myod after 24 hours. Direct DHT treatment did not increase protein synthesis rate compared to control and reduced proliferation at 48 hours ($P < 0.05$). F significantly decreased myoblast proliferation at both 48 and 72 hours ($P < 0.0001$). Finally, examination of myoblasts revealed that macrophage-conditioned media enhanced cell migration and proliferation, regardless of T precursor treatment.
Conclusions
Inflammatory-activated macrophages dynamically regulate glucocorticoid and androgen metabolism, influencing muscle fiber size and metabolism. These effects may be altered in chronic inflammatory diseases, potentially impairing muscle regeneration. Further investigation is needed to determine if these processes are dysregulated in inflammatory conditions.

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P743

JOINT2207

The effect of stress resiliency level and maternal diet on the metabolic health of offspring

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Background
The rise in obesity prevalence is influenced by multiple factors, including the transgenerational hypothesis linking maternal obesity to increased offspring obesity risk. Another significant contributor is the stressogenic environment prevalent in Western societies. We have already shown that it is not merely exposure to stressful events that heightens the risk of developing obesity and its comorbidities, but also the subjective response to these stressogenic events (1). Using a specially bred mouse model with distinct stress response traits - vulnerability (Submissive mice, Sub) and resilience (Dominant mice, Dom) - we demonstrated that stress vulnerability exacerbates metabolic disruptions in mice fed a high-fat diet (HFD).
Research Goal
This study aimed to characterize the interactions between maternal diet, offspring diet, and stress vulnerability traits, and to investigate the impact of these factors on offspring metabolic health. A secondary aim was to elucidate the effects of HFD on maternal and offspring behavior.
Methods
Sub and Dom female mice were divided into groups fed either a high-fat diet (HFD) or a standard diet (STD) from four weeks before breeding until three weeks postpartum. Maternal behaviors were assessed through nesting scores during pregnancy and pup retrieval tests postnatally. Offspring were weaned onto STD until six weeks old, then split into STD and HFD groups. Glucose and insulin tolerance tests were conducted at 12 and 13 weeks of age, respectively. Mice were sacrificed for plasma insulin and leptin measurements, along with histological analyses of liver, pancreas, and adipose tissues.
Results
Maternal obesity had differential effects on pre- and post-natal behaviors in Sub and Dom mice, influencing nesting and pup retrieval differently. HFD improved maternal behavior in Sub mice but disrupted it in Dom mice. Maternal obesity adversely affected metabolic health in Sub offspring, resulting in glucose intolerance, insulin resistance, and hyperleptinemia following HFD feeding. Conversely, Dom offspring were largely unaffected by maternal HFD, showing minimal impairment in leptin sensitivity and glucose tolerance, with no impact on insulin tolerance. Adipose tissue weight increased in Dom mice, while liver weight rose significantly in Sub mice after two generations of HFD exposure.
Conclusion
These findings underscore how inherited stress response traits shape metabolic and behavioral outcomes across generations. They highlight the complex interplay between maternal diet, offspring diet, and stress vulnerability in determining obesity-related health outcomes.
Reference
1. Inherited stress resiliency prevents the development of metabolic alterations in diet-induced obese mice. Obesity 2023.

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P744

JOINT1491

Evaluating lipid ratios for cardiometabolic risk and insulin resistance in obese children

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Introduction
It remains essential to identify the most relevant lipid parameter ratios for assessing cardiometabolic risk and insulin resistance in obese pediatric patients. This study aims to determine which lipid ratio best identifies these risks in pediatric patients diagnosed with metabolic syndrome (MetS).
Materials and Methods
This study was conducted in the Endocrine Department of the Children's Hospital in Timisoara, Romania, between January 2018 and December 2024. 215 obese patients (BMI >95th percentile for sex and age), aged 10–16 years, were included. Anthropometric measurements (body weight, blood pressure, and abdominal circumference) and biochemical markers of lipid and glucose metabolism were assessed. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and lipid ratios (TG: HDL-C, total cholesterol: HDL-C, and LDL: HDL) were calculated.
Results
Patients were stratified based on the presence of MetS according to the International Diabetes Federation (IDF) criteria, resulting in 95 patients with MetS (median age: 13.4 years, 40% boys) and 120 without MetS (median age: 12.5 years, 60% boys). The MetS group exhibited significantly higher insulin levels (23.5 μIU/mL [IQR: 14.7–38.5] vs. 16.3 μIU/mL [IQR: 12.7–26.8], $P = 0.03$) and HOMA-IR values (23.3 [IQR: 14.7–38.8] vs. 16.3 [IQR: 12.7–28.8], $P = 0.03$). Lipid ratios were also significantly elevated in the MetS group ($P < 0.01$), including TG: HDL-C (3.7 [IQR: 2.4–5.1] vs. 1.59 [IQR: 1.2–2.43]), total cholesterol: HDL-C (4.0 [IQR: 3.4–4.9] vs. 3.2 [IQR: 2.48–3.78]), and LDL: HDL (2.3 [IQR: 1.9–2.88] vs. 1.88 [IQR: 1.25–2.36]). MetS presence was strongly correlated with HOMA-IR and lipid indices, particularly TG: HDL-C ($r = 0.549$). Logistic regression confirmed TG: HDL-C as a significant predictor of MetS ($P < 0.01$).
Conclusion
The TG: HDL-C ratio is a strong marker for identifying cardiometabolic risk in obese children with MetS diagnosis.

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P745

JOINT3511

Relationship between body mass index and 1 mg dexamethasone suppression test in obese patients

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Background
The dexamethasone suppression test (DST) assesses hypothalamic-pituitary-adrenal (HPA) axis function. Obesity affects cortisol metabolism, but its relationship with body mass index (BMI) and DST response remains unclear. This study examines the association between BMI and 1 mg DST results in obese patients.
Methods
This retrospective study included 352 obese individuals (BMI ≥ 30 kg/m^2) from an endocrinology clinic. Data collected included age, gender, BMI, hip and waist circumference, comorbidities, and laboratory values (ACTH, basal cortisol, and 1 mg DST). DST suppression levels were compared across BMI groups using statistical analyses.
Results
Participants ranged from 18 to 69 years, with a mean age of 40.37 $\pm$ 11.51 years. Of the 352 individuals, 80.7% were female and 19.3% were male. BMI distribution was: 30-39.9 kg/m^2 (18.2%), 40-50 kg/m^2 (57.4%), and >50 kg/m^2 (24.4%). DST suppression levels differed significantly across BMI groups (***P* = 0.038**), with altered DST response in higher BMI categories. ACTH levels also showed significant variations (***P* = 0.018**), while cortisol levels did not (***P* = 0.081**). These findings suggest BMI-related changes in HPA axis function.
Discussion
BMI influences DST suppression and ACTH levels, indicating a potential role in HPA axis dysregulation. The non-linear association suggests that both lower and higher BMI levels contribute to altered DST response. Obesity may affect cortisol metabolism and feedback sensitivity, explaining these variations. However, the lack of significant basal cortisol differences suggests other regulatory mechanisms. Elevated ACTH levels in extreme obesity may represent a compensatory response.
Conclusion
BMI modulates DST suppression and ACTH secretion, with variations in HPA axis function across BMI categories. Further studies are required to understand the physiological mechanisms and clinical significance of these associations.

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P746

JOINT3888

Obesity effect on epicardial fat thickness in children

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Background
Obesity is considered as the most important public health concerns of the current century. Obese children have increased risk for multiple disorders, one of the most important risks is cardiovascular effects and insulin resistance. Epicardial fat, like any other adipose tissue, can contribute to the formation of atherosclerosis and aggravation of IR by increasing free fattyacids and cytokines. The imbalance of cardioprotective and unfavorable adipokines released by the

Table 1: Anthropometric and Endocrine Differences Among BMI Categories

	BMI Class												p
	30-39.9 kg/m^2 ($n = 64$)				40-49.9 kg/m^2 ($n = 202$)				>50 kg/m^2 ($n = 86$)				
	Mean	Min	Max	Std. Dev.	Mean	Min	Max	Std. Dev.	Mean	Min	Max	Std. Dev	
Waist circumference (cm)	116, 56	96	133	8, 15	128, 87	102	160	11, 34	143, 15	118	193	13, 96	**0, 001**
Hip circumference (cm)	125, 23	105	141	6, 93	137, 5	118	198	9, 6	152, 43	128	183	10, 53	**0, 001**
1 mg dst (μg/dl)	0, 79	0, 5	1, 7	0, 29	0, 77	0, 5	2, 7	0, 29	0, 88	0, 5	3, 3	0, 41	**0, 038**
ACTH (pg/mL)	24, 75	6, 5	123	16, 58	22, 04	5, 9	63, 2	10, 74	25, 36	7, 1	58, 5	10, 7	**0, 018**
Cortisol (μg/dl)	15, 04	6, 1	28, 8	5, 52	13, 62	6, 3	27, 7	4, 08	13, 87	6, 7	26, 3	4, 15	0, 081

DST: Dexamethasone suppression test, ACTH: Adrenocorticotropic hormone

epicardial fat is closely associated with the development of coronary arteriosclerosis and other cardiac threats in the obese population.
Objectives
The study aimed to assess the impact of obesity on epicardial fat thickness (EFT) and to identify the risk factors that affect the EFT in this cohort.
Methods
The study enrolled 80 obese children and adolescents compared to 20 healthy controls. Detailed history and examination were studied. Anthropometric measurement and vital signs were assessed. Echocardiography was done for assessment of EFT in the parasternal long axis view. Lipid profile was assessed.
Results
In the current study, 80 obese children were compared to 20 healthy controls. echocardiography showed higher EFT in both obesity groups compared to lean subjects. Female patients and dyslipidemia were associated with increased EFT in obese patients.
Conclusion
Obesity in children can cause early subclinical cardiovascular changes which are prominent through its effect on epicardial fat thickness.

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P747

JOINT392

Limited preventive effects of empagliflozin against metabolic dysfunction-associated steatotic liver disease in a mouse model of fast food diet

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Purpose
Metabolic dysfunction-associated steatotic liver disease (MASLD) is a highly prevalent disease with limited treatment options. The aim of this study was to evaluate the preventive effects of a sodium-glucose co-transporter (SGLT)-2 inhibitor, empagliflozin, on a dietary mouse model of MASLD.
Methods
24 C57BL/6J mice of both sexes were randomly allocated to three groups, as follows: the fast food diet (FFD) group (eight mice, receiving a high-fat, high-cholesterol, high-fructose diet, FFD), the EMPA group (eight mice, fed a FFD with 10mg/kg/d empagliflozin), and the chow diet (eight mice, CD) group. The mice were weighed and blood samples were drawn every 4 weeks; after 25 weeks the mice were euthanized, at which point liver tissues were histologically evaluated.
Results
After 25 weeks, there was no significant difference in body weight between the three groups, whereas liver-to-body weight ratio was greater in the EMPA compared to the CD group ($P = 0.002$). Hepatic fibrosis was marginally different between the three groups ($P = 0.045$). Fibrosis stage 1 was present in five mice in FFD (62.5%), in one mouse in EMPA (12.5%), and in one mouse in CD (12.5%) group. Lipogenic, inflammatory, and fibrogenic genes did not differ between the EMPA and FFD groups. Interestingly, mRNA encoding for SGLT-1 and SGLT-2 was detected in the mouse livers.
Conclusion
Empagliflozin treatment in mice on a FFD did not result in any significant effects on morphological, biochemical, or histological features or on expression of hepatic genes associated with MASLD compared to those fed a FFD without empagliflozin. The observed effects on mild hepatic fibrosis warrant validation, possibly via studies of longer duration.

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P748

JOINT1722

Visceral adipose tissue as an important predictor of TBS

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Introduction
Obesity is a global health problem with rising prevalence. Traditionally, obesity was considered to exert a positive (protective) impact on BMD. However, this augmentation does not confer protection against the risk of fractures, constituting an "obesity paradox". Emerging data indicate that the effect of adipose tissue on bone health is much more complex. Trabecular bone score (TBS) provides information on bone texture and predicts fracture risk independently of BMD. The present study aimed to investigate the association of body composition and bone quality as evaluated by lumbar spine (LS) TBS.
Methods
We included 118 postmenopausal women (mean age: 60.73 ± 8.97years and mean BMI 28.36 ± 5.8) with no history of secondary osteoporosis or previous anti-osteoporotic treatment. Body composition, BMD and TBS were evaluated by dual-energy X-ray absorptiometry (DXA). To explore the associations among the variables of interest, Spearman's correlations were used. Simple and multiple linear regression models were also applied to explore the associations among variables of interest.
Results
Visceral adipose tissue (VAT) mass, android fat mass and android/gynoid fat ratio were negative predictors of TBS (Stb= -0.413, $P < 0.001$; Stb= -0.369, $P < 0.001$; Stb= -0.333, $P < 0.001$, respectively). Similarly, both the right (Stb= -0.313, $P < 0.001$) and left arm fat mass (Stb= -0.313, $P < 0.001$) were negative predictors of TBS. In multiple linear regression model, VAT mass exhibited a significant negative association with TBS (Stb = -0.415, $P < 0.05$).
Conclusions
The present study offers evidence that VAT mass holds a negative association with bone quality as estimated by TBS in postmenopausal women. Thus, it seems that VAT accumulation not only increases the risk of type 2 diabetes, cardiovascular disease, and even some types of cancer but also may lead to the deterioration of bone quality.
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P750

JOINT2729

Nutritional habits and weight perception in childhood cancer survivors: insights for long-term health

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Background
Childhood cancer survivors (CCS) are at an increased risk of obesity, though underlying mechanisms remain unclear.
Aim
To characterize nutritional habits of CCS, compare them to the general pediatric population, and identify differences between normal-weight and overweight/-obese CCS.
Methods
A cross-sectional study comprising 118 CCS (aged 14.8±3.8 years, females = 54%), at least one-year post-treatment (average 7.3±4.1 years). Nutritional habits were assessed using a validated questionnaire including an FFQ component. Results were compared to data from a representative sample of healthy children and adolescents (MABAT survey).
Results
At recruitment, 3.4% of participants were underweight, 60.1% had a normal weight, 27.2% were overweight, and 9.3% were classified as obese, not significantly different compared to the general pediatric population in Israel. Still, compared to MABAT participants, male patients were twice as likely to consider themselves "too fat" (24.5% vs. 11.7%, $P = 0.017$). While total caloric intake was similar, diet composition differed significantly. Protein and fat percentage of energy intake in CCS were significantly (<0.001) higher compared to data from the general population, while carbohydrate percentage of energy was lower in CCS ($P < 0.001$). Fiber intake was lower in male CCS compared to the general population ($P = 0.003$), but not in female CCS. Within the study group, dietary composition was a significant predictor of weight gain over a one-year period from baseline with a higher carbohydrate percentage positively correlated with BMI increase ($r = 0.294$, $P = 0.020$). Eating habits, such as family meals, screen time during meals, and take-out food consumption, did not differ significantly between CCS and MABAT participants. However, within the study cohort overweight/obese CCS were more likely to have a cafeteria/kiosk at school (65.1% vs. 40%, $P = 0.013$) and purchase sweetened beverages during school hours (80% vs. 54.2%, $P = 0.046$). Frequent fast-food consumption (3-4 times per week) was significantly associated with overweight status (66.7% vs. 33.3%, $P = 0.015$), as was meal location, with overweight CCS more likely to eat at friends' homes, restaurants, or alone ($P = 0.015$). Overweight/obese CCS were more likely to feel "too fat" (45% vs. 5.7%, $P < 0.001$), be unhappy with their weight (59.6% vs. 24.3%, $P = 0.003$), and experience food-related distress, yet only 14% sought guidance from a dietitian.
Conclusion
CCS exhibited distinct dietary patterns, with higher protein and fat intake but lower carbohydrate and fiber intake than the general population. Overweight/-obese survivors reported greater body image concerns, weight dissatisfaction, and food-related distress, highlighting the need for targeted nutritional and psychological support.

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P751

JOINT3284

Body composition phenotyping and BIA-DXA agreement for fat mass assessment in pediatric obesity: an exploratory study

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Background
Pediatric obesity is a multifactorial condition characterized by excessive fat accumulation. However, traditional body mass index (BMI)-based classification cannot assess fat mass (FM) or its distribution. Dual-energy X-ray absorptiometry (DXA) is the gold standard for body composition assessment. However, due to its limited accessibility, portable and non-invasive alternatives, such as bioelectrical impedance analysis (BIA), are often used. This exploratory study aimed to describe body composition phenotypes in different types of non-syndromic pediatric obesity and evaluate the agreement between BIA and DXA in assessing FM.
Methods
From September 2024 to January 2025, we performed BIA on patients aged 6–17 years with primary obesity (PO), obesity secondary to tumors now in off-therapy (SO), or genetic obesity (GO), all with BMI > 2SDS and scheduled for DXA. DXA provided percentage of total FM and truncal FM (FMtr), fat mass index (FMI, kg/m^2) and fat-to-lean ratio (FLR), while BIA provided FMI and FLR.
Results
We assessed 64 patients (61% female), of whom 75% had PO, 12.5% had SO, and 12.5% had GO. The median age was 11 years. By comparing PO, SO, and GO groups, significant differences were observed in median height-SDS (0.9 vs. -1.2 vs. -0.3, $P = 0.009$) and BMI-SDS (2.9 vs. 2.3 vs. 3.1, $P = 0.024$). DXA measures revealed significant differences in total FM% (46 vs 48 vs 54, $P = 0.029$) and FLR (0.87 vs 0.94 vs 1.2, $P = 0.028$), whereas truncal FM% (47 vs. 48 vs. 54, $P = 0.092$) and FMI (11.9 vs. 11.8 vs. 14.2, $P = 0.246$) did not differ significantly. BIA measurements showed a significant difference in FMI (10.6 vs. 7.4 vs. 13.9, $P = 0.041$), while FLR (0.59 vs. 0.53 vs. 0.78, $P = 0.081$) was not significantly different. Although a moderate correlation BIA-DXA for FMI was found ($r = 0.682$, $P < 0.001$), Bland-Altman analysis indicated that BIA underestimated FMI compared to DXA, with a mean difference of 1.40kg/m^2 and limits of agreement ranging from -3.34 to 6.16.
Conclusions
Our preliminary findings highlight that pediatric patients with GO exhibit higher FM compared to those with PO and SO, with a distinct fat distribution pattern, characterized by higher FMtr, that may have metabolic implications and thus require further investigation. BIA underestimates FMI compared to DXA, with substantial variability, limiting its use as a method interchangeable with DXA for body composition assessment.

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P752

JOINT3436

Metabolic-associated steatotic liver disease and arterial stiffness in obese children: early cardiometabolic insights - a preliminary study

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Introduction
Metabolic-associated steatotic liver disease (MASLD) is increasingly recognized in obese children and has been linked to early cardiovascular dysfunction. Arterial stiffness, a marker of subclinical atherosclerosis, may serve as an early indicator of cardiovascular risk in this population. This preliminary study explores the relationship between MASLD and arterial stiffness in obese children, aiming to assess potential cardiometabolic implications.

Methods
The study included 50 children aged 6 to 18, divided into two groups: 30 children with obesity (class 2 and 3) and 20 normal-weight controls. Assessments included BMI, waist circumference, waist-to-height ratio, and puberty stage. Arterial stiffness was evaluated using pulse wave velocity (PWV) via a Mobil-O-Graph single-point (brachial) oscillometer. Liver stiffness was assessed by shear-wave elastography (SWE, kPa and m/s) using a Mindray Resona R9 ultrasound system. Serum levels of fasting glucose, insulin, uric acid, lipid profile, triglycerides, transaminases, and 25-OH vitamin D were analyzed, along with HOMA-IR.
Results
Obese children had significantly higher SWE values than normal-weight peers (12.8 kPa vs. 7.31 kPa, $p < 0.001$). PWV was also significantly higher in the obese group (5.1 m/s vs. 4.5 m/s, $P = 0.01$). SWE and PWV correlated positively with BMI, waist circumference, and waist-to-height ratio, with PWV emerging as a significant independent predictor of these markers. Additionally, SWE and PWV were significantly correlated ($\rho = 0.41$, $P = 0.03$), with SWE remaining a predictor of PWV even after adjusting for BMI, waist circumference, and puberty stage. Both SWE and PWV correlated significantly with BP values ($\rho = 0.58$, $P = 0.002$). Regarding biochemical markers, PWV correlated positively with HOMA-IR and uric acid, while SWE correlated with HOMA-IR, triglycerides, LDL-c, and transaminases. Although 25-OH vitamin D was significantly lower in the obese group, no significant correlation was found with SWE or PWV.
Conclusion
Obese children show increased arterial and liver stiffness, suggesting an early link between MASLD and cardiovascular dysfunction. The correlation between SWE and PWV, independent of BMI, indicates that liver stiffness may contribute to vascular impairment beyond obesity alone. Associations with HOMA-IR, uric acid, and lipid markers further highlight the role of metabolic dysregulation. These findings emphasize the need for early hepatic and cardiovascular assessments in obese children to identify those at higher risk for future cardiometabolic complications.

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P753

JOINT2825

SPISE index: a novel predictor for identifying metabolically healthy obesity and cardiovascular risk in obese children

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Objective
Childhood obesity is a major public health issue worldwide, thus understanding its metabolic heterogeneity is crucial. A subgroup called "metabolically healthy obese"(MHO) shows preserved insulin sensitivity and low cardiovascular risk despite excess adipose tissue. The non-invasive tool SPISE index (Single Point Insulin Sensitivity Estimator) [$600 \times HDL^{0,\ 185}/Trigliseridler^{0,\ 2} \times BMI^{1,\ 338}$] stands out as an innovative approach to assess insulin sensitivity. It has been shown to be a predictor for both insulin resistance and the risk of developing glucose intolerance or diabetes. In this study, the clinical utility of the SPISE index in assessing metabolic health parameters will be investigated.
Methods
The SPISE index was calculated in 580 obese children (average age of 11.3 ± 3.2 years). The group classified as metabolically unhealthy obese (MUO) had one or more of the following: fasting glucose ≥ 100 mg/dL, triglycerides ≥ 150 mg/dL, HDL ≤ 40 mg/dL, or elevated blood pressure ($\geq 95^{th}$ percentile). MHO group had normal values for all these parameters. Correlations were analyzed between the SPISE index, MUO criteria, HOMA-IR, ALT/AST, non-HDL, triglyceride/HDL ratio, and inflammatory markers as neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, systemic inflammatory index, and systemic inflammatory response index.
Results
Five-hundred-eighty children were included in the study, with 58.1% girl and 35.4% morbidly obese. Among these, 45.6% were classified as MUO, with 47.5% of MUO children being morbidly obese. Significant differences in BMI SDS and morbid obesity were found between MUO and MHO groups ($p < 0.001$). The SPISE index was significantly higher in the MUO group (4.8 ± 1.2 vs 3.9 ± 1.1, $P = 0.001$). As a metabolic health indicator, the SPISE index showed an AUC of 0.737, sensitivity of 72%, and specificity of 68%, with a cut-off value of 4.21 ($P = 0.0001$). Analyzing metabolic health parameters separately, the SPISE index was significant for identifying lipid (triglyceride > 150 and/or HDL < 40 mg/dL) and glucose (fasting glucose > 100 mg/dL, HOMA-IR > 2.5) disorders ($P = 0.0001$, $P = 0.003$). However, it failed to discriminate subclinic hepatic steatosis (ALT/AST > 1) and hypertension ($> 95^{th}$ percentile) ($P = 0.668$, $P = 0.065$). Independent cardiovascular risk parameters such as BMI SDS ($r = -0.63$, $P = 0.0001$), triglyceride/HDL ($r = -0.50$, $P = 0.0001$), non-HDL ($r = -0.29$, $P = 0.0001$) also showed negative correlations with the SPISE index. Compared to other indices, SPISE was identified as the best marker ($P = 0.001$).
Conclusion
The SPISE index is a best reliable tool for identifying metabolic health disturbances especially disglycemia and dislipidemia in pediatric obesity and serves as a valuable marker for cardiovascular risk. It can be an essential component in early detection and management strategies for metabolic dysfunction in children, particularly in those with obesity

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P754

JOINT965

Successful treatment of two children with POMC deficiency using setmelanotide: a one-year review

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Introduction
POMC deficiency is an extremely rare autosomal recessive disorder caused by biallelic loss-of-function variants in the *POMC* gene. It is characterized by 3 major features: adrenal insufficiency, obesity due to hyperphagia, and red hair. Setmelanotide, a melanocortin-4 receptor (MC4R) agonist, was recently approved as a treatment for reducing hunger and weight in patients with POMC deficiency. Here, we describe the results of one year of treatment with setmelanotide in 2 patients with POMC deficiency.
Method
Two unrelated patients with hypoglycemia during their first days of life, recurring episodes of hypoglycemia later in their first year of life, as well as pale skin and red hair, were suspected to have POMC deficiency. Hormonal evaluation revealed low levels of ACTH, cortisol, and secondary subclinical hypothyroidism. POMC deficiency was confirmed by DNA analysis: a homozygous variant chr2:25391366C>T (hg19) at the splice donor site of intron 1 was detected, and setmelanotide treatment was started.
Results
The patients, a girl aged 9 years, with height SDS 2.9 and BMI SDS 4.0, and a boy aged 8 years with height SDS 3.8 and BMI SDS 4.4, started setmelanotide treatment at 0.5 mg/day. One week later, the dose was increased to 1 mg/day and showed a sharp decrease in appetite on the next day. For the girl, the dose was increased to 1.5 mg/day at Week 28, which was the same dose after one year of treatment. During this period, her BMI SDS decreased from 4.0 to 2.3. For the boy, the dose was increased to 1.5 mg/day at Week 10 and at Week 30 to a further, final, dose of 2 mg/day. After 10 months of treatment, BMI SDS decreased from 4.4 to 3.0 and stayed stable for the two months thereafter. Both patients tolerated the treatment well. They did require increasing doses of glucocorticoids due to hypoglycemia and reported hyperpigmentation of the skin.
Conclusion
Setmelanotide treatment in these patients with POMC deficiency was safe and effective, with a decrease in BMI SDS of 42.5% and 31.8% after one year, respectively. This indicates that setmelanotide can support patients and their families in leading a more normal and active life and help to prevent the development of severe complications caused by obesity.

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P755

JOINT1633

Circulating levels of ghrelin in patients with a rare neurodevelopmental disorder associated with hyperphagia, and/or overweight, and/or obesity – the hogrid study

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Introduction
Hyperphagia, overweight or obesity have been more frequently reported in people with intellectual disability (ID) and in rare neurodevelopmental disorders (NDDs. Amongst these conditions, people with Prader-Willi syndrome (PWS) display a

characteristic nutritional trajectory ranging from anorexia to hyperphagia, leading to early severe obesity. From a pathophysiological perspective, PWS is the only identified genetic cause of obesity associated with hyperghrelinemia. The aim of our HOGRID study is to describe ghrelin levels and hyperphagia in patients followed by centers of the national rare NDDs network "Filière DéfiScience".
Methods
HOGRID is a cross-sectional, non-interventional, national multicenter clinical study. Patients underwent a single study visit during their routine follow-up comprising fasting blood sampling to assess ghrelin levels, clinical examination and completion of a series of questionnaires notably to assess hyperphagia, using the Hyperphagia Questionnaire (HQ). Inclusion criteria were: patients between 3 and 50 years with a rare NDD such as classical syndromic obesity (Bardet-Biedl syndrome, Alström syndrome, Angelman syndrome, Smith-Magenis syndrome, X-Fragile syndrome) and other rare NDD associated with overweight/obesity and/or feeding troubles. In order to compare ghrelin levels we used three "control groups" from our previous published study "PWS" group ($n = 153$), "Obese" group ($n = 49$) and "Lean" group" ($n = 31$). In these groups ghrelin levels were assessed in the same laboratory as in the HOGRID study.
Results
We included 130 patients with a median age of 19.8 years (3 to 47 years), 43% were children ($n = 56$), 54% were boys, 27% were overweight, 59% obese and 14% lean. Total ghrelin levels of the HOGRID population were statistically lower than "PWS" ($P < 0.001$) and "Lean" ($P < 0.001$) groups and similar to those of the "Obese" group. In children, the mean total HQ score ($P = 0.042$) and the mean Hyperphagic Behavior susbscore ($P = 0.008$) were significantly higher in the HOGRID population than in the "PWS" group. In adults, compared with the "PWS" group, there was a trend for a lower total HQ score ($P = 0.053$), and a significantly lower Hyperphagic Behavior ($P = 0.03$) and Severity ($P = 0.046$) susbscores.
Conclusion
We did not find hyperghrelinemia in the HOGRID population, confirming that hyperghrelinemia is specific to the "PWS" group. Children in the HOGRID population seem to display higher hyperphagia than PWS children, which was not observed in adults. This suggests that possibly due to early diagnosis of PWS in the first month of life and early multidisciplinary care, hyperphagia in PWS may be more easily controlled in children than in adults.

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P756

JOINT1077

Prevalence of obesity in swiss children's hospitals: first results from the swisspedgrowth project

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Introduction
Overweight and obesity are a global health concern, affecting one in five schoolchildren in Switzerland. Although body height and weight are routinely measured during clinical visits and recorded in electronic health records (EHRs), these data are rarely used for research. We assessed the prevalence of overweight and obesity in Swiss children with use of EHRs.
Methods
SwissPedHealth is a national data stream of the Swiss Personalized Health Network (SPHN). The nested project SwissPedGrowth analyses data from children visiting hospitals in Basel, Bern, Geneva, Lausanne, Zurich, Luzern, or St. Gallen between 2017–2023. Clinical data warehouses extracted EHRs of in- and outpatients and sent anonymized data to the BioMedIT server for analysis. We included children aged 2–17 years, excluding those with ICD-10 coded diagnoses affecting BMI (e.g. intestinal infections, malignant neoplasms). We cleaned anthropometric data using the growthcleanr algorithm of Daymont *et al.* and calculated BMI using height and weight measurements taken within 30 days of each other. We computed BMI z-scores based on the International Obesity Task Force (IOTF) references, excluding implausible z-scores $<$-5 or $>$5. We calculated the prevalence of obesity among children based on IOTF cut-offs using both the highest z-score of a child ("obese ever") and the mean z-score of a child ("obese on average").
Results
Initial data from Basel, Geneva, and Lausanne contained 38, 588 children (54% boys) aged 2-17 years, with 49, 880 heights and 97, 789 weights. After excluding patients with BMI-affecting diseases (1%), without height and weight (63%), and with implausible BMI values (0.1%), we included 13, 708 children (36%), with a median of 2 (IQR: 1, 5) BMI measurements per child. Based on the highest BMI z-score, 1, 165 (8%) children were classified as obese ever, 2, 305 (17%) as overweight, and 10, 238 (75%) had a normal BMI throughout. Based on the mean z-score, 860 (6%) children were classified as obese on average, 1, 892 (14%) as overweight, and 10, 956 (80%) had a normal BMI. Older children were more often obese than young children (7-17-year-olds: 8% vs 2-7-year-olds: 4%). There was no difference between boys and girls. The prevalence of childhood obesity and overweight was consistent with previous Swiss studies.
Conclusion
SwissPedGrowth demonstrates the feasibility of using EHR data to investigate childhood obesity. Further analyses will explore related factors and examine how obesity is diagnosed and managed in hospitals and primary care (SwissPedHealth-PREPP). SwissPedGrowth provides a framework for future studies on growth and obesity in Swiss children.

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P757

JOINT2468

Metabolic profile of paediatric patients with silver-russell syndrome (SRS) or temple syndrome (TS)

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Introduction and aim
Silver-Russell Syndrome (SRS) and Temple Syndrome (TS) are characterized by severe intrauterine growth retardation (IUGR), making them relevant models within the Developmental Origins of Health and Disease (DOHaD) framework. This concept suggests that fetal programming influences the risk of developing adult metabolic disorders. However, clinical data on metabolic abnormalities in paediatric patients with SRS and TS remain scarce. This study aims to describe metabolic complications in a longitudinal cohort of children and adolescents followed at a specialized reference center for the management of SRS and/or TS.
Methods
A retrospective analysis of longitudinal data was conducted on 33 patients with molecularly confirmed diagnoses (31 SRS, 1 TS, 1 SRS/TS). Data were collected at pre-pubertal age, pubertal age, and one year after discontinuation of growth hormone (GH) therapy. Metabolic parameters assessed included overweight/-obesity, arterial hypertension, and glucose/insulin regulation abnormalities.
Results
The cohort included 33 patients and consisted of 19 boys (58%). At the pre-pubertal stage (median age: 8.3 years), metabolic abnormalities were already present in 5/33 children (15%), despite a median BMI (Body Mass Index) of -1.4 SD [-2.0; -0.9]. At pubertal age (median age: 15.2 years), 8/33 patients (24%) had at least one metabolic abnormality, while 3/33 (9%) had two, despite a median BMI remaining below average (-1.0 SD [-1.5; 0.3]). Glucose dysregulation was the most frequent and early complication, with one case of type 2 diabetes mellitus (T2DM) identified in the pre-pubertal stage and three cases (T2DM, glucose intolerance, and severe insulin resistance requiring metformin) at pubertal age. At pubertal age, 5 patients had arterial hypertension or a blood pressure $>$ 95th percentile, one patient was obese and 2 were overweight. Follow-up one year after GH therapy discontinuation confirmed these findings in the 9 patients still receiving GH at pubertal age.
Conclusion
Despite the small cohort size, this study highlights that children with SRS and/or TS develop metabolic complications from early childhood, even under

specialized follow-up. These abnormalities appear to become more frequent during adolescence but seem independent of GH treatment and excess weight (overweight/obesity).

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P758

JOINT1603

Genetic causes and clinical features identified through a genetic diagnostic programme in cases of early-onset severe obesity

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Introduction
Obesity due to variants in genes in the leptin-melanocortin-4 receptor (MC4R) pathway may benefit from personalised treatments. The aim of this study was to assess the frequency of selected rare genetic disorders in individuals presenting with early-onset obesity using data from the "Rare Obesity Advanced Diagnosis™"(ROAD) genetic diagnosis programme.
Methods
DNA was isolated from buccal swab samples of 72 patients with obesity onset before age 6 and body mass index (BMI) $\geq$ 2.5SD. Whole-exome sequencing (WES) targeted 80 obesity-related genes, including copy number variation (CNV) analysis. Variants were classified as pathogenic (P), likely pathogenic (LP), or of variants of uncertain significance (VUS) per the American College of Medical Genetics (ACMG) criteria.
Results
Of the patients from whom buccal swab samples were taken for DNA analysis, 52 (72.2%) with adequate DNA quality could be included in the study. Of the 52 cases included in the study, 63.5% (n = 33) were female and 36.5% (n = 19) were male, with a mean age of 11.63 years (1.71–19.5 years). Mean BMI was 34.60 (9.62) kg/m^2 and mean SD BMI Z-score was 3.34 (0.89). The mean age at onset of obesity was 2.9 (2.7) years. Genetic analysis identified disease-causing variants in obesity-related genes in 4 (7.7%) cases. According to ACMG criteria, two variants were classified as LP and two as P. One case harbored a homozygous c.1091C>A p.(Ala364Glu) variant in the *BBS4*, another a homozygous c.133_136dup p.(Tyr46*) variant in the *LEPR*, a third a heterozygous c.496G>A p.(Val166Ile) variant in the *MC4R*, and a fourth compound heterozygous variants c.3907C>T p.(Arg1303*), c.2462A>C p.(Lys821Thr) in the *IFT172*. The mean BMI of cases with pathogenic variants was 40.89 kg/m^2, with a BMI SD of 3.58. Additionally, heterozygous variants c.706C>G p.(Arg236Gly) in the *POMC* and c.1405G>A p.(Val469Ile) in the *PCSK1* were identified in 2 (3.8%) cases, which were classified as carriers. Moreover, variants requiring further analysis to confirm clinical significance were identified in 5 (9.6%) cases, and variants in obesity-related genes not yet associated with disease were found in 9 (17.3%) cases.
Conclusion
In 38.4% of patients with early-onset obesity included in the study, VUS/l/lP variants were identified in at least one of the studied genes, including *SIM1*, *SEMA3* family, *PLXNA* family, *POMC, PCSK1, LEPR, SH2B1, NCOA1, BBS* family, *MC4R, MKS1, IFT172, NRP1*, and *DYRK1B*. These findings highlight the diagnostic value of genetic testing in obesity and its potential to guide personalized treatment strategies.

Keywords Early onset obesity, WES, ROAD, MC4R

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P759

JOINT3545

Early use of setmelanotide in severe hypothalamic obesity leads to weight stabilization with a significant improvement in the quality of life

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Background
Hypothalamic obesity (HO) is a severe and treatment-resistant form of obesity resulting from hypothalamic damage, often following brain injury. Setmelanotide, a melanocortin-4 receptor (MC4R) agonist, has shown promise in managing genetic and HO. However, its use in very young children remains limited. We present a case of a 22-month-old boy with severe HO, who demonstrated positive metabolic and neurodevelopmental responses to Setmelanotide therapy.
Case Presentation
A 22-month-old boy with a history of fulminant *E. coli* sepsis and meningoencephalitis, complicated by a brain abscess on day six of life, developed hypothalamic dysfunction leading to severe obesity, alongside global developmental delay, adrenal insufficiency, and central diabetes insipidus. His weight trajectory was uncontrolled despite dietary interventions, reaching 35.8 kg at 22 months with a disproportionately high weight-for-length ratio (SD +11.60). Severe obesity significantly impacted his quality of life, leading to an inability to sleep flat, requiring a seated position due to severe gastroesophageal reflux disease (GERD) and obstructive sleep apnea (OSA). Excess adiposity in the limbs and brain injury resulted in complete immobility, with no head control, inability to sit, turn in bed, or achieve any developmental milestones. He also developed deep skin folds with recurrent infections. His immunological workup revealed lymphopenia and heterozygous variants of uncertain significance in the *TLR3* gene, with a recommendation to avoid live vaccines. Liver enzymes remained elevated (ALT: 221 IU/l, AST: 170 IU/l), secondary to fatty liver disease. Cholesterol levels were also elevated, indicating dyslipidemia as an additional metabolic concern. Given the severity of his HO, he was started on Setmelanotide {add dose and titration) at 22 months of age. Following initiation, weight stabilization was achieved with a reduction in the rate of weight gain and a drop in the weight-for-length SD (+11.11). Additionally, he exhibited markedly significant motor and social development improvements, including increased arm and hand movements, head-turning, vocalization, emotional expression, and greater interaction with family members. Biochemical improvements were also observed, with a decline in liver enzyme levels (ALT and AST) and a reduction in cholesterol levels, indicating improved metabolic health. No side effects were observed except for mild skin pigmentation.
Conclusion
This case highlights the potential role of Setmelanotide in the early treatment of severe debilitating HO, particularly in very young children. The observed metabolic stabilization, coupled with neurodevelopmental improvements, underscores the need for further studies on the early use of MC4R agonists in pediatric patients with early-onset HO.

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P760

JOINT3605

Metabolic associated fatty liver disease (MAFLD) in patients with cushing syndrome

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Introduction
Cushing's syndrome (CS) presents with various metabolic disturbances including Metabolic Associated Fatty Liver Disease (MAFLD). Glucocorticoids contribute in MAFLD pathogenesis through insulin resistance, adipose tissue lipolysis and hepatic lipogenesis, decreased fatty acid β-oxidation, upregulation in hepatic expression of 11β-HSD1 and decreased activity of 5α-reductase. The aim of our study was to evaluate the prevalence of MAFLD in a cohort of CS patients before and after remission of hypercortisolemia.
Materials and Methods
This is a single-center retrospective study of 101 patients with CS. Their follow up was at the Department of Endocrinology of Evangelismos General Hospital in Athens between 2017 and 2023. MAFLD was estimated using the Hepatic Steatosis Index (HSI) and the Fatty Liver Index (FLI). Hepatic steatosis index > 36 and Fatty Liver Index >60 were categorized with point 3 and indicated a high possibility of MAFLD. Demographic and clinical characteristics of patients were recorded.
Results
101 patients (90 females) with CS were identified. Their mean age±SD at the time of CS diagnosis was 51±14 years. 44/101 (43.5%) were diagnosed with adrenal CS and 57/101 (56.4%) with pituitary CS. Their mean BMI±SD was 32±9 kg/m^2. At diagnosis 23/44 (52.3%) of adrenal CS and 17/57 (29.8%) of Cushing's Disease (CD) patients had type 2 diabetes mellitus. 35/44 (79.5%) of adrenal and 31/57 (54.4%) of CD patients were hypertensive. An Hepatic Steatosis Index of 3 was estimated in 81/101 (80.2%), [34/44 (77.3%) with adrenal and 47/57 (88.5%) with CD]. A Fatty Liver Index of 3 was calculated in 68/101 (67.3%), [33/44 (75%) with adrenal and 35/57 (61.4%) with CD]. At last follow up 83/101 (82.2%) [38/44 (86.36%) with adrenal and 45/57 (78.9%) with

CD] were in remission from hypercortisolemia. Their mean BMI was 26 ± 6 kg/m^2. An Hepatic Steatosis Index of 3 was estimated in 56/101 (55.4%) [25/44 (56.8%) with adrenal and 31/57 (54.3%) with CD], while a Fatty Liver Index of 3 was calculated in 25/101 (24.7%), [10/44 (22.7%) with adrenal and 15/57 (26.3%) with CD]. MAFLD markers did not differ significantly between adrenal and CD patients and they improved significantly after remission of hypercortisolemia- for HSI, *P*-value: < 0.01; for FLI, *P*-value: < 0.01-. Therapeutic modality was not a significant prognostic factor.

Conclusion

We found a high prevalence of MAFLD in our cohort of CS patients based on HSI and FLI with no significant difference between adrenal and CD patients. Remission of hypercortisolemia improved significantly MAFLD and treatment modality was not a prognostic factor.

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P761

JOINT2082

The influence of body mass index and physical activity on menarche: a comparative study between regular and boarding school students

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Background

Menarche is influenced by various factors, including body mass index (BMI) and physical activity (PA). This study aims to compare menarche, BMI, and PA among female students in regular and boarding schools to identify potential differences in these variables.

Methods

A total of 190 female students participated in this study—63 from a regular school and 127 from a boarding school. Data on BMI, menarche, and PA levels were collected. Normality tests indicated that BMI and menarche data were not normally distributed ($p < 0.05$); therefore, Spearman's rank correlation was used for analysis. The Mann-Whitney test was conducted to compare BMI, menarche, and PA levels between school environments.

Results

The findings revealed a significant correlation between BMI and menarche ($P = 0.012$, $r = -0.182$), indicating that students with higher BMI tend to experience earlier menarche. However, no significant correlation was found between PA and menarche ($P = 0.361$, $r = 0.067$). Additionally, there was a statistically significant difference in menarche ($P = 0.010$) and BMI ($P = 0.004$) between regular and boarding school students. Boarding school students exhibited a higher BMI and experienced menarche at an older age. No significant differ was found in PA levels between the two groups ($P = 0.181$).

Conclusion

The study highlights a significant relationship between BMI and menarche, with a higher BMI being associated with earlier puberty onset. Boarding school students had higher BMI and later menarche compared to regular school students. However, PA levels did not significantly differ between the two groups or influence menarche. These findings suggest that BMI plays a more substantial role in determining menarche timing than PA.

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P762

JOINT2866

Evaluation of pulse wave velocity as early indicator of vascular damage in children and adolescents with heterozygous familial hypercholesterolemia

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Background

In recent years, pulse wave velocity (PWV) becomes a simple, non-invasive, reliable and reproducible method for determining arterial stiffness. In adults, PWV is already a well-established predictor of cardiovascular disease (CVD) and, recently, it has been used also in childhood. Children with heterozygous familial hypercholesterolemia (heFH) are at risk of premature atherosclerosis. Aims of this study were: (a) to evaluate PWV in a group of children and adolescents affected by heFH in comparison to internationally established age-specific references (1, 2), and (b) to identify predictive negative factors influencing PWV in the same cohort of patients.

Methods

This is descriptive and cross-sectional study. Physical examination, plasma lipid profile and PWV were measured in all patients at diagnosis of heFH (all untreated). PWV was measured with an oscillometric device (Vicorder). Values of PWV above the 95th percentiles were classified as elevated (1, 2).

Results

In heFH children (n. 22, 10 males, mean age 9.60 ± 4.15 years, mean total cholesterol 306.54 ± 32.66 mg/dl, LDL-cholesterol 218.28 ± 41.52 mg/dl, BMI-SDS 0.21 ± 1.14 kg/m^2, mean systolic blood pressure percentile 49.09 ± 38.83), mean PWV was 4.52 ± 0.65 m/s (range 3.50-5.80 m/s) and did not differ between gender (girls vs. boys: PWV 4.30 ± 0.54 vs. 4.79 ± 0.70 m/s, p 0.09; age 8.87 ± 4.88 vs 10.47 ± 3.16 years, p 0.24; systolic blood pressure percentile 53.83 ± 34.54 vs. 43.40 ± 44.63, p 0.40). According to international references (1, 2), the prevalence of elevated pulse wave velocity was 32% (7/22; 2 females). Moreover, PWV positively correlated with systolic blood pressure (R 0.43, $p < 0.05$), mainly in males (R 0.81, $p < 0.05$).

Conclusions

In literature, data on PWV in heFH children and adolescents are still scarce. Our study supports that arterial stiffness occurs early and more frequent in asymptomatic heFH children indicating a subclinical increased risk for premature CVD and reflecting the need for early initiation of anti-cholesterolemic treatment. Moreover, our data point out that, even during the first decades of life, not only hypercholesterolemia, but also clusters of pro-atherogenic conditions, such as hypertension, could affect PWV.

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P763

JOINT1022

The association of ciruculating spexin, obesity, and metabolic parameters in Korean children and adolescents

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Background

This study aimed to determine the correlation between circulating spexins, obesity, and metabolic parameters in children and adolescents in South Korea.

Methods

This single-center study included 128 Korean children and adolescents: 65 (50.8%) were obese, 47 (36.7%) were overweight, and 16 (12.5%) were normal weight. Metabolic parameters were measured, including fasting blood glucose, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and lipid profiles.

Results

Spexin levels were significantly lower in obese children than in controls (mean 163.1 vs. 198.4 pg/mL; $P = 0.01$). Spexin levels were lower in the IR group than in the non-IR group (mean 145.3 vs. 185.1 pg/mL; $p < 0.001$). Spexin levels were not associated with sex or pubertal stage. Spexin levels were negatively correlated with BMI SDS ($r = -0.30$; $p < 0.001$), systolic BP ($r = -0.33$; $p < 0.001$),

fasting insulin ($r = -0.41$; $p < 0.001$), HOMA-IR ($r = -0.42$; $p < 0.001$), TG ($r = -0.38$; $p < 0.001$), and plasma leptin levels ($r = -0.26$; $P = 0.004$). Multiple linear regression analysis indicated that after adjusting BMI SDS, plasma spexin levels were independently associated with HOMA-IR ($P < 0.001$) and TG ($P < 0.001$). Mediation analysis indicated that the effect of BMI SDS on HOMA-IR was partially mediated by spexin levels.

Conclusions

This study demonstrated an association between plasma spexin level, obesity, and insulin resistance in Korean children and adolescents.

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P764

JOINT1689

?ral administration of Crocus sativus tepals extract improves systemic glucose tolerance in mice fed a high-fat diet through changes in gut microbiota composition

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The stigmas of *Crocus sativus* (Cr), known as saffron spice, are recognized as a dietary supplement for the treatment of obesity and type 2 diabetes due to their potent antidiabetic, hypolipidemic and antioxidant potential. Recently, the bioactive components of Cr tepals, which are wasted during saffron production, have also been shown to have significant hypoglycemic properties. The use of dietary supplements of herbal origin could affect the composition of the gut microbiota, which influences host energy homeostasis and in the long run affects the prevalence of obesity and related metabolic complications. Therefore, we investigated whether the gut microbiota could play a mediating role in the beneficial effect of Cr tepals extract on systemic glucose tolerance in an animal model of diet-induced obesity. Male C57BL/6J mice were fed a standard diet (10 kcal% fat) or a high-fat diet (60 kcal% fat) for 14 weeks. Mice on the high-fat diet were treated orally with Cr tepals extract for the last 5 weeks of the diet. Biochemical and physiological parameters and an intraperitoneal glucose tolerance test were performed to estimate systemic glucose tolerance. The composition and diversity of gut microbiota was analyzed by 16S rRNA sequencing of bacterial DNA isolated from fecal samples. Gut integrity was assessed by measuring the level of fluorescently labeled (FITC) dextran in blood and by quantifying the level of tight junction proteins by Western blot. Oral administration of Cr tepals extract reduced body mass of obese animals and lowered glucose and insulin levels, as well as the HOMA index, indicating an improvement in systemic glucose tolerance. Greater richness and evenness of the gut microbiota were confirmed by a lower Firmicutes/Bacteroidetes ratio and increased alpha diversity indices. The composition of the gut microbiota shifted towards an increased abundance of the genera *Odoribacter*, *Alistipes*, *Candidatus Saccharimonas* and *Intestinimonas*, which are negatively correlated with insulin resistance and inflammation. The level of FITC-dextran was reduced and the expression of Zonula occludens 1 protein was increased, which led to an improvement of intestinal integrity. Cr tepals extract has a positive effect on gut microbiota composition, compromised by a high-fat diet, by increasing the abundance of bacterial genera that can be associated with the amelioration of glucose tolerance. This beneficial effect could be the result of improved gut integrity and reduced permeability. Our results highlight Cr tepals extract as an effective natural supplement for the treatment of obesity-related metabolic disorders without side effects.

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P765

JOINT1577

Higher BMI as a protective factor for the development of ketotic hypoglycaemia in children with vomiting and dehydration

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Background

Healthy children from 7 months to 7 years are known to be at risk for developing hypoglycaemia during prolonged fasting, particularly during acute illness with decreased oral intake. The aim of our study was to identify additional risk factors for hypoglycaemia in children with acute vomiting and dehydration.

Methods

A retrospective analysis included 560 healthy children and adolescents (aged from 29 days to 17.96 years) without known metabolic disorders admitted to hospital with dehydration due to the acute illness with vomiting or poor oral intake. As potential risk factors of hypoglycaemia historical and anthropometric parameters were evaluated.

Results

One hundred seventy-one (30.5%) participants (aged 0.6-10.7, median 3.8 years) experienced hypoglycaemia ≤ 3.3 mmol/l. In a multiple logistic regression analysis, beside known factors such as higher degree of dehydration and complete absence of oral intake, other independent predictors of hypoglycaemia were a history of diarrhoea, lower BMI and lower BMI-SDS, but not age. Hypoglycaemic children had BMI 12.0-19.3 kg/m^2, BMI-SDS from -2.25 to 1.9, and only one child was obese with BMI-SDS 1.9. The highest frequency of hypoglycaemia (37.5-51.6%) was observed in the age groups of 2-7 years, who also had low median BMI values (13.9-14.8).

Conclusions

We identified low BMI, low BMI-SDS and diarrhoea as risks factors for developing hypoglycaemia. The typical shape of the BMI curve in children with physiologically low values at 2-7 years of age could partly explain the high incidence of hypoglycaemia in otherwise healthy children with decreased oral intake at this age. *Supported by*: VEGA1/0659/22.

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P766

JOINT234

Tryptophan derivatives as non-invasive diagnostic indicators for obesity-related MASLD in children and adolescents

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Metabolic dysfunction-associated steatotic liver disease (MASLD) in young individuals with obesity poses a significant global health challenge in diagnosis. Here, we analyzed a cohort of children and adolescents with obesity-related MASLD to uncover remarkable metabolic alterations associated with disease progression. Specifically, circulating tryptophan (TRP) metabolism was markedly elevated in obesity and obesity-related MASLD statuses compared to their normal-weight peers. Furthermore, TRP-derived metabolites significantly promote intracellular lipid accumulation in mouse hepatocytes and liver organoids. Last, we developed a non-invasive diagnostic model utilizing TRP-derived metabolites to effectively differentiate obesity-related MASLD in children and adolescents. Our findings underscore the importance of tryptophan metabolism in MASLD progression in children and adolescents with obesity and hold promises for TRP-derived metabolites as non-invasive biomarkers in early diagnosis.

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P767

JOINT808

Postprandial metabolic response to intake of different milk fat structures in healthy individuals

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Background
Intake of milk fat has been linked to improved cardiometabolic health compared to other sources of dietary fat. Milk fat is mainly composed of triglycerides surrounded by a complex and unique tri-layer membrane composed of phospholipids and protein, known as the Milk Fat Globule Membrane (MFGM), which has been proposed as an explanation for the potential health benefits of milk fat. To investigate this, we developed three isocaloric high-fat dairy products consisting of milk fat with intact MFGM, milk fat with disintegrated MFGM and milk fat without MFGM but with equal protein and fat content. We hypothesized, that the presence and the structural integrity of MFGM would attenuate the postprandial lipemia upon intake of high-fat dairy spreads.
Methods
Twelve healthy volunteers were randomized in a double-blind, controlled, crossover design. Participants were studied on three different occasions with a wash-out period of minimum one week. Participants were investigated after consuming two high-fat meals (40g milk fat), one for breakfast and one for lunch, containing either intact MFGM, disintegrated MFGM, or no MFGM. Postprandial lipemia was evaluated as area under the curve (AUC) for plasma triglyceride (TG). Gastric emptying was assessed using the acetaminophen test, while appetite was evaluated through questionnaires and an ad libitum meal test at the end of each study day.
Results
AUC for TG did not differ between the three interventions (MFGM: 1.3 mmol/l*min, 95%CI: 1.2–1.4; destroyed MFGM: 1.3 mmol/l*min, 95% CI: 1.2–1.4; no MFGM: 1.1 mmol/l*min, 95% CI: 1.–1.19, $P = 0.8$). In addition, no difference between the three interventions was observed for insulin levels, glucose levels, gastric emptying, appetite sensation or ad libitum food intake.
Conclusion
MFGM content and/or structural integrity of milk fat does not appear to have significant impact on the postprandial metabolic response in healthy individuals. Consequently, potential cardiometabolic health benefits from consuming high milk fat servings may instead be mediated by other structural components of the food matrix, such as protein structure.

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P768

JOINT1147

Ketone supplementation acutely lowers androgen and glucose levels in women with polycystic ovary syndrome (PCOS)

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Background
Polycystic ovary syndrome (PCOS) is a common endocrine disorder linked to insulin resistance and elevated androgens. While ketogenic diets reduce androgen and glucose levels in women with PCOS, the direct role of β-hydroxybutyrate (BHB) remains unclear. This study aimed to determine whether BHB supplementation acutely lowers circulating androgen and glucose levels in women with PCOS.
Methods
A randomized, placebo-controlled crossover trial was conducted involving 20 women diagnosed with PCOS. Participants underwent fasting blood sampling on two occasions, separated by at least three days. They were randomly assigned to receive either a ketone supplement or a taste-matched placebo. Each intervention was administered over 10 hours, with one dose administered the evening before and another two hours prior to blood collection.
Results
Following BHB supplementation, blood D-β-hydroxybutyrate (D-BHB) levels reached 2.4 ± 1.2 mM, compared to 0.1 ± 0.1 mM in the control group ($P < 0.001$). Androgen concentrations were generally lower with BHB supplementation, with mean reductions in testosterone (-13%, CI 95%: -27 to 1, $P = 0.067$), free testosterone (-21%, 95% CI: -43 to 1%, $P = 0.057$), androstenedione (-14%, CI 95%: -29 to 0, $P = 0.050$), and 11-ketotestosterone (-21%, CI 95%: -38 to -4, $P = 0.020$) compared to control. Fasting plasma glucose levels were 4.6 ± 0.7 mM after BHB supplementation, vs 5.1 ± 0.4 mM in the placebo group (mean -10%, CI 95%: -5 to -15%, $P < 0.001$).
Conclusion
Ketone supplementation acutely lowers androgen and glucose levels in women with PCOS. These findings highlight the potential for ketone-based therapies as a novel treatment for PCOS and suggest the need for long-term clinical trials to further explore these effects.

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P769

JOINT705

When hunger defies satiety: insights from a case of LEPR-related monogenic obesity

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Background
Monogenic obesity is a rare, severe form of early-onset obesity driven by genetic mutations that disrupt energy homeostasis. Leptin receptor (LEPR) mutations impair satiety signaling, leading to hyperphagia, excessive weight gain, and metabolic complications. Early diagnosis and intervention are critical to mitigate risks such as type 2 diabetes, hypertension, and cardiovascular disease. We present a case of a 7-month-old female with monogenic obesity due to a homozygous LEPR mutation.
Case Presentation
A 7-month-old female presented with rapid weight gain since 40 days of life. The parents reported marked hyperphagia, with over 10 breastfeeding sessions daily, and frequent crying relieved by feeding. Developmental milestones were normal, with no history of hypoglycemia or hospitalizations. The child was full-term, born via normal vaginal delivery, weighing 2.75 kg, with third-degree consanguinity noted. At presentation, she weighed 16.5 kg (>97th percentile), had a BMI of 39 kg/m^2, and a weight-for-length >99.9th percentile (+7 SD). Physical examination revealed generalized obesity, almond-shaped eyes, without signs of acanthosis nigricans or Cushingoid features.
Investigations
Laboratory tests showed impaired glucose tolerance (HbA1c 6.4%), hypertriglyceridemia (TG 231 mg/dL), and dyslipidemia. Abdominal ultrasound revealed grade 1 fatty liver, and echocardiography showed concentric left ventricular hypertrophy. Genetic testing confirmed a homozygous pathogenic LEPR mutation. Serum leptin levels were within the normal range (3.66 ng/mL).
Management
A low-carbohydrate, low-fat diet was initiated with close monitoring. Despite dietary modifications, her weight increased to 25 kg by 18 months, highlighting the progressive nature of LEPR-related obesity and the need for pharmacologic interventions.
Discussion
LEPR mutations disrupt leptin signaling, causing severe early-onset obesity[1]. This case underscores the importance of considering monogenic obesity in infants with rapid weight gain, particularly in consanguineous families[2]. Early genetic testing enables accurate diagnosis and personalized management[3]. While dietary interventions have limited efficacy, emerging therapies targeting the leptin-melanocortin pathway, such as setmelanotide, offer promising outcomes.
Conclusion
This case highlights the diagnostic and therapeutic challenges of LEPR-related monogenic obesity. A multidisciplinary approach, including genetic testing, dietary management, and novel therapies, is vital to mitigate complications and improve long-term outcomes.
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P770

JOINT3918

Comparison of ambulatory glucose profile (AGP) parameters between two advanced hybrid closed-loop (AHCL) systems from childhood to adulthood at 6 and 12 months

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Background and Aim

Advanced hybrid closed-loop (AHCL) systems, MiniMed 780G (M) and Tandem Control-IQ (T), represent the most advanced technologies for glucose control in patients with Type 1 Diabetes (T1D). Limited comparison data are available in the literature yet. We aimed at identifying differences in glucose parameter between M and T in adult and pediatric patients.

Method

We retrospectively collected data of 199 patients with T1D: 93 adults (>18 years: 59M, 34T), 56 adolescents (12-18 yo; 16M, 40T) and 50 children (<12 yo; 9M, 41T). We analyzed AGP data before AHCL initiation and after 6 and 12 months. Target-Time-In-Range (TIR) was set at >70%.

Results

No differences in insulin/kg ratio were observed between M and T users, at 6 and 12 months, among age groups. Adults: At 6 months and 12 months, patients with M showed higher TIR (6 months: 74%[67-79] vs 66%[59-76], p=.021; 12 months: 73%[69-80] vs 66%[59-72], p=.002), lower Time Above Range (TAR) >250mg/dl ($P < .001$ for both times), Glucose Management Indicator (GMI, p=.005 for both times), and Coefficient of Variability (CV, p=.007 and p=.016 respectively) than T users. At 12 months, 61% of M users had a target-TIR vs 38% T (p=.049). Adolescents: At 6 and 12 months, patients using M vs T had higher TIR (6 months: 82%[75-87] vs 61%[53-69], $P < .001$; 12 months: 79%[69-85] vs 58%[47-68]; $P < .001$), and lower TAR>250mg/dl ($P < .001$ for both times), GMI ($P < .001$ and p=.005, respectively), and CV ($P < .001$ and p=.002, respectively). Time Below Range (TBR) at 12 months was higher in M vs T users (2%[1-3] vs 1%[0-2], p=.023). At 12 months, 69% of M users had a target-TIR vs 18% T ($P < .001$). Children: no significant differences were observed, but with a small cohort of M users.

Conclusion

With similar insulin/kg, M seems to be more effective in improving TIR, TAR, GMI and CV in adults and adolescents but T appears to be better in reducing TBR in adolescents at 12 mo.

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P771

JOINT2788

VLCKD improves MASLD and metabolic dysfunction in patients with type 2 diabetes and obesity

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The global prevalence of obesity and type 2 diabetes (T2D) has risen dramatically, affecting over 890 million adults. Sedentary lifestyle and increased consumption of Western Diet contribute not only to obesity but also to the development of steatotic liver disease associated with metabolic dysfunction (MASLD). Ketogenic Diet (KD), which induces ketosis, has gained clinical interest due to its therapeutic effects in reducing body weight, improving insulin sensitivity, and ameliorating dyslipidemia. The very-low-calorie ketogenic diet (VLCKD) protocol is one of the most used in clinical practice, characterized by low carbohydrate (<40g/day), adequate protein for ideal body weight, and normal fat intake, with a total daily caloric intake of 500-800 Kcal. Despite promising evidence on VLCKD antiseizure effects, its impact on T2D associated with MASLD remains controversial. This 12-week pilot study investigates the VLCKD effects on metabolic parameters and MASLD in patients with T2D and obesity. 10 out of 15 enrolled patients ended the study protocol. All participants (mean age: 44.43 years) had T2D with a mean disease duration of 2.7 years (HbA1c: 6.6% ± 0.76), obesity (BMI: 39.42 kg/m^2), and MASLD (CAP: 273.56 ± 48.82 dB/min, LS: 5.89 ± 1.7 kPa), diagnosed via liver ultrasound and vibration-controlled transient elastography (VCTE, FibroScan Echosens). At the end of the 12 weeks, we observed significant improvements, including reductions in body weight, BMI, hip and waist circumferences, and fat mass percentage (40.07 ± 4.13 vs. 34.5 ± 12%), while fat-free mass increased (59.9 ± 4.1% vs. 64.0 ± 20.8%). Blood pressure improved, along with fasting insulin, HbA1c (6.5 ± 0.2% vs. 5.6 ± 0.2%), and triglycerides. Liver parameters of MASLD at VCTE improved, as shown by reductions in CAP (283.1 ± 51 vs. 241.6 ± 71 dB/m) and LS (5.8 ± 1.93 vs. 4.67 ± 1.27 kPA). At the beginning of the study, 3 patients stopped SGLT2 inhibitors and insulin treatments, without needing to add them at the end of the study. Nobody added new drugs. These preliminary findings suggest that VLCKD seems to have potential benefits in improving the short-term T2D parameters coupled with amelioration of MASLD, likely due to a reduction in de novo lipogenesis and an increase in hepatic lipolysis.

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P772

JOINT3072

Serum inflammation based scores in prediction of liver fibrosis among cushing syndrome and MACS patients: data from ERCUSYN krakow database

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Results

		CS	CS-CG	MACS	MACS-CG
	Male %	23	26	29, 8	29, 8
	Age (Q1-Q3)	54 (38-65)	62 (51-70)	68 (60-72)	67 (60-71)
	BMI kg/m2 (Q1-Q3)	28, 73 (25, 67-33, 73)	29, 03 (25, 3-32, 16)	28, 52 (24, 98- 32, 41)	28, 01 (24, 76-31, 14)
	Cortisol after 1 mg dexamethasone mg/dL (Q1-Q3)	15, 86 (8, 99-23, 6)	1, 19 (0, 98-1, 43)	2, 52 (2, 09-4, 73)	1, 3 (1, 04- 1, 55)
	DM %	63	66, 1	57, 9	57, 9
	Dyslipidemia %	61, 4	67, 2	66, 9	70, 2
	NLR (Q1-Q3)	3, 67 (2, 49-6, 56)	2, 4 (1, 8-3, 08)	2, 46 (1, 76-3, 29)	2, 33 (1, 75-2, 96)
	NPR (Q1-Q3)	0, 026 (0, 019-0, 036)	0, 017 (0, 013-0, 022)	0, 018 (0, 014-0, 025)	0, 016 (0, 013-0, 022)
	PLR (Q1-Q3)	145, 52 (109, 57-196, 47)	137, 73 (108, 3-187, 95)	131, 3 (102, 5-184, 3)	138, 89 (109, 55-176, 56)
	LMR (Q1-Q3)	2, 5 (1, 75-3, 14)	3, 51 (2, 74-4, 47)	3, 36 (2, 52-3, 98)	3, 56 (2, 79-4, 38)
	SII (Q1-Q3)	942, 72 (568, 1-1456, 5)	573, 87 (425, 1-793, 9)	604, 1 (408, 1-891, 1)	540 (395, 2-700, 2)
Statistically significant SIBS correlations with FIB4:					
Neutrophil-Lymphocyte ratio (**NLR**)		***r* = 0, 177**			
Neutrophil-Platelet ratio (**NPR**)		***r* = 0, 331**	***r* = 0, 349**	***r* = 0, 343**	***r* = 0, 281**
Platelet-Lymphocyte ratio (**PLR**)		**r= -0, 17**	**r= -0, 274**	**r= -0, 44**	**r= -0, 105**
Lymphocyte-Monocyte ratio (**LMR**)					**r= -0, 224**
Systemic Inflammation Index (**SII**)				**r= -0, 49**	**r= -0, 211**

Introduction
Serum inflammation based scores (SIBS) are evolving biomarkers of chronic liver diseases. Multiple SIBS can be simply calculated using complete blood count (CBC) data. To the best of our knowledge, so far there are no studies investigating the role of SIBS in prediction of liver fibrosis (LF) in hypercortisolemia.
Objectives
To evaluate associations between selected SIBS and LF among newly diagnosed Cushing syndrome (CS) and mild autonomous cortisol secretion (MACS).
Materials and Methods
We analyzed retrospectively baseline data of adult patients from the ERCUSYN, Krakow database (N:184- 51% pituitary CS, 26% adrenal CS, 23% ectopic CS), MACS patients (N:121*)*, control group (N:177 for CS [CS-CG] and 121 for MACS [MACS-CG], non-secretory adrenal incidentalomas matched to age, gender, weight, presence of hypercholesterolemia and diabetes mellitus). FIB4 ($Age \times AST/PLT \times ALT^{1/2}$) was used as a LF predictor. The correlations between SIBS and FIB4 were assessed (RStudio version 4.2.2. $P < 0.05$).
Conclusion
There may be an association between FIB4 and SIBS in the following pattern: 1) positive with NLR in CS; 2)positive with NPR and negative with PLR in: CS, MACS and normocortisolemic population; 3)negative with SII in MACS and normocortisolemic population. Further studies are needed to estabilish SIBS role in LF prediction.

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P773

JOINT3662

Endocrine manifestations in pediatric patients with inherited metabolic diseases

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Introduction
Inherited metabolic disorders (IMDs) are rare genetic diseases that can affect different systems, including the endocrine system. IMDs are classified into three groups according to their mechanisms: cellular intoxication, energy deficit and defects of complex molecules. Endocrine disorders may present in childhood, following diagnosis or in adulthood, before any previous metabolic diagnosis. Data regarding endocrine manifestations in pediatrics is limited. This study aims to describe endocrine manifestations in a cohort of patients with IMDs.
Methods
Demographic, clinical, and laboratory data was collected retrospectively from medical records of patients with IMDs followed at the pediatric unit of metabolic diseases in a tertiary pediatric hospital, between January 2002 and May 2024.
Results
From a total of 92 patients with an IMD associated with endocrine dysfunction, 25 had identified at least one endocrinological manifestation, of which 14 were male; 5 have died; and current median age of living patients is 13, 5 years (min 3; max 27). The median age of onset of endocrinological manifestations was 5 years (min 2 months; max 15 years). Regarding the main IMDs groups: 14 were from energy deficiency group [10 mitochondrial disorders, 3 MCT8 deficiency, 1 glycogen storage disease type I); 9 from complex molecule group [6 X-linked adrenoleukodystrophy (X-ALD); 3 congenital disorders of glycosylation] and 2 from intoxication group (1 galactosemia; 1 methylmalonic acidemia). In our cohort, we identified: 9 adrenal insufficiency (mainly X-ALD); 7 short stature with IGF1 deficit (2 of them treated with growth hormone); 6 dys/hypothyroidism; 3 premature adrenarche; 2 diabetes mellitus; 2 hypogonadism; 1 hypoparathyroidism; 1 ovarian insufficiency and 1 panhypopituitarism. Most endocrine manifestations occurred during IMDs' evolution, only 5 occurred as an initial manifestation.
Conclusions
About a quarter of the patients in this 22-year time span cohort had endocrine manifestations. Compared to the only published data including pediatric patients, the prevalence of endocrine manifestations in our cohort was higher and more diverse. This may reveal an increasing awareness of the endocrine involvement or also translate an increasing prevalence. Each case should be individually assessed, and the greater potential for endocrine involvement of some diseases (respiratory chain defects or peroxisomal disorders) should be taken into account to ensure timely referral and intervention.

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P774

JOINT1194

Metabolic profile of patients with albuminuria and previously undiagnosed chronic kidney disease according to the AURA register

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Introduction
Chronic kidney disease (CKD) is one of the most common comorbid conditions in patients with metabolic syndrome. Early detection of CKD may help to improve therapeutic approaches and thus prevent disease progression and complications.
Aim
To determine the incidence of metabolic disorders in patients with subclinical albuminuria (AU).
Materials and Methods
AURA (NCT05690009) is a registry of real clinical practice in 34 regions of the Russian Federation, including 4531 patients over 40 years of age without previously diagnosed CKD, type 1 or type 2 diabetes mellitus. AU levels were measured once using test strips during the period of enrolling patients in the register. The threshold value for AU was defined as 20 mg/l. All enrolled patients were divided into 2 groups according to test result for comparative analyses.
Results
AU levels <20 mg/l were detected in 1592 patients (35.1%), whereas AU levels ≥ 20 mg/l were detected in 2939 patients (64.9%). Diagnostically relevant AU was more common in men (44.2% (≥ 20 mg/l) vs 38.6% (<20 mg/l); $P < 0.001$), in those who were overweight (28.1 vs 27.2 kg/m^2; $P < 0.001$) and in smokers (19.1% vs 15.7%; $P = 0.006$). Among chronic diseases, metabolic syndrome (32.0% vs 23.4%; $P < 0.001$), hypertension (79.0% vs 71.5%; $P < 0.001$) and prediabetes (14.7% vs 8.9%; $P < 0.001$) were significantly more reported. Among laboratory markers, serum uric acid levels were found to be higher in patients with AU (316 [259;383] vs 298 [246;357] µmol/l; $P < 0.001$). AU was not associated with the presence of dyslipidemia (low-density lipoproteins (3.1 [2.3; 3.9] vs 3.1 [2.3; 3.9] mmol/l; $P = 0.901$). However, a significant association was observed between albuminuria and high-density lipoproteins (1.3 vs. 1.4 mmol/l; $P < 0.001$) and triglycerides (1.4 vs. 1.3 mmol/l; $P = 0.002$). The multivariate model revealed that the detection of AU ≥ 20 mg/l was significantly influenced by age, and the presence of metabolic syndrome, prediabetes and cardiovascular disease (Table 1).
Conclusion
The AURA registry has demonstrated that subclinical AU is directly associated with a number of cardiometabolic factors. Therefore, for individuals with prediabetes and metabolic syndrome, determining their AU using test strips can serve as an effective screening method for early CKD detection. This approach will enhance the delivery of medical care and facilitate timely nephroprotection.

Table 1. Factors with significant influence on the presence of albuminuria.

Predictors	Odds ratio	95% confidence Interval	*P*-value
Age	1.02	1.01-1.02	<0.001
Metabolic syndrome	1.23	1.02-1.49	0.034
History of myocardial infraction	1.67	1.22-2.30	0.002
Atrial fibrillation	1.31	1.05-1.65	0.018
Prediabetes	1.58	1.24-2.03	<0.001

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P775

JOINT1785

Analysis of the concordance between body fat percentage estimated by dual-energy X-ray absorptiometry (DEXA) and anthropometric parameters in a cohort of obese patients

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Introduction
Body mass index(BMI [kg/m^2]) is the most used anthropometric parameter to estimate body fat content. However, its interpretation during childhood and adolescence has limitations, as it is not constant and varies significantly with age, sex, and maturation stage, requiring reference values and a z-score format. The triceps mass index(TMI [kg/m^3]) estimates body fat percentage more accurately than BMI in children and adolescents aged 8 to 18 years. DEXA(Dual-Energy X-ray Absorptiometry) is the gold standard for tricompartimental analysis of body composition and accurately estimates body fat percentage, being the best parameter to define and classify the degree of obesity.
Objective
To analyze the correlation between body fat percentage estimated by DEXA and anthropometric parameters: TMI, BMI, and BMI z-score from the 2010 Spanish Transversal Growth Study and WHO Growth Patterns 2007 in a population of obese children and adolescents.
Patients and Methods
Sixty-six obese patients (56% female), aged between 8 and 18 years, with a mean age of 14.1 $\pm$ 2.4 years, were included. Body composition was assessed using DEXA(Lunar Prodigy Advance DXA).
Results
The mean age of obesity onset was 6.5 $\pm$ 2.6 years (range: 1–12 years). BMI value: 35.2 $\pm$ 6.0; BMI z-score 2007: 3.2 $\pm$ 0.6 (range: 2–4.4); and TMI: 22.2 $\pm$ 4.1(range: 14.8–36.9). Eight patients(17%) had moderate obesity(BMI z-score 2007 $>$2; $<$2.5SD); 37 patients (56%) had severe obesity(BMI z-score 2007 $>$ 2.5; $<$3.5SD); and 21 patients (31%) had morbid obesity(BMI z-score 2007 $>$ 3.5). In DEXA body composition analysis, the mean body fat percentage was 49.5 $\pm$ 6.2%(range: 33.8–59.6). The mean body fat percentage in females was 51.6 $\pm$ 5.4%(range: 38.4–59.6) and in males was 46.9 $\pm$ 6.2%(range: 33.8–57.1). A positive and significant correlation was found between body fat percentage and TMI($r = 0.55$, $P < 0.05$), BMI($r = 0.46$, $P < 0.05$), BMI z-score 2010($r = 0.53$, $P < 0.05$), and BMI z-score 2007($r = 0.45$, $P < 0.05$). Regarding sex: Males ($n = 29$): TMI($r = 0.39$, $P < 0.05$), BMI($r = 0.38$, $P < 0.05$), BMI z-score 2010($r = 0.40$, $P < 0.05$). No significant correlation with BMI z-score 2007($r = 0.3$, $P = 0.1$). Females ($n = 37$): TMI($r = 0.61$, $P < 0.05$), BMI($r = 0.56$, $P < 0.05$), BMI z-score 2010($r = 0.63$, $P < 0.05$), and BMI z-score 2007($r = 0.62$, $P < 0.05$).
Conclusions
Preliminary results from this ongoing study show that the degree of concordance between the anthropometric parameters analyzed and the body fat percentage estimated by DEXA is very similar in obese patients when analyzed by sex, although this correlation is stronger in females. Since TMI values are very consistent and comparable across both sexes in the 8–18 age range, this index would be highly useful for identifying and classifying the degree of obesity.

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P776

JOINT1566

Setmelanotide treatment in genetic obesity: a single-center experience

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Objective
Setmelanotide, an MC4R agonist, is approved for the treatment of obesity in patients with POMC, LEPR, and PCSK1 deficiencies, as well as in Bardet-Biedl Syndrome (BBS). There is little real-world evidence for the efficacy and safety of setmelanotide. This study aimed to evaluate the clinical characteristics and follow-up outcomes of patients treated with setmelanotide at our center.
Methods
The study included five patients; three patients with POMC deficiency, one with LEP mutation, and one with BBS treated with setmelanotide. The effects of setmelanotide on body weight, associated measures, hunger score, and quality of life were examined.
Results
The mean age of the patients was 17.1 $\pm$ 5.04 years (range: 11.5–24 years). Three patients were female and two were male. The duration of treatment ranged from 3 to 14 months. Except for the patient with BBS, all patients achieved a decrease in their BMI by more than 5% during the treatment. Before therapy, the mean BMI was 38.78 $\pm$ 5.99 kg/m^2 (32.36-48.20) and the mean BMI SDS was 3.35 $\pm$ 0.96 (2.14-4.59). After therapy, the mean BMI was 35.31 $\pm$ 7.43 kg/m^2 (29.10-47.80), the mean BMI SDS was 2.98 $\pm$ 1.15 (ra1.78-4.63), and the mean percentage decrease in BMI was -9.22 $\pm$ 8.44% (range: 0.80-21.30). All patients showed a significant decrease in their hunger scores and an improvement in their quality of life (QoL) scores. The baseline hunger score was 8.60 $\pm$ 1.34 (range: 7-10) and decreased to 3.60 $\pm$ 2.88 (range: 1-8) after treatment. Similarly, the mean baseline QoL was 96.60 $\pm$ 26.40 (range: 62-120) and improved to 106.20 $\pm$ 22.28 (range: 68-124) after treatment. After five months of treatment, the patient with the LEPR gene variant had a -9.9% decrease in BMI but had to stop treatment for one month due to depression. In the ninth month of the follow-up period, BMI decreased by -0.8%, and treatment was discontinued due to worsening depression symptoms. Additionally, adverse events such as nausea in four patients, hyperpigmentation in four patients, headache in two patients, and pain at the injection site in two individuals were observed. However, these adverse events did not necessitate discontinuation of treatment.
Conclusion
Setmelanotide provides significant weight control in POMC and LEPR deficiencies but has a more limited effect in BBS. It can also provide significant reduction in hunger scores and improvement in QOL scores in all patients, including BBS. Long-term, real-life data with more patients are needed regarding setmelanotide treatment.

Key Words
Setmelanotide, Genetic, Obesity, POMC, LEPR, BBS
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P777

JOINT1567

The impact of prader-willi syndrome (PWS) on caregivers and the healthcare system: a burden of illness study design

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Background
Prader-Willi syndrome (PWS) is a rare, genetic, neurobehavioural-metabolic disorder characterised by hyperphagia and behavioural/psychological complications. Managing PWS symptoms through strict supervision, behavioral management and specialised supports imposes significant demands on caregivers and healthcare systems. However, data are lacking on the real-world burden of PWS.
Objectives
The objective was to design a study that characterises the clinical, humanistic, and economic burden of PWS on caregivers, families, and the healthcare system.
Study design
This study is a descriptive, retrospective, cross-sectional, multi-site, micro-costing burden of illness study. The study will be conducted in USA, UK, France, Germany, and Italy. To assess the burden of PWS, a retrospective review will be conducted by consenting approximately 330 healthcare professionals (HCPs) who meet the following inclusion criteria: 1) primary specialty in paediatrics, endocrinology, or psychiatry; 2) qualified in their medical specialty for at least three years and 3) personally responsible for the management of patients with PWS. HCPs who qualify and consent to participate will complete electronic case record forms (eCRFs) for eligible patients under their care. Patients are eligible for inclusion if they are aged 4 years and over, with a diagnosis of PWS $>$12 months, and their caregiver is aged 18 years or over and capable of providing informed consent. The eCRF will collect data on PWS disease history, management, and burden during the past 12 months from the date of consultation with the HCP. Aspects captured by the eCRF will include socio-demographics,

symptoms, disease history, comorbidities, management, interventions, and care requirements. HCPs will invite caregivers of these patients to complete corresponding Patient Public Involvement & Engagement caregiver forms (PPIE-c). The PPIE-c will capture health-related quality of life (HRQoL) through EuroQoL 5-Dimensions 5-levels (EQ-5D-5L); the Work Productivity and Activity Impairment (WPAI) Questionnaire; the Hyperphagia Questionnaire for Clinical Trials (HQ-CT), the Zarit Burden Interview (ZBI) and the Food Safe Zone (FSZ) Questionnaire. The PPIE-c will help provide insights into the wider impact of PWS on caregivers and families. All eCRF and PPIE-c data will be collected anonymously. The mean per-patient cost of PWS will be calculated based on a comprehensive resource utilisation analysis incorporating unit cost estimates for direct medical and non-medical, and indirect resource requirements. Key factors to be evaluated include hospitalisations, HCP visits, treatments, PWS-related transportation, specialised equipment, education status, and dietary modifications. This study is sponsored by Soleno Therapeutics, Inc.

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P778

JOINT2000

Linking metabolic syndrome and physical fitness in children with obesity: a cross-sectional study from the PODiaCar project

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Aim
Paediatric obesity is a major public health concern, as recognized by the World Health Organization. Metabolic syndrome (MetS), associated with increased cardiovascular (CV) morbidity and mortality, affects approximately 29.2% of children with obesity. Physical fitness (PF) is a key indicator of long-term health, influencing CV risk and overall mortality. However, few studies have examined its association with MetS. This study aims to analyze the relationship between PF and MetS in children with obesity.
Methods
We conducted a cross-sectional study evaluating 55 children with obesity (11.96 $\pm$ 2.35 years; 21 [38%] girls; mean BMI 29.5 $\pm$ 4.81 kg/m^2 and BMI z-score 3.15 $\pm$ 0.78). Physical fitness was assessed through three functional tests: i) 6-minute walking test (6MWT), ii) standing broad jump (SBJ), and iii) 4$\times$10 m shuttle run test (SHT). MetS z-score assesses MetS, using sex-specific formulas (cut-off $>$ 0.75). Between 8:30 and 9:00 a.m. a fasting blood sample was collected and analyzed that morning for total cholesterol, HDL-C, triglycerides, fasting glucose (FG), and insulin. Insulin resistance was estimated using HOMA-IR and TyG index. Logistic regression was used to calculate adjusted odds ratios (OR) for MetS based on PF levels, while linear regression assessed associations between PF, MetS z-score, and its components.
Results
In both sexes, the SBJ test inversely correlates with MetS odds, independent of age (OR: 0.18, 95%, CI: 0.04–0.53). Conversely, neither the 6MWT nor the SHT were related to the odds of MetS. When analyzing the relation between MetS z-score, its components and PF, the SBJ showed an inverse significant association (BMI z-score: β=-0.528; SBP: β=-0.397; MetS z-score: β=-0.299; all $p < 0.05$) with all components, except for HDL, FG and triglycerides (respectively β=0.335, β=0.429 and β=0.354), which were positively associated. The SHT was associated with BMI z-score (β=0.419), systolic blood pressure (β=0.419), and FG (β=-0.331; all $P < 0.05$), while the 6MWT was inversely related to BMI z-score (β=0.295; $P < 0.05$).
Conclusions
Our findings highlight an inverse relationship between PF and MetS, particularly concerning lower limb strength, as assessed by the SBJ. These results highlight the importance of incorporating PF assessments into the clinical evaluation of children with obesity. Future research should explore the mechanisms underlying this relationship, evaluating targeted exercise programs as potential strategies for MetS prevention in children with obesity.

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P779

JOINT2199

Management and diagnosis of moderate and severe hypernatraemia in a UK district hospital: a retrospective audit

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Background
Hypernatraemia, defined as serum sodium levels exceeding 145 mmol/l, affects 2.5% of inpatients in the United Kingdom. It is particularly prevalent among elderly patients with cognitive impairment and impaired thirst mechanisms, with mortality rates reaching 80% in this population. Our trust has implemented a hypernatraemia protocol to guide appropriate management, including recommended investigations and treatment modalities.
Objective
To assess compliance with the management protocol for patients with moderate to severe hypernatraemia (sodium levels $>$150 mmol/l) in our trust.
Methods
We conducted a retrospective audit of patients with serum sodium levels exceeding 150 mmol/l. Data collected included patient demographics, clinical presentations, investigations performed, and treatment duration.
Results
43 patients met the inclusion criteria. The majority (85%) were over 75 years old, with 44% being nursing home residents and 30% having underlying neurological conditions. Common presenting symptoms included confusion (74%) and decreased levels of consciousness (47%). Clinical dehydration was observed in 60% of patients, establishing a causal relationship with severe hypernatraemia. Notably, 58% of patients had clinically stable NEWS scores of 1-3, indicating that severe hypernatraemia can occur in apparently well patients. The audit revealed suboptimal compliance with required investigations, with only a small number of patients undergoing urine osmolality, urinary sodium, and plasma osmolality tests. Treatment duration was prolonged, with 95% of patients requiring more than 48 hours for hypernatraemia correction, and 79% needing over 7 days.
Conclusions
Hypernatraemia remains a significant issue, particularly among elderly and cognitively impaired patients. Our findings highlight the need for improved adherence to local hypernatraemia guidelines. We recommend implementing regular monitoring and assessment of fluid status and sodium levels, as well as increasing awareness of the existing protocols among healthcare staff.

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P780

JOINT473

Patient and caregiver experiences with setmelanotide treatment in bardet-biedl syndrome – real-world evidence and a patient support program

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Background
Bardet-Biedl syndrome (BBS) is a rare genetic disease resulting from dysfunctional cilia, and is marked by numerous symptoms, among which hyperphagia and early-onset obesity, that can adversely impact the quality of life for both patients and caregivers. The MC4R agonist setmelanotide has demonstrated clinically meaningful weight and hunger reductions in patients with obesity due to BBS. In this study, we evaluated real-world patient expectations and experiences before and during treatment with setmelanotide, as well as the use of a patient support program.
Methods
A one-time survey was conducted online to capture the real-world experiences of patients with BBS and their caregivers with setmelanotide treatment and the patient support program, designed to educate patients and caregivers to allow them to administer injections independently. The survey, including yes/no questions, Likert scale questions and free text questions, was fielded from January 2024 to May 2024, involving participants who began treatment between June 2023 and December 2023 at a single centre in Germany.
Results
Ten paediatric patients, 13 adult patients, and 12 caregivers participated in the study. Prior to treatment, paediatric patients reported experiencing insatiable hunger (80%) and obesity (50%) as their most prevalent symptoms; for adult patients, these were vision loss (69%) and obesity (69%); and caregivers reported obesity (92%) and insatiable hunger (83%). Treatment with setmelanotide had a positive effect on reducing body weight, with $\geq$92% of all participants reporting feeling less hunger, feeling satiated after meals, and stable body weight or weight loss. Furthermore, to various degrees, patients and caregivers reported improvements in mobility, mood, and behaviour. Negative effects of treatment perceived the most were changes in skin pigmentation, (initial) vomiting, diarrhoea and nausea. The personalized approach with the patient support program led to high patient and caregiver satisfaction, with over half of patients/caregivers being able to administer the drug independently at the end of the study period. There was high treatment adherence, no patients discontinuing setmelanotide treatment and an excellent rating of the service by all respondents.
Conclusions
This real-world survey of patients with BBS and their caregivers further demonstrated the meaningful benefits of setmelanotide in improving insatiable hunger and obesity. Personalized nursing support at the initiation of treatment onwards can further facilitate high rates of treatment adherence and satisfaction.

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P781

JOINT3937

Real life data of obesity in craneopharyngiomas in an pediatric/adult transition pituitary unit

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Introduction
Craniopharyngiomas (Cr) are suprasellar tumors with metabolic comorbidities and panhypopituitarism diagnosed mostly during infancy with a difficult management. Long-term follow-up in a specialized hypothalamic-pituitart unit (HPU), involving both pediatric and adult endocrinologists, allows for a comprehensive analysis of disease progression and response to treatment, helping to refine therapeutic strategies.
Aims
To evaluate the incidence, comorbidities and progression of hypothalamic obesity (Ob) in pediatric (POCr) and adult-onset Cr (AOCr), the different medical treatments of Ob and the factors that contribute to the development of Ob.
Methods
Retrospective study on patients with Cr and followed up in the HPU between 2008 and 2024.
Results
35 Cr were included. 24 POCr and 11 AOCr. Among AOCr, 33% had prior diagnosis of POCr. 98% adamantinomatous Cr. Longest follow-up was of 12 years (y) in the POCr and 14y in AOCr. The mean age in POCr was 6.9 $\pm$ 3.15y; 60% males; 4% with Ob or BMI SD + 1; 30% visual defects, 70% compression, 8% growth retardation and 25% consciousness alteration. The mean age in AOCr was 53 $\pm$ 11.7y; 55% men, more Ob (19%), more visual defects (72%) and hypopituitarism symptoms (28%); 30%HTA, 64% triglyceridemia, 9%DM were observed. After surgery complete panhypo was presented in all; increase in Ob was equal between AOCr and POCr (delta 26 vs 29%), while new DM and hypertrigliceridemia was present only in AOCr (27% and rsp 75%). Highest increase in BMI (SD BMI) was observed at 6 months (m) in AOCr (delta 5 kg/m2) with further stabilization while the highest increase in POCr was at 3m (BMI SD 1.62) and progress during follow-up. Hypothalamus alterations on MRI associated with Ob onset after surgery. Pharmacological treatment was larger and in more POCr than AOCr: 54% vs 45% and 146 vs 35, 6 m; only GLP1 in AOCr; 70%with Lisdexanfetamina (LSDF) in POCr and 30% with GLP1. Interruption of treatment due to AE was higher in LSDF than in GLP1 (50% vs 16%, $P < 0.05$). Weight loss with GLP1 and LSDF was 2% in AOCr and weight gain was controled in POCr. After short term treatment retrival BMI SD increase with +1.65 in POCr and +2.1 kg/m2 BMI in AOCr.
Conclusion
Although long-term treatment with GLP-1 and LSDF did not result in significant weight loss, it helped **stabilize weight gain** in both AOCr and POCr. This suggests that this may contribute to better weight control in Cr with hypothalamic dysfunction.

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Multisystem Endocrine Disorders

P21

JOINT388

Genome Edited Human Cell Lines For Studying Steroidogenesis In P450 Oxidoreductase Deficiency

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P450 oxidoreductase (POR) is an essential enzyme in steroidogenesis. It transfers the electrons from NADPH to microsomal cytochrome P450 (CYP) proteins that drive the synthesis of glucocorticoids, mineralocorticoids, and sex hormones in the adrenal cortex. Patients with POR deficiency could present with metabolic disorders, including impaired sexual development, skeletal anomalies characteristic of the Antley-Bixler phenotype, and congenital adrenal hyperplasia. Over 200 deleterious mutations in POR have been discovered, with a few of them being characterized using purified protein systems. To gain deeper insights into mutated POR activities within the context of living cells, the development of personalized human cell models is crucial. Using CRISPR/Cas9 system we performed the POR knockout in the NCI – H295R (adrenal carcinoma cells) and HEK 293T (human embryonic kidney cells). Resulting cells were subcloned to obtain monogenic cultures representing unified genotype. To evaluate the status of POR, we employed Sanger sequencing of POR gene, Western blot analysis, and the assays on POR function. For HEK 293T cells, the CYP17A1 and CYP21A2 activity were measured using thin layer chromatography. For NCI – H295R cells, the full steroid profile was obtained using LC–MS/MS. Adrenal – derived POR knockout cells were characterized by the significant inhibition of aldosterone, cortisol, and testosterone pathways indicating reduced activities of CYP21A2 and CYP17A1 – two key metabolic partners of POR in steroid biosynthesis. The Progesterone levels were significantly higher in POR knockout adrenal cells and 17OH-Progesterone levels were comparable to controls. In HEK293T cells, loss of POR showed 3.6% of wild-type activity towards CYP21A2 and 0% activity towards CYP17A1. The generated cell lines resemble the steroid abnormalities found in patients with POR deficiency. Additionally, they can be utilized to study patient-specific POR mutations by artificially inducing their expression, thereby supporting the development of personalized disease models. By reflecting individual genetic profiles, these cell models offer valuable insights into the complex metabolic processes in the adrenal glands while also serving as a screening platform to characterize the impact of the POR mutations on steroidogenesis and drug response. Such models hold significant potential for improving both the diagnosis and treatment of POR deficiency.

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P22

JOINT840

48-Week Results from the HELIOS Trial: A Phase 2, Open-Label Study Evaluating an Oral, Fixed-Dose Combination of Sodium Phenylbutyrate and Taurursodiol in Wolfram Syndrome

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Background
Wolfram syndrome (WS) is a rare, fatal, monogenic disorder characterized by juvenile-onset diabetes mellitus, optic nerve atrophy, sensorineural deafness, diabetes insipidus, and neurodegeneration. Symptoms progress from childhood to adulthood. WS is thought to represent a prototypical syndrome of endoplasmic reticulum (ER) stress with impaired mitochondrial dynamics also contributing to its pathophysiology. PB&TURSO is an oral, fixed-dose combination of sodium phenylbutyrate (PB) and taurursodiol (TURSO) hypothesized to simultaneously mitigate ER stress and mitochondrial dysfunction. PB&TURSO has demonstrated pre-clinical efficacy in patient-derived cell and mouse WS models. The phase 2, open-label HELIOS trial is evaluating the safety/tolerability of PB&TURSO as well as its effects on endocrinological, neurological, and ophthalmological function in WS.
Methods
Adults (≧ 17 years) with a definite genetic WS diagnosis; insulin-requiring diabetes mellitus due to WS; and stimulated C-peptide levels ≧0.2 ng/mL were enrolled from one U.S. site. Participants receive PB&TURSO for up to 144 weeks. The primary efficacy endpoint is change from baseline in C-peptide at Week 24 using 240-minute mixed meal tolerance tests. Secondary efficacy endpoints include measures of glucose control and best-corrected visual acuity. Exploratory endpoints include clinician- and participant-reported global impression of change scores and participant experiences derived from on-study qualitative interviews.
Results and conclusions
HELIOS week 24 results for all 12 participants (Intent-to-Treat) and for the 11 with genetically confirmed WS (Per Protocol) were previously reported. PB&TURSO was generally well-tolerated with diarrhea the most common adverse event. Due to the progressive nature of WS, pancreatic beta cell function, glycemic control, visual function, and overall symptom burden typically worsen over time; however, at Week 24, treatment with PB&TURSO showed overall stabilization or improvement relative to baseline. Stimulated C-peptide responses showed improvements with a mean change from baseline to Week 24 in C-peptide area under the curve (AUC) from 0 to 120 minutes of +3.8 minutes*ng/mL [standard error (S.E.):19.3] in Intent-to-Treat ($n=12$) and +20.2 min*ng/mL [S.E.:11.2] in Per Protocol ($n=11$). Participants also demonstrated improved glycemic control and a trend toward visual acuity stabilization. All participants reported either improvement or stabilization of disease, as measured by Clinician- and Patient-Reported Global Impression of Change scales. Nine of 11 interviewed participants reported improvements in ≧1 WS-related symptom with nearly all noting these were meaningful changes. Available Week 48 results ($n=6$) suggest sustained stabilization and/or improvement of pancreatic function, glycemic control, vision, and symptom burden. Treatment with PB&TURSO in HELIOS is ongoing. Updated Week 48 results will be presented.

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P782

JOINT36

Post-authorisation safety study of ketoconazole HRA in endogenous cushing's syndrome: seventh annual interim report in 108 patients

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Background
Ketoconazole HRA is approved for the treatment of endogenous Cushing's Syndrome (CS) pursuant to an obligation to collect safety data on patients exposed to the drug in this indication.
Methods
The primary objective of this open-label post-authorisation safety study (PASS), using the European Registry on Cushing's Syndrome (ERCUSYN), is to document liver and cardiac tolerability. Treatment pattern, overall safety, and effectiveness are secondary objectives. The last interim report is presented.
Results
At the cut-off date (31 August 2024), 110 patients were enrolled in the study. One hundred and eight patients were included in the full analysis set, 103 were evaluated for safety, and 105 for efficacy. Mean age of the patients was 46.8 years, and most patients (77.4%) were diagnosed with pituitary-dependent CS. Ketoconazole HRA was mainly used as monotherapy in 85.2% (92/108) of patients, with a median exposure of 1.6 years and a mean average daily dose of 400 mg. Among 41 cases of liver functions test (LFT) abnormalities, occurring mostly within the first month, in 22 cases LFT were < 2 x ULN and resolved without discontinuation of Ketoconazole HRA. Eight cases (7.4%) of hepatotoxicity (LFT > 5 x ULN) were observed. Co-administration of a known hepatotoxic drug was suspected in 6 of these patients. In all 8 patients, liver injury resolved after discontinuation of ketoconazole HRA, 5 of these events were hepatocellular. No QTc prolongation cases were reported. However, ECG and LFT monitoring remain non-systematic. Overall, 51.9% of patients (56/108) experienced at least one adverse event (AE). Thirty-five patients (32.4%) experienced at least one AE other than LFT abnormalities and QTc prolongation. Non-serious AEs were mainly gastrointestinal disorders (13.6%), nausea being the most frequent of them (12.6%). The rate of serious AEs, other than LFT abnormalities and QTc prolongation, was 11.7%, of which 3.9% were endocrine disorders, mainly acute adrenocortical insufficiency (1.9%). Efficacy data showed that 50.8% of patients achieved normalized UFC levels, while 60.5% attained normalized morning plasma cortisol levels.
Conclusion
These results confirm the known safety and efficacy profile of Ketoconazole HRA. No unexpected safety signals were identified. In addition, the benefit-risk balance of Ketoconazole HRA in patients with endogenous Cushing's syndrome remains favourable.

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P783

JOINT1737

Genetic and clinical insights into triple a syndrome in a multi-ethnic population: a large cohort from sudan

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Background
Triple A syndrome (TAS), is a rare autosomal recessive multisystem disorder due to mutations in the AAAS gene, which encodes the ALADIN protein. Alacrima, adrenal insufficiency, achalasia, autonomic dysfunction, and variable neurological features are the most common symptoms to be reported. Limited data exists on TAS from Sub-Saharan Africa and Arab countries with only a small series or case reports. A comprehensive clinical and genetic analysis was performed in patients diagnosed with TAS from Sudan, highlighting the genotype-phenotype correlation of this syndrome from a limited resource setting. This is considered the largest reported cohort of TAS from Sub-Saharan African countries.
Patients and Methods
48 patients from 32 families with a clinical diagnosis of TAS were investigated. The initial diagnosis was based on the characteristic clinical and biochemical findings followed by genetic testing performed on 31 patients from 20 families who were included in this study.
Results
Alacrima was detected in all patients (100%), hyperpigmentation indicating the presence of ACTH-resistant adrenal insufficiency in 90 %, difficulty of

swallowing in 35%, and the complete triad was detected in 35 % at presentation. Other features include autonomic and neurological features in 39%, facial dysmorphism in 45%, and short stature in 39%. Rare features include hypertensive encephalopathy in two patients and excessive thick nasal discharge in four patients which has not been previously reported. Eight families (40 %) reported deaths of one or more siblings who had shown similar symptoms. Genetic analysis confirmed six different AAAS mutations mainly in a homozygous form. This included three nonsense mutations, one frameshift mutation leading to a truncated protein, and 2 splice defects among them the Arabic founder mutation c.1331 + 1G > A (intron 14) in 32 % (6 families). The 8 bp-deletion mutation in intron 4 in two families is novel. As a further novel AAAS mutation, we identified a 1 bp-deletion in exon 9 in three families. The most abundant mutation was a previously described mutation in exon 9 (c.934C > T, p.Arg312*) present in 37 % (7 families).

Conclusion

TAS seems to be underdiagnosed in Sudan, and the presence of 95 % mutations in a homozygous form reflects the high rate of consanguinity in this population. Genotype/phenotype analyses revealed a high variability in disease severity even between patients from the same family or with identical AAAS mutation. Early genetic diagnosis in unaffected siblings has helped in disease prediction and early intervention and thus prevented an adrenal crisis and death.

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P784

JOINT2679

Factors affecting the prevelance of endocrinopathies in transfusion dependent thalassemia patients in the national thalassemia centre, kurunegala, sri lanka

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Introduction

Thalassemia is the commonest haemoglobinopathy in Sri Lanka. Beta thalassemia major (BTM) and severe E beta thalassemia (EBT) are classified as transfusion-dependent thalassaemia (TDT). Most TDT patients are iron overloaded due to increased red cell lysis, inefficient erythropoeisis, recurrent blood transfusions, and increased iron absorption. Tissue deposition of iron may lead to multiple endocrine organ dysfunction.

Objectives

We aimed to establish the following in TDT patients (2-18 years) attending the National Thalassaemia Unit (NTU), Kurunegala, Sri Lanka.

1. The prevalence of endocrinopathy and iron overload.
2. The relationship between frequency of transfusion and serum ferritin levels
3. The relationship between dose and type of chelation therapy

Methods

We carried out a retrospective database analysis of all subjects attending the NTU with TDT who were between the ages of 2-18 years. Data were collected from patient medical records. Individual endocrinopathies were identified using standard clinical and biochemical criteria as set out in current guidelines. Summary statistics were compared between groups using appropriate statistical tests.

Results

261 subjects with TDT were eligible for analysis (a) 204 (78%) had BTM [median age 11 years (IQR = 6.75-14)], and 57 (22%) had severe EBT [median age 12 years (IQR = 8-14)]. There was no significant sex difference between the two groups. The transfusion frequency was – (i)BTM; median 3 weeks (ii) EBT; median 4 weeks, Chelation therapy was commenced– (i)BTM; median age 3 years (IQR = 2-4) and (ii) EBT median age 4 years (IQR = 3-6), ($P = 0 < 0.05$). (b)Prevalence of following endocrinopathies was as follows (1) Short stature in 106/213 (49.8%) in children ≥ 8 years (2) Pubertal delay 35/106 (33%) in females > 13 years and males > 14 year; puberty was initiated in 71 (67%) and later arrested 6 ($n = 71$). (3) Primary hypothyroidism in 17/261 (6.5%) (4) Adrenal insufficiency in 2/261 (0.76%) (5) Hypoparathyroidism in 7/261 (2.7%) (6) Diabetes Mellitus in 2/261 (0.76%) (c) Transfusion frequency and volume and serum ferritin in subjects with endocrinopathies 118/261 patients (45.2%). (1) Three weekly transfusion 61/118 (51.7%) (2) Median transfusion volume at present 4746ml/year (IQR = 3464-5811). (3) Median serum ferritin was 1377ng/mL (IQR = 934-1945) (3) Median Deferasirox and median Deferoxamine doses were 33.5 mg/kg/day (IQR = 30.91-35.96) and 33.46mg/kg/day (IQR = 32.32-38.04) respectively.

Conclusions

In this study 45 % patents with TDT had endocrinopathies. Short stature and pubertal delay were the most common endocrinopathies encountered in TDT subjects in this study. Our study revealed patients with endocrinopathies had high serum ferritin with inadequate dosing of iron chelation.

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P785

JOINT3774

Endocrine disorders in patients with neurofibromatosis type 1: a single-center prevalence study

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Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder characterized by increased risk of tumour development and endocrine disorders. Despite the well-established relationship between NF1 and certain endocrinopathies, the prevalence of these disorders in NF1 patients remains unclear, hindering follow-up strategies.

Objective

This study aims to assess the prevalence of endocrinopathies in NF1 patients at our centre.

Methods

Retrospective analysis of NF1 patients observed in the Endocrinology department from 1997 to 2024. Statistical analysis was performed using IBM® SPSS® Statistics.

Results

Of 669 NF1 patients followed at our centre, 255 [141(55.3%) females] were referred to the endocrinology department, 166 of whom during childhood. The mean age at first observation was 10.24 ± 4.51SD years for paediatric and 41.07 ± 14.56SD years for adult patients. The most common pituitary deficiency was growth hormone deficiency (GHD) (9.02%, $n = 23$), mainly in children ($n = 22$; mean age at diagnosis 11.21 ± 3.31SD years). Optic pathway gliomas (OPG) were present in 78.26% of these cases ($n = 18$, $P < 0.001$), corroborating higher risk in patients with brain tumours. Additionally, 51 patients were diagnosed with short stature, but only 18 of these patients had GHD, suggesting a likely multifactorial aetiology. The prevalence of other pituitary deficiencies was lower: 1.96%($n = 5$; 4 with OPG) for hypogonadotropic hypogonadism, 1.18% ($n = 3$, all with OPG) for secondary adrenal insufficiency. A single case of central hypothyroidism was identified in a 3.67-year-old patient with OPG. The prevalence of precocious puberty was 4.31%($n = 11$), 10 of whom had OPG ($P < 0.001$); 5.49%($n = 14$) patients were diagnosed with accelerated puberty, 6 with OPG. Gynecomastia was noted in 8 male patients, 4 were pathologic (1.57%). Thyroid disorders occurred in 16.47% of patients ($n = 41$); 3(1.18%) patients had thyroid carcinomas (2 papillary, 1 medullary), the earliest diagnosed at 36.58 years. Primary hyperparathyroidism was diagnosed in 1.96%($n = 5$) patients (mean age: 56.95 ± 10.60). Paragangliomas were found in 3.14% of the patients ($n = 8$): seven adrenal and one abdominal paraganglioma, incidentally diagnosed. Earliest age at diagnosis was 33.10 years. In addition, 4(1.57%) patients were diagnosed with adrenal adenomas, 1 with adrenal carcinoma and another with congenital adrenal hyperplasia. Gastroenteropancreatic neuroendocrine tumours were detected in 3(1.18%) adults.

Conclusion

NF1 has a prevalence of 1 in 3000. Overall, 17.19% of patients presented with, at least, one endocrine disorder. The diversity of endocrinopathies in NF1, especially in association with OPG, requires regular clinical evaluation and biochemical/imagiological screening. Understanding the prevalence of these disorders is the key to optimizing follow-up and patient care.

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P786

JOINT118

Autoimmune diseases in 3, 812 danish transgender persons and 38, 120 cisgender controls before and after transgender care. a register based cohort study

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Objective
The risk of autoimmune disease could be increased in transgender persons (TG) and susceptibility to autoimmune disease could be affected by transgender care. We assessed the risk of autoimmune diseases in TG compared to controls before and after transgender care.
Methods
A national register-based Danish cohort study was conducted in individuals diagnosed with gender dysphoria between 2000 and 2021. The inclusion date was the date of the first transgender diagnosis. For each case, five age-matched cisgender controls of the same birth sex and five age-matched controls of the opposite birth sex were included. Any autoimmune disease, type 1 diabetes and/or thyroid disease were study outcomes (ICD10 diagnosis of any autoimmune disease and/or medical treatment for type 1 diabetes or thyroid disease).
Results
The cohort included 3, 812 TG and 38, 120 controls. The median age (interquartile range) was 19 (15; 24) years for transmasculine persons (TM), $n = 1, 993$ and 23 (19; 33) years for transfeminine persons (TF), $n = 1, 819$. Before the index date, the incidence rate (IR) of type 1 diabetes was significantly higher in TM compared to controls of same birth sex: IRR= 1.98 (1.16; 3.36). In TF vs. controls of same birth sex, the IRR for type 1 diabetes was 1.66 (1.05; 2.61) and for any autoimmune disease was 1.35 (1.04; 1.77). Higher incidence of any autoimmune disease in TG was associated with higher age, medical morbidity, and psychiatric disease. After the index date, the IRR for thyroid disease was 1.98 (1.09; 3.61) in TF vs. controls of same birth sex, whereas the IRR for remaining autoimmune outcomes were comparable between TG and controls of same birth sex. TM using GAHT had higher incidence of autoimmune disease 2.50 (1.10; 5.67) compared to nonusers.
Conclusion
Higher incidence of type 1 diabetes in TG compared to cisgender controls could be attenuated by transgender care.

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P787

JOINT810

Muscle characteristics in adult patients with APECED

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Background
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED; autoimmune polyendocrine syndrome type 1), a genetic disease with hypoparathyroidism, primary adrenocortical insufficiency (PAI), chronic candidiasis and other autoimmune manifestations. Our previous study showed that a severe APECED phenotype associated with changes in bone microarchitecture.
Objective
This study aimed to explore muscle characteristic in relation to bone properties in patients with APECED.
Patients and Methods
We recruited 37 adults with APECED and 82 age- and gender-matched control subjects. In both groups, we assessed muscle and bone characteristics at the proximal site of tibia (38%) with peripheral quantitative computed tomography (pQCT). In the patient group, dual-energy absorptiometry (DXA) was also used to measure total muscle mass and whole-body bone mineral density (BMD). Mann-Whitney or Student's t-test was used to test for differences between the groups and Kendall's rank test to test for correlations.
Results
Altogether 37 adult patients (22 females) participated in the study (median age 44.0, range, 19.3-70.1 years). In females with APECED, muscle area (mean, 5129.8 vs 5706.4 cm^2, $P = 0.004$) and tibial cortical thickness (mean, 4.6 vs 5.1 mm, $P = 0.006$) as well as height (mean, 161.4 vs 164.8 cm, $P = 0.026$) were smaller in comparison to control subjects. At tibial site, their muscle area correlated positively with bone area, bone density, cortical thickness, periosteum circumference, but not with height. In control females, muscle area correlated only with muscle density at tibial site. For APECED females with PAI ($n = 14$), muscle area at tibial site was smaller (median, 4766.9 vs 5927.6 cm^2, $P = 0.025$) than in patients without PAI ($n = 4$). In males with APECED, muscle area (mean, 5963.8 vs 7222.8 cm^2, $P < 0.001$) and tibial cortical thickness (mean, 5.1 vs 5.9 mm, $P = 0.002$) and periosteal circumference (median, 72.7 vs 78.4 mm, $P = 0.012$), as well as height (median, 173.0 vs 182.7 cm, $P = 0.003$) were smaller in comparison to control males. There were no correlations between muscle area and any tested bone parameters at tibial site in males with APECED or in control males. DXA-derived values showed no correlation between total muscle mass and whole-body BMD in females or males with APECED. However, muscle area in pQCT at tibial site correlated with whole body BMD in DXA ($\tau = 0.621$, $P < 0.001$) in females but not in males with APECED. Significance Our findings show that the inferior bone parameters in subjects with APECED are associated to some extent with muscle properties. Physical performance testing could shed light to clinical implications of these findings.

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P788

JOINT2214

EMPOWER-TRANS* - development and implementation of innovative, digital information and training concepts for children with gender incongruence/gender dysphoria (GI/GD) and their families

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In recent years there has been a steady increase in the number of children and adolescents whose sex assigned at birth does not match their self-perceived gender identity. The desire to resolve this distress often leads to the utilisation of gender reassignment medical treatments, such as hormonal and surgical interventions. Treating and informing this group of people is complex and requires the involvement of various specialist disciplines. There are also particularly high quality standards for the care of minors. There are only a few specialist centres and specialist practices available for this throughout Germany. The resulting long waiting times can further increase the level of suffering. The intervention consists of two elements: Patients and their families have access to multi-perspective, guideline-compliant information via a digital platform. A comprehensive digital training intervention provides the opportunity to address the topics in greater depth and respond to individual needs at an early stage. It is also possible to exchange information with other people affected. The two concepts are intended to provide larger groups of patients throughout Germany with highly qualified, guideline-based medical psychoeducation, which means a sustainable increase in efficiency compared to the currently practised resource-intensive individual initial information at a few specialist centres/specialist practices. The aim of the project is to develop and test a digital information and training programme by researchers from various disciplines. The children and young people affected and their carers should receive comprehensive information and help with self-management in everyday life. As the support is offered digitally, the specialised human and financial resources can be used optimally. This means that frequently requested information can be provided even before an initial consultation with a doctor. As a result, initial consultations can be shorter and more personalised. This in turn increases the capacity for making appointments and shortens waiting times. If successful, the service provides those affected with rapid access to high-quality and comprehensive information, reduces high levels of psychological stress and helps to avoid underuse and inappropriate care.

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P789

JOINT3889

Clinical presentation and genotype-phenotype association of 95 patients with pathogenic mutation in the menin gene

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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is a rare hereditary tumor syndrome primarily associated with an increased risk of primary hyperparathyroidism (PHP), pituitary adenomas, and pancreatic-duodenal neuroendocrine tumors (DP-NET). Until now, no genotype-phenotype has been identified.
Materials and Methods
Consecutive patients with class 4 or 5 mutations followed at Rigshospitalet, Copenhagen (covering half of the Danish MEN1 population), were included. The aim of the study was to describe the clinical presentation and possible association to genotype using survival statistics with log-rank test. We focused on 5 outcomes; age at diagnosis of the 3 main MEN1 manifestation and age of surgery for PHP and DP-NET.
Results
The study included 96 patients (61 females). Mean age at data extraction was 45 $\pm$22 years, mean age at genetic diagnosis was 33 $\pm$19 years. Seventy-seven (80%) had PHP, 10% by age 20, 70% by age 40, 90% by age 60, and 100% by age 80. Sixty-one (79%) underwent parathyroidectomy. Pituitary adenomas were identified in 25 (26%) of patients, 5% at age 20, 20% at age 40, 30% at age 60, and 50% at age 80. Three patients had pituitary surgery. DP-NET were present in 67 (70%) patients, 5% at age 20, 35% at age 40, 75% at age 60, and 95% at age 80. Seventeen (25%) underwent pancreatic surgery. Nine patients died (3 MEN1 related), mean age 74 (range 49 to 93) years. Genetic variants: Frameshift 36/95, missense 24/95, nonsense 19/94, intron variant 11/95, splice variant 4/95, structural variant 1/95 (deletion exon 3-10). The variants were initially grouped in 3: 1) nonsense, frameshift and deletion (truncated protein) 2) missense (affecting protein function), 3) intron and splice variants (abnormal splicing). We found no significant genotype-phenotype, but the result of the initial analyses prompted us to compare missense variants with the rest. For all outcomes missense variants had a better prognosis with the lowest *P*-value for development of PHP and for surgery for DP-NET. By the age of 40 around 50% of patients with missense mutations had PHP vs. 80% among the rest ($P = 0.03$) and non with missense variants had surgery for DP-NET at the age of 40 vs. 20% among the rest ($P = 0.07$)
Conclusion
We confirmed almost 100% penetrans of both PHP and DP-NET. The prognosis was good with a life expectancy close to the background population. Our data suggest that missense variants might be associated with a slightly better prognosis.

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P790

JOINT2564
Is hypernatremia related to insulin resistance in type 1 myotonic dystrophy?
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Myotonic dystrophy type 1 (DM1) is a dominantly inherited multi-system disease caused by expanded CTG repeats in the 3' untranslated region of the *dystrophia myotonica protein kinase* (DMPK) gene. Similar to other repeat disorders, the expanded trinucleotide repeat is unstable with a tendency to increase repeat size with age. The clinical spectrum ranges from lethal presentations in infancy to mild, late-onset disease. DM1 causes myotonia, muscle weakness and cardiac, lung and cognitive impairment, early onset cataracts and various endocrine disorders including insulin resistance, goiter (*Ben Hamou A OJRD 2019*) and an unexplained trend to high blood sodium level (*Smals AG Neth J Med. 1980*). A neurogenic cause was not confirmed (*Descloquement K SFE 2008*). Mexiletine is known to improve myotonia by blocking muscle sodium channels Nav1.4. In addition, cardiac conduction disorders which represent the 2nd cause of mortality in DM1 are linked to alterations in MBNL1 causing dysregulation of alternative splicing of the *SCN5A* gene which encodes voltage-gated sodium channels Nav1.5 (*Freyermuth F Nat Comm 2016*) and depends on insulin signaling through the PIP3 pathway (*Polina I PNAS 2020*). In view of recent advances in the knowledge of voltage-gated sodium channels and their link with glucose metabolism, the hypothesis of a relationship between hypernatremia and levels of insulin resistance in DM1 was investigated.
Objective
To compare serum sodium levels, phenotype and genotype between 3 groups of DM1 patients according to their degree of insulin resistance explored in the frame of a University Reference Center of Neuromuscular Diseases.
Methods
Retrospective cross-sectional study in 100 DM1 patients classified into 3 groups: 44 DM1 with normal OGTT, 36 with glucose intolerance and 20 with diabetes after a systematic OGTT except if diabetes was already known. Patients treated with diuretics, SGLT2 inhibitors or cortisone were excluded.
Results
Sex ratio, number of CTG repeats and natremia did not differ between the 3 groups. Median age ($P < 0.0001$) and BMI ($P < 0.05$) differed between the 3 groups. Natremia positively correlated with the number of *CTG* repeats ($r = 0.37$; $P < 0.001$). Patients with natremia $\geq$ 143 mmol/l had more pacemakers, indicating a higher severity of the disease ($P < 0.05$).
Conclusion
these results suggest that natremia measurement could be an inexpensive marker of cardiac DM1 severity, ultimately poorly correlated with insulin resistance. The relationship with voltage-gated sodium channels needs to be further investigated.

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P791

JOINT172
Systematic analysis and network mapping of disease associations in autoimmune polyglandular syndrome
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Autoimmune polyglandular syndrome (APS) is a complex disorder in which endocrine, non-endocrine organ-specific and systemic autoimmune diseases coincide. The purpose of our work was to provide a data-driven perspective to the field, in addition to traditional clinical observations and patient classification strategies. Our study was conducted in a tertiary medical center in Hungary. Medical records of 7559 outpatients were analyzed, autoimmune origin was proved in 3180 cases of which 380 (12%) were diagnosed with APS. Data handling and manipulation were done both in Python and R. Network analysis, clustering and dimensionality reduction were used for visualization purposes. The median age of the patients at the diagnosis of APS was 32 years, with 84% of them being female. APS started 7 to 8 years earlier in men than in women. Type 1 diabetes mellitus and coeliac disease manifested significantly earlier than other component diseases of APS. Hashimoto's thyroiditis was the most common manifestation in our cohort, accounting for 67.4% of individuals, followed by Graves' disease and type 1 diabetes mellitus (26, 8% and 20, 8% of the cases, respectively). Twenty-eight distinct autoimmune disorders were diagnosed forming 113 combinations. Combinations occurring at least 10 times, or more were responsible for 51, 3% of cases. The network analysis and the dimensionally reduced projection mapping differentiated HT and GD as the cornerstones of APS among the component diseases. However, an almost complete overlap of the associated conditions was found. Thyroid autoimmunity was frequently associated with gastrointestinal and systemic manifestations and these patterns of associated conditions substantially differed from that of T1D, AD or CeD when assessing them as first manifestations, raising the question of a common biological causality behind the co-occurrence. In conclusion, APS is more prevalent than it is shown in the literature. Implementing screening and follow-up protocols focusing on additional autoimmune disorders is crucial in patients with autoimmune diseases. Clinical registries are also essential for the assessment of the true prevalence of the syndrome.

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P792

JOINT2329
Endocrine involvement in a wide cohort of children and adults affected by 22q11.2 Deletion Syndrome
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Introduction
Several studies have investigated single endocrine manifestations of 22q11.2 Deletion Syndrome (22q11.2DS), however, data on the comprehensive endocrinological involvement in children and adults are currently scanty.
Aim
The present study addresses the broad spectrum of endocrine manifestations in 22q11.2DS across all age groups, investigating genotype-phenotype correlations and disease-onset, to refine follow-up strategies.
Materials and Methods
Retrospective cross-sectional study on 71 patients with 22q11.2DS. Clinical, biochemical and genetic data were retrieved from medical records.
Results
We included 71 patients (M/F 37/34; 38 children and 33 adults; median age 13.8, range 1.2-51.5 years). Endocrine manifestations were found in 32/71 patients (45.1%, 16 children and 16 adults). Hypocalcemia due to hypoparathyroidism was the most common feature (28/32 patients), with neonatal onset in 16/28 patients (57.1%), half of whom were symptomatic. Later-onset hypocalcemia occurred in 12 patients (7 children and 5 adults), all asymptomatic. Chronic hypoparathyroidism was present in 44% of patients with neonatal onset and 67% with later-onset, affecting globally 21% of patients. Thyroid dysfunction was observed in 12/71 patients (16.9%, 5 children, 7 adults), 11 with primary hypothyroidism and one with early-onset Graves' disease; 2 euthyroid patients presented thyroid autoantibodies. Thyroid disease was significantly associated to hypoparathyroidism (8/28 vs 4/43 patients; $P = 0.034$). Short stature, reported in 20.8% of patients (23.7% of children, 15.2% of adults), was neither due to growth hormone deficiency nor linked to major comorbidities (palatal defects, infections, heart disease). Obesity was more prevalent in adults than children (27.3% vs 5.6%) and resulted associated with psychiatric disorders ($P = 0.033$) and their medications ($P = 0.003$), with 4.7-fold increased risk in psychiatric patients. The latest-onset endocrinopathy occurred at the age of 30 years. Most patients (46/55, 83.6%) had a classic deletion (CD, 2.5-3 Mb), 8 patients (14.5%) short deletion (<2.5 Mb) and one (1.8%) long deletion (>3 Mb). Hypoparathyroidism and hypothyroidism were more prevalent in CD patients (45.7% and 19.6%, respectively). However, no correlation was found between deletion length and endocrinopathies, whereas neonatal pathologies positively correlated with CD ($P = 0.021$).
Conclusions
This study provides the first comprehensive analysis of endocrinological involvement in pediatric and adult patients with 22q11.2DS, featuring all age groups. The most common conditions were hypoparathyroidism, hypothyroidism, and short stature. Our findings highlight the importance of monitoring patients at all ages and might suggest that check-ups frequency could be reasonably reduced after the age of 30 years for those without existing endocrinopathies.

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P793

JOINT1669

Associations of healthy lifestyle with all-cause and cardiovascular disease mortality in patients with cardiovascular-kidney-metabolic syndrome: two prospective cohort

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Background
Cardiovascular-kidney-metabolic (CKM) syndrome is a newly defined condition involving metabolic risk factors, chronic kidney disease, and cardiovascular disease (CVD), which significantly increases the risk of mortality. While a healthy lifestyle has been shown to improve health outcomes in the general population, its impact on CKM patients remains unclear. This study investigated the association of a healthy lifestyle with all-cause and CVD mortality in CKM patients.
Methods
We analyzed 79, 350 CKM patients from the UK Biobank (2006-2010, follow-up until 2021) and 9, 823 CKM patients from NHANES (2007-2018). The CKM patients were categorized into stages 0-4, with stages 3 and 4 classified as advanced CKM. A healthy lifestyle score (0-7 points) was created based on seven factors: no current smoking, moderate drinking, healthy diet, regular physical activity, adequate sleep, low sedentary behavior and appropriate social connection. Primary outcomes were all-cause and CVD mortality from linked health records and death registries. Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality risk.
Results
During follow-up, the UK Biobank recorded 7, 299 all-cause deaths and 1, 685 CVD deaths, and NHANES reported 833 all-cause deaths and 266 CVD deaths. Cox regression models showed that higher lifestyle scores were associated with reduced risks of all-cause (HR: 0.82, 95% CI: 0.80-0.83) and CVD mortality (HR: 0.81, 95% CI: 0.77-0.84) in the UK Biobank. In NHANES, higher scores were associated with 18% (95% CI: 0.78-0.87) and 15% (95% CI: 0.77-0.94) lower risks of all-cause and CVD mortality, respectively. Regular physical activity and low sedentary behavior were beneficial for the risk of all-cause and CVD mortality in both databases ($P < 0.05$). Compared with participants with advanced CKM syndrome and unfavorable lifestyle (0-2 points), those with non-advanced CKM syndrome and favorable lifestyle (6-7 points) had the lowest risk of all-cause and CVD mortality. In the UK Biobank, the HRs were 0.23 (95% CI: 0.20-0.26) and 0.13 (95% CI: 0.10-0.17), respectively; In NHANES, the HRs were 0.22 (95% CI: 0.11-0.41) and 0.25 (95% CI: 0.08-0.80), respectively.
Conclusion
We found that adherence to a healthy lifestyle was significantly associated with a reduced risk of mortality in patients with CKM syndrome, with more pronounced benefits observed in the early stages. These findings highlight the potential benefits of promoting a healthy lifestyle to improve long-term survival in patients with CKM syndrome.

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P794

JOINT46

First comprehensive quantification of the human endocrinome: patterns in hormone distribution and their physiological significance

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Background
Despite the fundamental role of the endocrine system in human physiology, basic questions such as the total number of human hormones and their cumulative abundance have remained unanswered. While specific hormone circuits are well-studied, the relative abundance patterns across the entire human endocrinome remain undefined, limiting our understanding of system-wide endocrine regulation.
Methods and Findings
We conducted an integrative analysis of the human endocrinome by leveraging clinically validated reference ranges across major endocrine subsystems. We compiled data for the routinely assayed hormones spanning all endocrine glands and hormone-secreting tissues, validated our findings using published datasets, and developed strict inclusion criteria to systematically evaluate 7, 996 candidate molecules from published databases. This rigorous curation yielded a comprehensive list of 187 bona fide human hormones. Our analysis revealed that the total mass of circulating hormones in healthy young adults is approximately 40 mg (39.5 ± 1.5mg for men, 41.5 ± 1.5mg for women), with an estimated uncertainty under 5%. Two hormones, Adiponectin and DHEA-S are dominant, constituting over 90% of both total hormone mass and copy number. We identified marked sexual dimorphism, with females having approximately half the number of circulating hormone molecules compared to males in terms of absolute number (≈ 14 μmol vs ≈ 25 μmol). Analysis of abundance patterns revealed previously unrecognized relationships between hormone type, functionality, and abundance. These include the unexpected striking predominance of DHEA-S, usually referred to as merely another hormone precursor reservoir, and systematic deviations from established signal propagation patterns in hypothalamic-pituitary axes that suggest previously overlooked regulatory mechanisms. The main limitation of our study is the paucity of large unbiased datasets of hormone levels in healthy adults, as most hormones are not part of routine screening tests, creating inherent selection bias in existing clinical data.
Conclusions
This first comprehensive quantification of the human endocrinome establishes fundamental parameters of hormone abundance and distribution. Our systematic analysis reveals unexpected patterns in sexual dimorphism, hormone abundance

hierarchies, and signal propagation schemes that challenge current paradigms of endocrine regulation. These findings provide an essential framework for developing targeted endocrine profiling approaches and understanding system-wide hormone dysregulation in pathological states.

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P795

JOINT2950

Respiratory and sleep disorders in children with prader willi syndrome: prevalence and characterization

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Introduction

Prader Willi Syndrome (PWS) has a broad clinical spectrum whereas respiratory disorders are major causes of morbidity and mortality across the lifespan. The approach must include close monitoring to minimize the risks.

Aim

To describe respiratory and sleep patterns in a cohort of PWS children.

Materials and Methods

Retrospective evaluation of respiratory and sleep patterns in a cohort of 25 pediatric PWS patients admitted at Ricardo Gutierrez Children hospital from 2002 to 2024. Variables analyzed were body mass index (BMI kg/m^2), pituitary function (TSH, free T4, cortisol), recombinant human growth hormone treatment (rhGH 1 mg/m^2/d), tonsils volume; obstructive sleep apneas (OSA), central apneas (CSA), nocturnal hypoventilation by Polysomnography (PSG) and daytime sleepiness by multiple sleep latency test (MSLT).

Results

Median age at admission was 3.3yr (0.4 to 13.6yr), 52% boys. The genetic mechanism was the deletion of 15q11.2-q13 chromosomal region (60%) and maternal uniparental disomy (40%). Hypothyroidism was diagnosed in 21% and none had adrenal insufficiency until their last examination. Basal median BMI was 2.35 SDS (-1.9 to 11 SDS). Median time between diagnosis and respiratory evaluation was 4.9yr (0.8 to 18.9yr). Anamnesis revealed snoring in 56% and clinical examination showed tonsillar hypertrophy in 83% of the cases. Twenty-one patients were evaluated prior to rhGH indication: 18/21 (86%) had OSA, 3 CSA and 1 nocturnal hypoventilation. Ulterior indications were only clinical follow up in 8/21, tonsillectomy in 5/21, tonsillectomy and non-invasive mechanical ventilation in 1. Seven patients were suitable to begin rhGH treatment whereas 4 patients required specific interventions before rhGH indication. Three patients were already under rhGH at first respiratory evaluation: 1 had mild OSA. None of the patients who underwent tonsillectomy developed velopharyngeal insufficiency post-surgery. Sleep disorders were diagnosed in 5/25: narcolepsy in 3 cases and cataplexy in 2. Individualized medical interventions were implemented. Six patients under rhGH developed respiratory disorders during follow-up (1 to 4 yr): 5 tonsillar hypertrophy and OSA, and 1 CSA concomitant with respiratory infection. Median ΔBMI was 0.01 (-0.37 to 2.86 SDS). In patients under rhGH there was no significant correlation between the occurrence of respiratory events and ΔBMI.

Conclusion

Respiratory and sleep disorders were a prevalent comorbidity in this cohort of PWS children and detected only by careful anamnesis and specific tests performed by trained specialists. Regular examination of respiratory and sleep disorders before and during rhGH treatment should be included in the multidisciplinary approach of PWS.

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P796

JOINT605

Evaluation of the relationship between metabolic-associated fatty liver disease and sarcopenic obesity in patients with diabetes

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Objective

To assess the relationship between metabolic-associated fatty liver disease (MAFLD) in patients with diabetes and sarcopenic obesity (SO) indices.

Materials and Methods

The study included 92 patients with diabetes (45 men and 47 women). The average age of patients was 55.90 ± 14.18 years and duration of diabetes was 16.80 ± 9.34 years. Muscle strength (MS) was assessed using hand dynamometry measuring arm strength. Muscle function (MF) was assessed using the 4-meter walking speed test. Muscle mass (MM) and fat mass (FM) were assessed using dual-energy X-ray absorptiometry (DXA) ("lunAR prodigy") as the ratio of appendicular muscle mass (AMM) to height (AMM/m^2), AMM to weight (AMM/weight), FM to height (FM/m^2). The body mass index (BMI), waist circumference (WC), and glycated hemoglobin (HbA1c) were determined. The presence of MAFLD was determined based on the results of ultrasound examination of the liver and calculated diagnostic indices (ST-index, FLI). Statistical processing was performed using the statistical program «Statistica 10.0».

Results

In patients with diabetes, 86% of cases taking into account the ST- index and 96% of cases taking into account the FLI were found to have SO. FLI is positively associated with the age of patients ($r_s = 0.46$; $p < 0.05$), BMI ($r_s = 0.92$; $p < 0.05$), WC ($r_s = 0.90$; $p < 0.05$), FM/m2 ($r_s = 0.69$; $p < 0.05$), AMM/m2 ($r_s = 0.46$; $p < 0.05$) and negatively associated with MS ($r_s = -0.34$; $p < 0.05$), MF ($r_s = -0.32$; $p < 0.05$), AMM/weight ($r_s = -0.64$; $p < 0.05$). ST- index is positively correlated with patients' age ($r_s = 0.68$; $p < 0.05$), BMI ($r_s = 0.88$; $p < 0.05$), WC ($r_s = 0.92$; $p < 0.05$), FM/m^2 ($r_s = 0.70$; $p < 0.05$), AMM/m^2 ($r_s = 0.34$; $p < 0.05$) and negatively correlated with MS ($rs = -0.33$; $p < 0.05$), MF ($r_s = -0.45$; $p < 0.05$), AMM/weight ($r_s = -0.62$; $p < 0.05$). FLI and ST-index are not correlated with the duration of diabetes and the level of Hb1c ($p > 0.05$).

Conclusion

In patients with MAFLD and diabetes, 86% to 96% of cases show SO associated with the patient's age and independent of the duration of diabetes and the Hb1c level. MAFLD in diabete is associated with a change in body composition due to a decrease in MM and an increase in FM, the degree of decrease in MS and MF.

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P797

Abstract Unavailable

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P798

JOINT3328

Decoding clinical heterogeneity in ornithine transcarbamylase deficiency: novel mutations and therapeutic outcomes from a longitudinal cohort study

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Objective

To characterize the clinical spectrum, genetic landscape, and long-term therapeutic efficacy in pediatric-onset ornithine transcarbamylase deficiency (OTCD).

Methods

A retrospective longitudinal cohort study of 7 OTCD patients (3 males, 4 females) with confirmed biochemical/genetic diagnoses and ≥24-month follow-up (median 38 months, range 16-41). Comprehensive analyses integrated metabolic profiling, next-generation sequencing, and multidisciplinary outcomes assessment (neurological, hepatic, developmental).

Results Clinical presentation

Age at diagnosis ranged from 10 days to 7.3 years. Hyperammonemic crises (71.4%, 5/7) manifested as recurrent vomiting (100%), encephalopathy (60%), and seizures (40%), with 42.9% (3/7) exhibiting pre-existing neurodevelopmental delays. **Genetic landscape:**Seven distinct *OTC* mutations identified, including two novel pathogenic variants (c.241T>C, c.490T>G; ACMG Class IV) unreported in global databases. **Therapeutic trajectories:**Medical therapy cohort ($n = 2$): Intermittent hyperammonemia (45-78 μmol/l) persisted in patients receiving sodium phenylbutyrate or arginine/citrulline, correlating with

suboptimal adherence (30% missed doses). Despite episodic vomiting (1-2 annual episodes), anthropometric parameters remained age-appropriate. **Transplant cohort ($n = 5$):** All achieved complete metabolic normalization (ammonia ≤ 40 µmol/l, stable hepatic function) post-transplant, with neurodevelopmental improvement (ΔDQ +1.2-2.3 SD) and age-appropriate cognition (DQ 85-102) at final assessment.

Conclusions

This study establishes three critical insights for OTCD management:

1. Diagnostic urgency: Plasma amino acid profiling with urinary orotic acid quantification enables rapid triage of suspected cases.

2. Therapeutic hierarchy: Liver transplantation delivers superior outcomes for severe phenotypes, achieving sustained metabolic control and neurocognitive recovery.

3. Precision care imperative: Novel mutation identification reinforces genotype-phenotype correlations, while suboptimal pharmacotherapy adherence highlights the need for structured transition programs.

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P799

JOINT3886

Successful transition strategies in turner syndrome

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Background

Since 2019, there have been special centers in Germany that provide guideline-based treatment for girls and women with Turner syndrome (TS). The involvement of paediatric and internal medicine disciplines is a prerequisite for ensuring compliance with examinations and drug therapies during the transition to adulthood. The Clinic for paediatric endocrinology and diabetology at Charité-Universitätsmedizin Berlin and the adult's outpatient center for endocrinologic diseases at the HELIOS-Klinikum Berlin-Buch were certified for treating TS patients in 2020 improving health outcomes in TS throughout the lifespan. Transition only started in 2021 due to the covid-pandemia.

Design and Methods

Retrospective analysis of women transferred between paediatric endocrinology at the Charité-Universitätsmedizin Berlin and the adult outpatient clinic for endocrinological diseases at the HELIOS-Klinikum Berlin-Buch. Descriptive analyses included age at transfer, attendance at transfer meetings and subsequent appointments, adherence to hormone and other therapy, and attendance at recommended regular check-ups. Attendance at two visits to the adult outpatient clinic was defined as a successful transition.

Results

Since 2021, all women with TS whose treatment was no longer continued in paediatrics were referred to adult medicine within the Turner Center's transition consultation hours ($n = 13$). Age at transition visit ranged from 17-21 years (mean 18.8 years). All women had completed school and all but one were in training or a student. Further care in adult medicine was desired. Almost all girls attended the first visit to the adult center (12/13), the overall drop-out rate was 15% (2/13). 100% of the successfully transferred girls with ovarian insufficiency were on regular hormone replacement therapy. All successfully transferred girls received cardiac MRI, whereas referral to specialised outpatient units according to Gravholt consensus recommendations was often lacking. So far, the transition process is not being financed by health insurance for all patients.

Conclusion

The designation of TS centers can improve guideline-based management of women with Turner syndrome across the lifespan. The rate of successful transition in our center is high, as is the rate of women taking their hormone replacement therapy regularly and attending recommended check-ups. This is an important step in the prevention of conditions such as cardiovascular disease and bone disease in women with Turner syndrome.

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P800

JOINT2686

Algorithmic approach for the of hashimoto's thyroiditis: a case control indian study

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Background

The varied and non-specific nature of diagnostic criteria of Hashimoto's thyroiditis often leads to sub optimal diagnosis and resultant sub optimal management. The aim of this study is to propose a comprehensive diagnostic scoring algorithm based on reproducible multi-component objective clinico-investigative criteria.

Methods

A case-control study of patients who underwent surgical thyroidectomy, were compared with a set of clinical, biochemical, pathological parameters in patients with Hashimoto's thyroiditis ($n = 60$) and controls ($n = 60$), in order to design a comprehensive multi-parametric scoring system. We analysed twelve criteria - Age, Sex, goiter grade, associated pathology, duration of disease, euthyroid/hypothyroid status; family history, presence of auto-immune features, anti-thyroid peroxidase titer, anti thyroglobulin antibody titer, thyroid cytopathological diagnosis of HT, extent of thyroidectomy. All these features were analysed and scored in comparision with histopathology as gold standard. A different validation cohort of 36 patients were reviewed and classified according to the score. Linear correlation and descriptive statistics were performed with SPSS 20.0 version.

Results

The study parameters were dichotomized in to major criteria (euthyroid/hypothyroid status; family history, presence of auto-immune features, anti-thyroid peroxidase titer, anti thyroglobulin antibody titer, thyroid cytopathological diagnosis of HT) and minor (Age, Sex, goiter grade, associated pathology, duration of disease, extent of thyroidectomy) criteria. Diagnostic accuracy of various combinations of major criteria were – with $6 = 100\%$; $5 = 100\%$; $4 = 100\,\%$; $3 = 100\%, 95\%, 85\%$; $2 = 90\,\%$; $1 = 82\,\%$. Finally, score of atleast $\geq$ 3/6 major criteria, with mandatory elevated anti Tg and anti TPO Ab titer was diagnostic of HT. This diagnostic accuracy was statistically significant compared to controls.

Conclusions

This multi-parametric scoring algorithm appears to be a practical, accurate and straightforward in the accurate diagnosis and subsequent optimal management of Hashimoto's thyroiditis.

Keywords Hashimoto's thyroiditis; goiter; histopathology; thyroidectomy; thyroglobulin)

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P801

JOINT2204

Efficacy and safety of finerenone in type 2 diabetes with chronic kidney disease

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Background and Aims

Finerenone, a non-steroidal mineralocorticoid receptor antagonist, has been shown to reduce albuminuria and slow chronic kidney disease (CKD) progression in patients with type 2 diabetes mellitus (T2DM). However, real-world data on its impact on kidney function and albuminuria reduction in patients with different CKD stages remain limited. This study aimed to evaluate the effects of finerenone on estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR) in patients with T2DM and CKD stages 3A–4.

Materials and Methods

A total of 45 patients with T2DM and CKD stages 3A–4 were included in the study. The mean age was 63.3 ± 5.7 years, with a diabetes duration of 7.2 ± 4.5 years (data are presented as mean $\pm$ SD). The baseline HbA1c was $7.6 \pm 0.15\%$, serum creatinine 115.6 ± 3.7 µmol/l, and potassium 4.1 ± 0.07 mmol/l. Patients were stratified by CKD stage: 28 with stage 3A (eGFR 45–60 mL/min/1.73m^2), 10 with stage 3B (eGFR 30–44 mL/min/1.73m^2), and 7 with stage 4 (eGFR 25–30 mL/min/1.73m^2). Baseline ACR was <30 mg/g in 27 patients, 30–300 mg/g in 14 patients, and >300 mg/g in 4 patients. Finerenone was initiated at 10 mg/day in patients with eGFR 25–59 mL/min/1.73m^2 and 20 mg/day in those with eGFR ≥ 60 mL/min/1.73m^2, with monthly potassium monitoring and dose adjustments as needed. The data were compared using Student's t-test and correlation analysis.

Results
After 3 months of treatment, eGFR increased by 6% (54.04 ± 2.35 mL/min/1.73m^2, $P < 0.05$), while ACR decreased by 13% (46.27 ± 14.57 mg/g, $P < 0.05$). The most pronounced improvement in eGFR and ACR was observed in patients with CKD stage 3A and 3B. A significant inverse correlation was found between eGFR and ACR ($\rho = -0.62$, $P < 0.05$), with the strongest association in CKD stage 3A ($\rho = -0.71$). Serum potassium levels remained stable (4.04 ± 0.04 mmol/l, $p > 0.05$), and no cases of hyperkalemia (>5.0 mmol/l) were reported.
Conclusion
Finerenone effectively improved kidney function and reduced albuminuria in patients with T2DM and CKD stages 3A–4. The most significant benefits were observed in patients with CKD stage 3A–3B. Treatment was well tolerated, with no significant hyperkalemia. These findings support the use of finerenone in early-stage diabetic kidney disease to slow disease progression.

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P802

JOINT306

Clinical characteristics and influencing factors of children with MT-TL1 gene m.3243A>G mutation: a phenotypic study based on 11 han chinese patients

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Background
The *MT-TL1* gene encodes mitochondrial tRNA $^{leu\ (UUR)}$, playing a crucial role in mitochondrial protein synthesis. Mutations in this gene are associated with various mitochondrial diseases, often exhibiting clinical phenotypic heterogeneity. This study aims to retrospectively analyze 11 pediatric inpatients carrying the same *MT-TL1* gene mutation to explore phenotypic variation and potential influencing factors.
Methods
We retrospectively analyzed 11 pediatric patients diagnosed with *MT-TL1* gene mutations at our hospital between 2012 and 2024, along with their family histories. Clinical data were collected and analyzed, including demographics, age at diagnosis, clinical manifestations, imaging, and laboratory Results Phenotypic differences between the patients were systematically compared to evaluate the heterogeneity of the m.3243A>G mutation in children.
Results
Despite all 11 patients carrying the same *MT-TL1* mutation, their clinical presentations varied significantly. The average diagnostic delay was 3.35 years. Neurological symptoms were present in 81.8% of the patients, 72.8% had endocrine issues, 18.2% had visual impairments, and 9.1% experienced bilateral hearing loss. Cardiac abnormalities were found in 63.6% of patients, 81.8% had gastrointestinal symptoms, 36.4% exhibited hypertrichosis, and 27.3% had used a ventilator. Plasma lactate levels were elevated in 90.1% of patients, with 80% exceeding 5 mmol/l. Additionally, 81.8% showed exercise intolerance and muscle weakness. Based on the diagnostic criteria, 45.5% were diagnosed with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), 18.2% were diagnosed with both MELAS and neuropathy, ataxia, and retinitis pigmentosa (NARP), and 54.5% were diagnosed with mitochondrial myopathy. Family history analysis revealed that three patients had relatives retrospectively diagnosed with mitochondrial myopathy, two were diagnosed with diabetes, and two with Kallmann syndrome.
Conclusion
This study highlights the clinical heterogeneity of the same *MT-TL1* gene mutation in pediatric patients. Over 80% of the patients exhibited symptoms such as epilepsy, imaging abnormalities, short stature/malnutrition, gastrointestinal symptoms, elevated lactate levels, and muscle weakness. More than one-third of patients experienced stroke-like episodes, developmental delays, myocardial damage, elevated liver enzymes, abdominal pain, and hypertrichosis. Pediatric patients with these recurrent symptoms should be considered for m.3243A>G mutation screening.

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P803

JOINT952

The role of MRI and ferritin in assessing iron overload and endocrine dysfunction in thalassemia major: focus on pituitary MRI findings

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Background
Thalassemia major, a transfusion-dependent disorder, is commonly associated with chronic iron overload, resulting in significant endocrine dysfunctions such as impaired growth and delayed puberty. While serum ferritin is widely used as a marker of iron burden, it lacks specificity in predicting organ-specific damage. Magnetic resonance imaging (MRI) provides a more detailed evaluation of iron deposition, particularly in the pituitary gland, liver, pancreas, and heart. Understanding these correlations is critical for early diagnosis and effective management.
Objective
To assess the relationship between ferritin levels, MRI findings, and endocrine dysfunction, with a specific focus on pituitary MRI changes in thalassemia major.
Methods
A systematic review of 20 studies published from 2000 to 2025 was conducted, encompassing over 2,000 patients. The analysis included data on MRI-detected iron overload in the pituitary, pancreas, liver, and heart and their correlations with endocrine dysfunction. Relative impacts of iron burden were calculated based on MRI findings and ferritin correlations.
Results
- Pituitary Findings: MRI revealed reduced pituitary volume, hypointense T2* signals (<20 ms), and structural abnormalities. These findings were associated with hypogonadotropic hypogonadism and growth hormone deficiency, contributing to delayed puberty and stunted growth. The relative impact of pituitary iron overload was 80%, with a moderate ferritin correlation (0.8).
- Pancreatic Findings: Low T2* values (<20 ms) correlated with diabetes mellitus and glucose intolerance. The relative impact was 50%, and ferritin showed a weak correlation (0.5), highlighting the superior predictive value of MRI for pancreatic iron.
- Liver Findings: Liver iron concentration (LIC >7 mg/g dry weight) moderately correlated with ferritin (0.7) and was linked to thyroid and adrenal dysfunction, with a relative impact of 70%.
- Cardiac Findings: Low T2* values (<20 ms) reflected iron overload associated with cardiomyopathy risk. Ferritin showed a weak correlation (0.4), with a relative impact of 40%.

Conclusion
MRI is crucial in detecting organ-specific iron overload and its association with endocrine dysfunctions. Pituitary MRI findings strongly correlate with hormonal abnormalities and growth retardation, emphasizing its diagnostic and prognostic value. Ferritin, while accessible, often underestimates localized iron burden. Combining MRI with ferritin measurements improves diagnostic accuracy and facilitates early, targeted interventions to manage endocrine complications effectively.
Keywords
Thalassemia major, MRI, iron overload, ferritin, endocrine dysfunction, growth retardation, pituitary abnormalities.

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P804

JOINT2146

Assessment of facial morphologic features in patients with polycystic ovary syndrome using deep learning:a multi-center cross-sectional study

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Aim
To investigate the application of deep learning-based facial recognition methods to facilitate the diagnosis of PCOS by leveraging the distinctive phenotypic features associated with the condition.
Methods
A muti-center, cross-sectional study was conducted from three tertiary hospitals in China from June 2023 to August 2024. A total of 163 participants with polycystic ovary syndrome (PCOS) and 162 non-PCOS women were recruited. Images were captured from multiple angles and were supplemented with clinical and metabolic data, including body mass index (BMI), glycated hemoglobin (HbA1c), blood lipid profiles, and sex hormone levels. Three convolutional neural network architectures (VGG-Net, ResNet-50, Inception-ResNet-v2) and Gradient-weighted Class Activation Mapping (Grad-CAM) were employed to distinct discriminative features in patients with PCOS.
Results
The mean age in participant with PCOS was 26.56 years old and have a higher body mass index (BMI), reduced number of menstrual cycles per year, elevated total testosterone and worse glycolipid metabolism than those without PCOS. Inception-ResNet-v2 achieved the highest accuracy for PCOS diagnosis, at 82.1%, whereas ResNet-50 and VGG-16, with an accuracy of 78.57% and 73.21% respectively. Inception-ResNet-v2 (AUC = 0.886) demonstrates the best performance for PCOS diagnosis, with its curve furthest from the diagonal. Additionally, the study employed Grad-CAM to visualize the model's focus on specific facial regions, particularly the jawline, nose, and forehead, which are indicative of PCOS traits such as hirsutism and acne.
Conclusions
Our findings demonstrated facial morphologic features in patients with PCOS was distinct and Artificial intelligence (AI)-based PCOS detection could achieve satisfactory sensitivity for detecting the patients with PCOS, which suggested the feasibility and potential of AI-driven facial recognition as a non-invasive and efficient tool for PCOS screening.
Keywords
polycystic ovary syndrome, facial recognition, deep learning.
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P805

JOINT2116

Telomere length in patients with type 2 diabetes: impact of chronic kidney disease

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Background and Aims
Telomeres are nucleoprotein structures located at the ends of chromosomes, playing a crucial role in maintaining genomic stability. In most somatic cells, telomeres progressively shorten with each cell division, eventually leading to replicative senescence or apoptosis when critically short. Previous research has demonstrated that patients with type 2 diabetes mellitus (T2DM) exhibit an increased rate of telomere shortening. However, data on telomere length in patients with both T2DM and chronic kidney disease (CKD) remain limited. The aim of this study was to assess the association between telomere length and CKD in patients with T2DM.
Materials and Methods
We analyzed 105 subjects divided into three groups. The first group included 65 patients with T2DM and CKD (mean age: 70.9 ± 8.0 years; diabetes duration: 5.9 ± 2.5 years; HbA1c: 7.1 ± 1.7%; serum creatinine: 145.0 ± 87.0 µmol/l; estimated glomerular filtration rate (eGFR): 44.0 ± 11.0 mL/min/1.73m^2; albumin/creatinine ratio (ACR): 36.0 ± 74.0 mg/g). The second group included 25 patients with T2DM but without CKD (age: 53.2 ± 6.8 years; diabetes duration: 3.7 ± 2.2 years; HbA1c: 7.6 ± 2.2%; serum creatinine: 89.6 ± 14.9 µmol/l; eGFR: 81.3 ± 12.2 mL/min/1.73m^2; ACR: 18.0 ± 9.7 mg/g). The third group included 15 control subjects without T2DM or CKD (age: 50.3 ± 3.8 years; HbA1c: 5.45 ± 0.3%; serum creatinine: 100.7 ± 22.5 µmol/l; eGFR: 83.0 ± 22.8 mL/min/1.73m^2; ACR: 11.0 ± 4.4 mg/g). Telomere length was measured in whole blood using monochrome multiplex quantitative PCR by calculating the telomere-to-single-copy gene (T/S) ratio.
Results
Telomere length (T/S ratio) was significantly higher in both groups of patients with T2DM compared to controls (0.989 ± 0.767 in T2DM with CKD, 1.11 ± 0.789 in T2DM without CKD, 0.535 ± 0.341 in controls; $P < 0.05$). No significant difference was observed between T2DM patients with and without CKD. Additionally, no significant correlation was found between telomere length and eGFR or ACR in any group.
Conclusion
Telomere length was shorter in patients with T2DM compared to controls, but CKD did not further contribute to telomere attrition. The pathogenetic and prognostic significance of telomere shortening in T2DM warrants further investigation.
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P806

JOINT1063

Prevalence, incidence and risk factors for dysnatremia in european community-dwelling older adults – a secondary analysis of the DO-HEALTH trial

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Background
Plasma sodium disorders (dysnatremia) are the most common electrolyte disorders in hospitalized patients. However, data on their prevalence and incidence in community-dwelling and generally healthy older adults are currently scarce. The aim of this study was to estimate the prevalence and incidence of dysnatremia among community-dwelling older adults from five European countries.
Material and Methods
We performed a secondary analysis of DO-HEALTH, a multicenter clinical trial including community-dwelling participants aged ≥70 years from Austria, France, Germany, Portugal, and Switzerland, without major health events in the five years prior to inclusion. The trial duration was three years with yearly in-person clinical visits and blood samples. Data about sodium were collected yearly. Dysnatremia was defined as sodium levels <135 mmol/l (hyponatremia) or >145 mmol/l (hypernatremia). Incidence rates (IR) and 95% confidence intervals over the study period were estimated using negative binomial regression models.
Results
Out of the 2157 DO-HEALTH participants, 2141 (99.3%) had available sodium at baseline. At baseline, the overall prevalence of any dysnatremia, hyponatremia and hypernatremia were 3.4%, 2.4%, and 1.0%, respectively. Participants with dysnatremia at baseline were more likely to be older, have a lower body mass index and use thiazide or thiazide-like drugs, compared to participants with normonatremia. Over the three years of follow-up, the overall IR of dysnatremia, hyponatremia and hypernatremia were 3.3 (2.7-3.9), 2.1 (1.6-2.7) and 1.2 (0.9-1.6) per 100 person-years, respectively. The use of five or more medications and the use of thiazide or thiazide-like drugs at baseline were significantly associated with higher incidence rates of any dysnatremia and higher incidence rates of hyponatremia over the follow-up. No difference in the incidence rates of any dysnatremia, hyponatremia and hypernatremia were observed by sex or age.
Conclusion
In a large sample of European generally healthy community-dwelling older adults, the prevalence of any dysnatremia was 3.4%. Over three years of follow-up, the overall incidence rate of any dysnatremia was 3.3 per 100 person-years, with higher rates among individuals using more than five medications and using thiazide or thiazide-like drugs. These findings suggest that careful monitoring of sodium levels may be relevant even in generally healthy older adults.
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P807

JOINT3723

Endocrinopathies in turkish children with inborn errors of immunity: a single-center experience

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Objective
Inborn errors of immunity (IEI) represent a heterogeneous group of genetic disorders. We aimed to investigate endocrine disorders in children with IEI.
Materials Methods
This study included 84 patients with IEI who were evaluated in the pediatric endocrinology clinic between September 2019 and September 2023.
Results
Our findings revealed that 15.6% of the 32 patients with 22q11.2 deletion syndrome had permanent hypoparathyroidism. Hypergonadotropic hypogonadism was identified in one of four female patients with ataxia-telangiectasia (AT) and in all four females with severe congenital neutropenia (SCN) due to *HAX1* deficiency. Autoimmune thyroiditis (AIT) was detected in four of the 15 patients with common variable immunodeficiency (CVID). Additionally, hypergonadotropic hypogonadism was observed in one of nine males with CVID. Among the CVID patients, one presented with AIT, type1 diabetes mellitus (T1DM), hypoparathyroidism, and primary adrenal insufficiency. Of the 307 patients followed for selective IgA deficiency (sIgAD), 26 also received care in pediatric endocrinology. Among the sIgAD cases 3.2% had AIT, and 4.5% had T1DM. A patient with a STAT1 gain-of-function (GOF) variant was diagnosed with T1DM, AIT, and growth hormone deficiency, while a patient with a novel STAT3-GOF variant developed neonatal DM.
Conclusion
Autoimmune thyroiditis and T1DM were the most prevalent endocrine disorders in IEI patients. Primary ovarian insufficiency in females with SCN and AT, and primary testicular failure in a male patient with CVID was detected. Combined endocrine disorder involving T1DM, AIT, hypoparathyroidism, and primary adrenal insufficiency was identified in a patient with CVID for the first time.

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P808

JOINT3405

A case of atypical wolfram syndrome with late diagnosis and without diabetes inspidus component

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Introduction
Wolfram syndrome is a rare autosomal recessive disorder that begins in childhood, characterized by symptoms such as type 1 diabetes, optic atrophy, hearing loss, and neurogenic bladder. In this case, a 22-year-old male patient with chronic renal failure, whose diabetes insipidus symptoms were masked, and whose diagnosis was delayed, is presented. The patient's diagnosis, with multisystem involvement, was confirmed through genetic analysis.
Case
A 22-year-old male patient, diagnosed with diabetes since the age of 3, neurogenic bladder, bilateral sensorineural hearing loss, and chronic kidney failure for 6 years, presented to the emergency department due to the depletion of his home catheter. Upon finding a blood glucose level of 420 mg/dl, he was referred to the internal medicine clinic with a preliminary diagnosis of hyperglycemia. On physical examination, syndromic findings such as growth and developmental delay, bilateral hallux valgus, optic atrophy, and hearing loss were observed. Given the multisystemic symptoms, early-onset diabetes, and syndromic features, the patient, who was not considered to have polyuria due to chronic kidney disease, was initially suspected to have Wolfram Syndrome (DIDMOAD). However, the diagnosis was excluded due to the absence of diabetes insipidus symptoms. Other syndromic diabetes diagnoses such as MODY, mitochondrial genetic disorders, and Mauriac syndrome were also considered, but genetic tests yielded results incompatible with these conditions. Finally, after consultation with the Diabetes Research Excellence Center at the University of Exeter, genetic analysis revealed a homozygous WFS1 gene mutation, confirming the diagnosis of Wolfram Syndrome.
Discussion
This case highlights the challenges encountered in diagnosing Wolfram Syndrome. Wolfram syndrome is a rare disorder that begins with diabetes at an early age and presents with multisystemic effects. Atypical clinical courses can complicate the diagnostic process, and thus the entire spectrum of the disease should be considered, rather than just the classic triad. The masking of diabetes insipidus symptoms due to chronic kidney failure was a significant factor that delayed the diagnosis. Accelerating the genetic testing process is crucial for early diagnosis and disease management. A systematic evaluation of a patient who had been undiagnosed for a long period, along with consultation from an international center, led to the correct diagnosis. Early diagnosis of Wolfram Syndrome is vital for managing its progressive complications. Therefore, it is recommended that patients with early-onset diabetes and multisystemic findings undergo detailed genetic analysis.

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P809

JOINT1142

Coexistence of thyroid autoimmunity with adrenal disease: clinical implications and insights

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Introduction
Thyroid autoimmunity and adrenal disease are two of the most frequently observed endocrine disorders that often coexist in clinical practice. The interplay between these conditions is particularly evident in autoimmune polyglandular syndromes (APS). The coexistence of thyroid autoimmunity, most commonly Hashimoto's thyroiditis (HT) or Graves' disease (GD), where in first can be seen thyroid function declining and in second case thyroid function increased with toxicity. Whereas Addison's disease (AD) is associated with declining function of adrenal cortex. Coexisting thyroid and adrenal autoimmune disorders in most cases can produce significant diagnostic and therapeutic challenges.
Materials and Methods
Published data from the past two decades from sources such as MEDLINE, PubMed, Scopus, and Web of Science were systematically analyzed to evaluate the coexistence of GD or HT with AD in APS. Data were extracted on laboratory findings, blood pressure patterns, and clinical presentations.
Results
The frequency of coexistence of GD or HT with primary adrenal insufficiency (AD) in the context of APS is summarized as follows. GD is less commonly associated with AD compared to HT. The prevalence of GD in patients with AD is estimated to be around 5-10%. HT is more frequently observed in patients with AD. The prevalence of HT in patients with AD is approximately 40-50%. Conversely, adrenal insufficiency is found in about 2-5% of patients with established autoimmune thyroid disease, including HT. According to literature coexistence of GD and AD, as seen in APS. Interestingly, coexistence both thyroid autoimmune diseases like GD or HT and AD high level TRab/TSI detected in 50-70% cases, mostly stimulating type, the TPOab were registered in 50-70% cases, 21-Hydroxylase autoantibody were positive in 85-90% cases. Clinical parameters in combination of GD with AD showed higher blood pressure than only GD. Heart rate also were elevated in combination than seen in AD without GD. Blood ACTH level were elevated, blood pressure, heart rate, blood sugar levels were more lower than in AD.
Conclusion
Coexistence of HT and AD is marked by elevated TSH, low Free T4, positive TPOAb, and low cortisol with elevated ACTH. AD contributes to electrolyte imbalances and hypotension. In contrast, GD with AD presents suppressed TSH, elevated Free T4/Free T3, positive TRAb, and similar adrenal insufficiency findings. Tachycardia from GD and hypotension from AD complicated management. Early diagnosis and treatment of both thyroid and adrenal dysfunction are essential to prevent severe complications like adrenal crisis or myxedema coma.

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P810

JOINT442

Chronic hypoparathyroidism video-based CME series improved physician knowledge to prepare for an era of emerging therapies

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Background
Managing chronic hypoparathyroidism is challenging; but innovative therapies are shifting treatment paradigms from reliance on oral calcium and activated vitamin D analogs to restoring parathyroid hormone (PTH) receptor activation in critical tissues like the kidneys and bones. However, many endocrinologists and nephrologists lack familiarity with these approaches and in evaluating their efficacy. To address these gaps, we developed a series of continuing medical education (CME) activities, to improve physician knowledge across 4 learning needs:.
1. The burden of hypoparathyroidism.
2. Limitations of current therapies.
3. Mechanisms of emerging therapies.
4. Expectations for these emerging therapies.
Methods
Three online video/synchronized slide-based CME activities were launched in May, June, and October 2024—each featuring different expert endocrinologists and patients with hypoparathyroidism sharing their diagnosis/management experiences and recent clinical data.[1-3] The effects of each activity were assessed using a multi-question, repeated pairs, pre-assessment/post-assessment study design. We analyzed results across all 3 activities in Jan-2025, with questions grouped according to the 4 identified learning needs. Differences pre- and post-assessment were evaluated using McNemar's test.
Results
Confidence in understanding the burden of chronic hypoparathyroidism improved for 37% of endocrinologists and 35% of nephrologists, as did implementing best practice guidelines for 40% of endocrinologists and 36% of nephrologists. Significant improvements in knowledge were also observed, particularly regarding the burden of living with hypoparathyroidism. Baseline knowledge of the mechanisms and expectations of emerging therapies was limited, but notable gains were made (Table).
Conclusions
This study highlights the effectiveness of online CME in improving chronic hypoparathyroidism knowledge. Further education is needed, particularly on the mechanisms and applications of emerging PTH therapies, to enhance provider confidence and transform patient care.

Table 1: Correct Pre- and Post-Assessment Response Rates According to Learning Needs.

			Correct response rates			
Learning Need	**Specialists**	**n**	**Pre**	**Post**	**Δ**	***P* value**
Burden of hypoparathyroidism	Endocrinologists	281	60%	76%	16%	$P<.001$
	Nephrologists	133	59%	76%	17%	$P<.001$
Limitations of current therapies	Endocrinologists	420	81%	90%	9%	P = NS
	Nephrologists	183	68%	78%	10%	$P<.001$
Mechanisms of emerging therapies	Endocrinologists	341	22%	31%	9%	$P<.001$
	Nephrologists	124	21%	24%	3%	$P<.001$
Expectations of emerging therapies	Endocrinologists	178	9%	21%	12%	$P<.001$
	Nephrologists	89	12%	13%	1%	$P<.001$

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P811

JOINT701

Case-based rare disease CME significantly improves competence in diagnosing mct8 deficiency in pediatric/endocrinology practice

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Background
A diagnosis of MCT8 deficiency is easily missed in paediatric/endocrinology practice due to poor familiarity with this rare disease and failure to order or adequately interpret thyroid function tests for babies with hypotonia, missed motor milestones and/or other red flags. Thyroid hormone analysis is a key step in diagnosis but often missed. To increase the recognition and diagnosis of patients presenting with potential MCT8 deficiency, we developed a CME-accredited interactive online case-based educational activity featuring 2 cases for learners to diagnose.
Methods
Physicians worked through 2 cases, answering questions along the way with evidence-based feedback regarding correct responses.[1] The education effects were assessed using a 3-question, repeated pairs, pre-assessment/post-assessment study design. One question assessed confidence. Differences from pre- to post-assessment were evaluated using McNemar's test. The activity launched in February 2024 and data were collected through mid-January 2024.
Results
1,816 endocrinologists and paediatricians participated in the education, with 983 completing both cases and all pre- and post-assessment questions. Significant improvements were seen, with 22/62 (35%) endocrinologists having correct responses at baseline, improving to 48/62 (77%) post case completion ($P<.001$). The corresponding figures for paediatricians were 276/921 (30%) pre-assessment vs 792/921 (86%) at post-assessment ($P<.001$). In particular, significant improvements were observed in physicians' ability to differentiate MCT8 deficiency from a condition with a similar presentation and select the right diagnostic tests, as well as in their knowledge of the burden of MCT8 deficiency for patients and their families. After participating in the activity, 55% of endocrinologists and 60% of paediatricians had measurable improved confidence in their ability to diagnose MCT8 deficiency.
Conclusions
This study demonstrates the success of online, interactive case-based education in improving clinicians' competence in diagnosing MCT8 deficiency.
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P812

JOINT1868

Multiple endocrine neoplasia type 4 (MEN4) syndrome due to rare pathogenic variant of CDK1B gene: a case report

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Introduction
MEN4 syndrome is a rare autosomal-dominant disorder characterised by the co-presence of multiple neuroendocrine tumors, mainly of pituitary and parathyroid origin, with fewer than 100 cases reported since the diagnosis was established in 2006.[1,2] The prevalence of genetically confirmed MEN4 resulting from likely pathogenic or pathogenic variants is 0.07% in patients with suspected MEN1.[2] The underlying molecular mechanism involves loss of function of the tumor suppressor protein p27 due to heterozygous mutation in the *CDKN1B* gene.[3] We present a case of a patient diagnosed with MEN4 syndrome resulting from a reported once across databases but never published in literature, pathogenic variant in the CDKN1B gene.
Case presentation
A 45-year-old female patient presented to the ward with suspected hypopituitarism. Symptoms on admission comprised amenorrhoea for a year, fatigue, dyssomnia, and arthralgia. She denied headaches, vision impairment, polydipsia, or polyuria. The patient's history included obesity, hypertension, and hepatic steatosis. The hormonal work-up confirmed anterior hypopituitarism with mild hyperprolactinemia. The pituitary MR visualized a pituitary tumor sized 24x22x25 mm. The patient was scheduled for trans-sphenoid surgical excision. The pathology result indicated pituitary neuroendocrine tumor, with a weak-positive immunostaining for LH and alpha-subunit and a Ki67 proliferative index of less than 1%. Furthermore, the patient was diagnosed with mild primary hyperparathyroidism. Both parathyroid scintigraphy and neck ultrasound failed to detect affected glands. A single nodule was found on the thyroid ultrasound and later confirmed as a BIII lesion on FNA biopsy. Given the suspicion of multiple endocrine neoplasia, genetic testing was performed. After ruling out MEN1 syndrome, Sanger sequencing confirmed the presence of a heterozygotic, pathogenic variant of *CDKN1B* gene – a deletion at coding DNA position 285, located in the first exon of the gene. Resultant frame-shift mutation leading to premature termination codon presence precipitates nonsense-mediated decay of the aberrant mRNA. The patient's family history was non-specific (parents or siblings are not available for testing, and the only child was negative on genetic screening). Computed tomography of the chest, abdomen and pelvis did not reveal any other pathological lesions so far. Since then, the patient has remained under active surveillance.
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P813

JOINT181
Coexistence of papillary and medullary thyroid carcinomas in a patient with MEN2A
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Background
The rare coexistence of medullary thyroid carcinoma (MTC) and papillary thyroid carcinoma (PTC) in Multiple Endocrine Neoplasia type 2A (MEN2A) presents unique challenges in diagnosis and treatment.
Case Presentation
We report a 28-year-old Chinese female diagnosed with MEN2A, initially presenting with multifocal MTC on fine needle aspiration of right thyroid nodules. The patient underwent total thyroidectomy, tracheoesophageal groove clearance, and right neck dissection. Histopathological examination of the thyroidectomy specimen revealed dual pathology: multifocal MTC in both lobes and unifocal PTC at the isthmus. Regional lymph node involvement was significant, with most showing metastatic MTC, and three level 6 lymph nodes exhibiting metastatic PTC.
Discussion
MEN2A is an autosomal dominant hereditary syndrome characterized by MTC, pheochromocytoma, and primary hyperparathyroidism, resulting from germline mutations in the RET proto-oncogene. These mutations lead to tumorigenesis through gain-of-function alterations. Although MTC is nearly universal in MEN2A and typically multifocal and bilateral, the coexistence of MTC and PTC in the same thyroid gland is extremely rare. Such cases may present as a mixed tumor with dual differentiation or as a collision tumor. Recent studies suggest that RET point mutations may also induce oncogenic activity in thyroid follicular cells, potentially contributing to PTC development. Distinguishing between MTC and PTC is crucial for management as treatment strategies differ significantly. While the American Thyroid Association (ATA) guidelines recommend TSH suppression to reduce recurrence risk in PTC, this is ineffective for MTC due to the absence of TSH receptors on thyroid C cells. Consequently, patients with dual pathology require a tailored therapeutic strategy to optimize the management of both malignancies.
Conclusion
The coexistence of MTC and PTC in MEN2A underscores the need for comprehensive histopathological evaluation and genetic analysis to guide appropriate clinical management.
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P814

JOINT3312
A case report of mccune-albright syndrome with hepatic focal nodular hyperplasia and review of literature
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Objective
We report the first case of McCune-Albright syndrome (MAS) complicated with hepatic focal nodular hyperplasia (FNH) in China, summarize the clinical features and possible related factors of MAS complicated with hepatobiliary system complications, and review the literature.
Method
A retrospective analysis was conducted on the clinical data of a patient with McCune-Albright syndrome (MAS) complicated by hepatic focal nodular hyperplasia (FNH) who was admitted to the Department of Pediatrics, First Affiliated Hospital of Sun Yat-sen University on November 25, 2011, and the relevant literature was reviewed.
Result
The patient, a female now aged 17, was diagnosed with McCune-Albright syndrome (atypical, café-au-lait spots, peripheral precocious puberty) at our hospital at the age of 5 years and 3 months due to "breast development for 3 months, vaginal bleeding 4 times, and accelerated growth." Genetic testing revealed a GNAS gene mutation in the peripheral blood. She has been regularly followed up in our hospital for 12 years since then, during which her ovaries exhibited continuous hyperfunction that was difficult to control. She also had comorbidities of Cushing's syndrome, pituitary hyperfunction, and multifocal pituitary adenomas. In the 6th year of follow-up, liver function abnormalities appeared, and hepatic imaging suggested hepatic adenoma and focal nodular hyperplasia, which largest lesion measured approximately 91*77* 72 mm (volume 262.3 cm^3). The pathological examination confirmed focal nodular hyperplasia. Due to the family's wishes, no surgical intervention was performed, and close follow-up was conducted instead. During this period, the lesion progressively enlarged to 99*82* 81 mm (volume 341.9 cm^3), after which it tended to stabilize and began to decrease in size. After a follow-up period of 6 years to date, the lesion has reduced to 56*26* 26 mm (volume 19.7 cm^3). During this period, liver function fluctuated with the size of the lesion, and liver function is currently normal.
Discussion
This case is the first reported in China of McCune-Albright syndrome (MAS) complicated by hepatic focal nodular hyperplasia, and the characteristics of lesion progression are reported, aiming to enrich the clinical spectrum of MAS and raise clinical awareness and attention to hepatobiliary system involvement in MAS. It is proposed that a high mutation dose of the GNAS gene, a high disease burden, and frequent or continuous autonomous ovarian function activity may be risk factors for hepatobiliary system involvement in MAS.
Keywords
McCune-Albright syndrome, hepatic focal nodular hyperplasia.
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P815

JOINT115
Quality of XLH care in the nordics: perspectives of parents with children with XLH
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Introduction
X-linked hypophosphataemia (XLH) is a genetic orphan disease that causes growth impairments, rickets in children, and lifelong osteomalacia throughout the life span. A 2019 international survey showed <2% of adults received all aspects of best care as laid out in the recent Haffner *et al* recommendations, however data on children's real-world XLH care and lived experiences is lacking. This research aims to evaluate parent/caregiver satisfaction with XLH care in children and identify barriers to optimal care.
Methods
Double-blind, virtual, 1-hour interviews were conducted in local language in January 2024. Interviewees included 8 parents/caregivers from Sweden (4), Finland (2) Denmark (1) and Norway (1); and 1 healthcare provider (HCP) from Finland. Interviews covered four themes: experiences of XLH care, treatments, understanding the burden of XLH, and improving XLH care. Key words were used to identify concepts discussed and quantify the qualitative data.
Results
Recruitment proved challenging due to XLH's rarity and the limited number of specialist HCPs. While engagement through patient advocacy groups (PAGs) was successful in Sweden, uptake was lower in other countries. Among the parents/caregivers interviewed ($n = 8$), all reported their child received care from endocrinologists and dentists, but none had support from psychologists or social workers. While satisfaction with specialist care was high, 25% noted communication gaps with their general practitioner (GP). Burdens of XLH care included frequent administration of phosphate and alfacalcidol and organizing life around care; 63% found it challenging to plan logistics for care, with some facing travel times of up to 5 hours for treatments. Interviewees suggested several improvements that could reduce the burden of XLH on families, including the need for a coordinating XLH care provider (38%), increased knowledge and awareness of the condition among GPs and hospital care providers (38%), and better access to optimal treatments (75%).
Conclusion
These findings identify key areas for improving the care experience of children with XLH, particularly by enhancing access to coordinated care and mitigation of logistical and communication challenges. Increasing physician knowledge and alleviating frustrations related to treatments options could further help reduce the burden on families. Future research should prioritize close collaboration with patient groups to facilitate more effective recruitment and engagement.

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P816

JOINT3428

Association between body mass index (BMI) and immune-related adverse events among cancer patients receiving immune checkpoint inhibitors: a single institution analysis

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Whether overweight/obesity has an impact on immune checkpoint inhibitor (ICIs) toxicity and efficacy is currently under debate. The present study was aimed at evaluating the occurrence of irAEs among cancer patients on ICI therapy according to baseline BMI and gender.
Patients and Methods
We performed a retrospective analysis of 130 patients (93 males and 37 females, male/female ratio 2.5:1; median age 67 years, range: 32-85) with different types of cancer treated with ICIs at a single center. The primary tumours were: non-small-cell lung carcinoma ($n = 72$, 55%), melanoma ($n = 30$, 23%), renal cell carcinoma ($n = 17$, 13%), and others ($n = 3$, 3%).
Results
At baseline evaluation, median BMI in the whole cohort was 22 (range 18,1-36,7), and median body weight 70,5 kg (range 47 – 117). According to WHO classification, 3 patients (2.3%) were defined as underweight, 83 patients (63,8%) as normal weight, 37 patients (28.5%) as overweight and 7 patients (5.41%) as obese. During follow-up, any irAEs occurred in 42 patients (32%; median age 69 years), with significant differences between sexes (28 males and 14 females, F to M ratio 2:1; $P = 0.007$). Among them, 41 (31.5% of the whole cohort) developed thyroid dysfunction (hypothyroidism and/or thyrotoxicosis) without difference by sex ($P = 0.578$), primary hypothyroidism being the most common irAEs (39 patients; 30% of the whole cohort). Twenty-nine patients developed also non-endocrine AEs [cutaneous ($n = 10$), gastro-intestinal ($n = 9$), pulmonary ($n = 2$) and rheumatic ($n = 8$)], and difference by sex was significant ($P = 0.009$). Development of AEs was associated with higher BMI: the prevalence of AEs was 59.5% in overweight/obese patients *vs* 40.5% in normal weight patients ($P < 0.001$). Patients who developed AEs had higher body weight (75,5 $\pm$ 12 kg *vs* 70.2 $\pm$ 11 kg, $P = 0.017$) and BMI (25 $\pm$ 3.5 kg/m^2 vs22.7 $\pm$ 3 kg/m^2, $P = 0.002$) than patients who did not, in both sexes. At uni- and multivariate regression analyses, BMI was confirmed as an independent predictor of risk for developing AEs ($P < 0.001$), with overweight/obese patients having a OR of 3.182 compared to normal weight/underweight patients. BMI $\geq$25 kg/m^2 and AEs occurrence were associated to a better ECOG performance status ($P = 0.012$, and $P = 0.013$, respectively), although no differences in PFS and OS emerged.
Conclusion
Occurrence of ICI-related toxicities was more frequent in overweight/obese patients compared to normal weight/underweight patients. A BMI $\geq$25 kg/m^2 was associated with increased risk for developing AEs in both sexes. No clear association between BMI and immunotherapy efficacy/prognosis was observed.

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P817

JOINT619

Different faces of polycystic ovary syndrome: contrasting clinical and biochemical profiles in adolescents and adults

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Objective
To compare the clinical and biochemical presentation of polycystic ovary syndrome (PCOS) in adolescent girls and adult women, focusing on differences in prevalence, age of presentation, symptoms, biochemical data, imaging findings, treatment response, and outcomes.
Methods
This review synthesized data from 18 studies published between 1990 and 2024, involving approximately 1,200 patients. The findings highlight distinct variations in PCOS characteristics and management strategies across these age groups.
Results
Adolescent girls demonstrated a prevalence of 5%-10%, particularly higher in those with obesity, compared to 6%-20% in adult women. Adolescents typically presented during early to mid-puberty with symptoms such as menstrual irregularity, acne, and mild hirsutism, while androgenic alopecia and infertility were rare. Adults commonly presented in late adolescence or early adulthood with more severe hirsutism, infertility, and androgenic alopecia. Biochemically, adolescents had mild hyperandrogenemia, reduced sex hormone-binding globulin, and early signs of insulin resistance, with more severe markers seen in obese subgroups. Adults exhibited pronounced dyslipidemia, insulin resistance, and greater metabolic abnormalities. Imaging findings were inconsistent in adolescents, while adults consistently demonstrated larger ovarian volumes with polycystic morphology. Adolescents responded well to lifestyle modifications, with metformin improving insulin sensitivity and ovulation. In adults, oral contraceptives effectively managed hyperandrogenism and menstrual irregularity, with insulin-sensitizing agents enhancing fertility outcomes.
Discussion
The observed differences in PCOS presentation between adolescents and adults can be attributed to developmental and hormonal factors. In adolescents, the overlap of normal pubertal changes with PCOS symptoms complicates diagnosis, and obesity exacerbates insulin resistance and hyperandrogenism. Conversely, prolonged exposure to hyperandrogenemia and metabolic dysfunction in adults contributes to more severe manifestations, including infertility and endometrial complications. These differences highlight the need for age-specific diagnostic criteria and management strategies. Adolescents show greater plasticity in their metabolic and hormonal systems, making lifestyle interventions particularly effective. Early intervention reduces long-term risks such as type 2 diabetes and cardiovascular disease. Adults often require more aggressive pharmacological interventions to address chronic complications. Understanding these distinctions can guide tailored therapeutic approaches to improve patient outcomes at different life stages.

Recommendations
1. Early identification and intervention in adolescents can prevent long-term complications of PCOS.
2. Adults require advanced therapies to manage severe symptoms and fertility issues.
Conclusion
Recognizing the differences in PCOS presentation and management between adolescents and adults is essential for effective age-appropriate care, minimizing long-term health risks, and improving quality of life.

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P818

JOINT677

The role of pituitary MRI in assessing endocrine dysfunction and growth defects in thalassemia major

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Background
Thalassemia is a chronic transfusion-dependent disorder often associated with iron overload. Excess iron deposition in the pituitary gland leads to endocrine dysfunctions such as growth hormone (GH) deficiency and hypogonadotropic hypogonadism, significantly impacting growth and pubertal development. Magnetic resonance imaging (MRI) has emerged as a critical tool for evaluating pituitary iron overload and its correlation with endocrine dysfunctions.
Objective
To assess the role of pituitary MRI in detecting iron overload and its association with endocrine abnormalities and growth defects in patients with thalassemia major.
Methods
A systematic review of 20 studies involving over 1,500 thalassemia major patients was conducted. MRI findings of pituitary iron overload, reduced T2* relaxation times, and structural abnormalities were correlated with endocrine dysfunctions such as GH and gonadotropin deficiencies. Growth and pubertal outcomes were also analyzed.
Results
1. MRI Findings:.
• Pituitary iron overload was a consistent finding, with reduced T2* relaxation times (<20 ms) correlating with increased serum ferritin levels and liver iron concentration (LIC).
• Structural abnormalities included reduced pituitary volume, hypoplastic glands, and abnormal shapes.
2. Endocrine Dysfunction:.
• Growth hormone deficiency (GH) was observed in studies such as Noetzli *et al.* (2012), with delayed height velocity and impaired catch-up growth.
• Hypogonadotropic hypogonadism was common, presenting as delayed or arrested puberty, particularly in studies by Wood *et al.* (2015) and Jain *et al.* (2021).
• Additional hormonal abnormalities included secondary hypothyroidism, adrenal insufficiency, and gonadotropin suppression.
3. Growth Implications:.
• Short stature, delayed puberty, and stunted skeletal growth were prominent in patients with significant pituitary iron deposition.
• Long-term MRI monitoring and chelation therapy adjustments, as shown by Agha *et al.* (2023), improved growth trajectories in some patients.
4. Clinical Utility of MRI:.
• Studies such as Kildemoes *et al.* (2023) emphasized the accuracy of T2* MRI in quantifying pituitary iron and guiding chelation therapy.
• MRI findings predicted the severity of endocrine dysfunctions and provided insights into individualized management plans.
Conclusion
Pituitary MRI plays a pivotal role in detecting iron overload and predicting endocrine dysfunctions in thalassemia major. By identifying structural and functional abnormalities, MRI guides timely interventions to mitigate growth and pubertal defects. Incorporating routine MRI assessments into patient management protocols can significantly improve long-term outcomes.
Keywords
Thalassemia major, pituitary MRI, iron overload, growth hormone deficiency, hypogonadotropic hypogonadism, T2* relaxation time, endocrine dysfunction.
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P819

JOINT674

Comparative analysis of MRI and ferriscan in thalassemia major and intermedia: implications for growth, puberty, and endocrine health"

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Background
Thalassemia Major (TM) and Thalassemia Intermedia (TI) are distinct forms of beta-thalassemia, characterized by differences in transfusion dependence and iron overload patterns. Non-invasive imaging techniques, including T2* MRI and FerriScan (R2 MRI), have advanced the management of iron burden. However, differences in their diagnostic efficacy and their implications on growth, puberty, and endocrine functions in TM and TI remain underexplored.
Objective
This study aims to evaluate the differences in MRI (T2*) and FerriScan findings between TM and TI and their correlation with growth retardation, delayed puberty, and endocrine dysfunction.
Methods
A review of studies comparing MRI and FerriScan findings in TM and TI was conducted. Key parameters analyzed include liver iron concentration (LIC), cardiac iron overload, and extramedullary manifestations. Findings were correlated with growth patterns, pubertal development, and endocrine outcomes, including hypogonadism and short stature.
Results
• **Liver Iron Concentration (LIC):** FerriScan was more sensitive in detecting LIC in both TM and TI, particularly at higher iron burdens. T2* MRI tended to underestimate LIC, especially in TM patients with severe iron overload. In TI, FerriScan provided superior detection of moderate LIC, highlighting differences in iron deposition patterns.
• **Cardiac Iron Overload:** T2* MRI identified higher myocardial iron deposition in TM than in TI, where cardiac involvement was less frequent but associated with high-output heart states.
• **Growth Retardation:** Chronic iron overload and anemia in TM led to significant growth delays. In TI, the lower frequency of transfusions and delayed recognition of iron overload further exacerbated growth impairment.
• **Pubertal Delays:** Hypogonadism and delayed puberty were prevalent in both conditions, with higher severity in TM due to heavier transfusion burdens and iron toxicity. In TI, unrecognized iron overload compounded endocrine dysfunction.
• **Endocrine Dysfunction:** Hypogonadotropic hypogonadism, diabetes, and hypothyroidism were frequently observed in TM patients with severe iron burden. In TI, iron-related endocrine dysfunction occurred but was often overlooked due to milder transfusion dependence.
Conclusion
FerriScan demonstrated greater accuracy in measuring LIC, particularly in TM patients with high iron burdens and TI patients with moderate overload. MRI findings, when combined with FerriScan, provide critical insights into iron-related complications, enabling better management of growth, puberty, and endocrine outcomes. Regular imaging-guided chelation improves growth and endocrine function, but the implementation remains suboptimal in TI compared to TM. This underscores the need for tailored iron monitoring strategies for both conditions.
Keywords
Thalassemia Major, Thalassemia Intermedia, MRI, FerriScan, Iron Overload, Growth, Endocrine Dysfunction, Puberty.
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P820

JOINT2857

An intricate case of postmenopausal hyperandrogenism: causes and consequences

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Introduction
New-onset moderate-severe post-menopausal hyperandrogenism is associated with significant metabolic disorders that increase the risk of cardiovascular disease and mortality, prompting early diagnosis and treatment.

Case Report
We present the case of a 58-year-old nulliparous woman, menopaused at 55 years, with medical history of autoimmune thyroiditis, mild hypothyroidism, and important cardiometabolic comorbidities (arterial hypertension, heart failure, coronary stent, poorly controlled type 2 diabetes mellitus requiring insulin treatment, hyperlipidemia), that was referred to the Endocrinology Department to evaluate slowly progressive androgenic alopecia and hirsutism developed over the last 8 years, exacerbated 3 years before presentation. Clinical examination revealed a BMI of 38 kg/m^2 with abdominal fat distribution, blood pressure of 160/100 mmHg, frontotemporal alopecia, increased terminal hair growth, particularly on the face, trunk, forearms and thighs, skin hyperpigmentation, and acanthosis nigricans. Initial biological evaluation showed significantly elevated total testosterone:13.87 nmol/l(reference range 0.10-1.42) and estradiol: 39 pg/ml (postmenopausal <10) with FSH and LH at the lower limit of normal values. Serum ACTH, cortisol, DHEAS, TSH, prolactin, and 17-OH-progesterone were within the normal range, while IGF-1 and random GH levels were elevated (IGF1 $=$ 308 ng/ml, reference range <225, 24 hours random serum GH between 1 ng/ml and 2.15 ng/ml). After undergoing a long dexamethasone suppression test (5 days, 4x0.5 mg/d), serum cortisol was adequately suppressed (<1.8 mg/dl), DHEAS was suppressed more than 60% but testosterone levels exhibited a paradoxical increase (17.74 nmol/l, N<1.42). Abdominal-pelvic MRI revealed bilateral increased ovarian volume with a 9-mm right ovarian mass and a right adrenal adenoma of 14/9 mm. Alpha-fetoprotein, CA 125, CEA, and CA 19-9 levels were normal. The patient was referred to the Surgery department to undergo bilateral oophorectomy for definitive diagnosis and treatment.
Discussion
Multiple causes of hyperandrogenism may be considered in this case: 1. Adrenal hyperandrogenism/Cushing syndrome – ruled out due to adequate DHEAS and cortisol suppression, 2. Ovarian hyperandrogenism – either hyperthecosis or virilizing ovarian tumor, considering the imaging evidence of enlarged ovaries together with an ovarian mass and high non-suppressible testosterone which make this hypothesis the most likely, 3. Autonomous GH secretion- cannot be ruled out, needing further evaluation after the surgical intervention and optimal control of diabetes mellitus.

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P821

JOINT2643

Endocrine monitoring when initiating immunotherapy in cancer patients: a quality improvement project

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Introduction
Immune checkpoint inhibitors have revolutionised cancer therapy in recent years and as the use of this increases, we have recognised the side effects of developing endocrinopathies. Common endocrinopathies include thyroid disease and hypophysitis. Thus, a protocol is needed to help monitor endocrine disorders when initiating and during immunotherapy for cancer patients to diagnose and manage these endocrinopathies earlier.
Aim
Quality improvement project (QIP) to establish baseline monitoring test for endocrine disorder when initiating immunotherapy for cancer treatment and implementation of new trust guidelines to help aid this.
Method
Retrospective single-centre study looking at baseline test for monitoring of endocrine disorders in patients started on immunotherapy for cancer treatment. Blood test for endocrine disorder monitoring including cortisol levels, Thyroid Function Tests (TFTs) and HbA1c.
Results
Cycle 1: 22 patients identified on immunotherapies including Anti-PD-1 Pembrolizumab (11patients) and anti-PD-L-1 such as Atezolizumab (7patients) and Durvalumab (4patients). Pembrolizumab had 55%cortisol, 73% TFTs and 18%HbA1c checked. Atezolizumab had 71% cortisol, 29% TFTs and 14%HbA1c checked. Durvalumab had 50% cortisol, TFTs and HbA1c checked. After cycle one of QIP an informative departmental teaching was carried out and we developed local trust guidelines to help recommended endocrine test monitoring. Cycle 2 included 80 patients 20 patients on Pembrolizumab 100% had cortisol and TFTs checked but only 30% HbA1c. 20 patients on Atezolizumab 100% TFTs, 70% cortisol and 50% HbA1c checked. 20 patients on Durvalumab 100% TFT, 60% cortisol and 50% HbA1c checked. 20 patients on Nivolumab 100% TFTs, 60% cortisol and 60% HbA1c checked.
Conclusion
The use of immunotherapies in cancer treatment has increased. PD-1 inhibitors are commonly associated with thyroid abnormalities (5-10%) and can occur 4-10weeks after initiation of treatment. Diabetes Mellitus (DM) incidence of 1% including new-onset type1 DM or worsening type2 DM. CTLA-4 inhibitors are commonly associated with hypophysitis (3-6%) and usually present in 8-10weeks of initiation of treatment. Our QIP showed in the first cycle more information and awareness were needed for patients and clinicians on complications of developing endocrinopathies and the need of monitoring this. Repeat cycle showed increase in baseline endocrine blood test when initiating immunotherapy with TFTs at 100% tested. Our team developed local trust guidelines for baseline endocrine monitoring for patients on immunotherapy treatment. We plan to repeat our study in 6months time with a larger sample size and looking at 3months monitoring of endocrine blood test to see if any patients developed endocrinopathy complications.

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P822

JOINT947

Large pheochromocytoma and primary hyperparathyroidism associated with a rare mutation in the succinate dehydrogenase a (SDHA) gene

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Background
Pheochromocytoma/Paraganglioma (PHEO/PGL) and primary hyperparathyroidism (PHPT) are rare endocrine disorders with distinct etiologies. While PHEO commonly arises from neural crest-derived adrenal chromaffin cells, PHPT typically results from hyperactive parathyroid adenomas. Germline mutations in succinate dehydrogenase (SDH) genes, particularly SDHA, SDHB, SDHC, and SDHD, are implicated in the pathogenesis of PHEO/PGL. SDHA gene mutations are rare and not well characterized, with limited evidence linking them to primary hyperparathyroidism. We present the case of a young woman with concurrent PHEO and PHPT, harboring a novel heterozygous germline SDHA gene mutation.
Case Presentation
A woman in her early 40s presented with recurrent abdominal pain, profound anemia (hemoglobin: 5.6 g/dl), hypercalcemia (ionized calcium: 1.41 mmol/l), and significantly elevated parathyroid hormone (iPTH: 317.5 pg/mL). A large left sided renal mass was identified on an abdominal CT scan. Surgical pathology confirmed a 16.3 cm PHEO, displaying typical zellballen architecture and positive immunohistochemical staining for synaptophysin, chromogranin, and vimentin. Persistent hypercalcemia and elevated iPTH levels led to a neck ultrasound, which revealed a 1.9 x 0.8 x 1.2 cm hypoechoic, hypervascular nodule adjacent to the left thyroid lobe, suggestive of a parathyroid adenoma. Subsequent surgical removal of two hyperplastic parathyroid adenomas normalized serum calcium levels. Genetic testing identified a novel heterozygous germline SDHA gene mutation (p.E640G, c.1919 A$>$G), classified as a variant of unknown significance (VUS), contributing to the expanding spectrum of SDHA-related disorders. Over a seven-year follow-up period, the patient demonstrated an indolent clinical course, with no evidence of metastasis despite the large size of the initial PHEO. Serial PET-CT imaging (F-FDG and Ga-DOTATATE) and normal plasma metanephrines consistently showed no signs of disease progression. To date, the coexistence of PHEO and PHPT associated with SDHA gene mutations has not been previously documented. Additionally, the indolent course during an extended follow-up period is particularly significant, as it contrasts with the typically aggressive course often observed in SDHA-related PHEO/PGL.
Conclusion
This unique case highlights the importance of genetic testing in atypical presentations of endocrine neoplasms to understand risk of disease progression and guide surveillance. Further research is warranted to clarify the role of novel SDHA gene variants in coexisting endocrine disorders.

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Pituitary, Neuroendocrinology and Puberty

P23

JOINT1742

Genetic basis of patients with congenital gonadotropin deficiency

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Background

Congenital gonadotropin (GN) deficiency is a condition that falls under the umbrella of hypogonadotropic hypogonadism (HH). The defect may occur either in the hypothalamus or the pituitary. Congenital GN deficiency can be a characteristic feature of several disorders: (i) congenital hypogonadotropic hypogonadism (CHH), further classified into normosmic CHH (nCHH) or Kallmann syndrome (KS); (ii) combined pituitary hormone deficiency (CPHD); and (iii) other GN deficiency associated syndromes (*e.g.* CHARGE syndrome, septo-optic dysplasia [SOD]). Herein, we investigated the clinical and genetic overlap between these clinical entities.

Methods

All probands with congenital GN deficiency ($n=571$) underwent detailed phenotyping. Pathogenic (P), likely pathogenic (LP), and variants of unknown significance (VUS) were depicted for known CHH and CPHD genes in respective conditions. Further, oligogenicity was assessed in the CHH cohort and controls ($n=601$). Genetic overlap between CHH, CPHD and syndromic GN deficiency was further studied.

Results

276 KS, 248 nCHH, 29 CPHD, and 18 syndromic GN deficiency were included in the study. In addition to HH, skeletal anomalies, cleft lip and palate, and dental agenesis were observed in all subgroups. Notably, altered sense of smell and robust GN response to LHRH test in CPHD patients were observed. 53% of KS probands harbored rare variants in CHH genes (40% were P/lP, 13% VUS); while 33% of nCHH probands carried rare variants in CHH genes (23% P/lP, 10% VUS). *FGFR1, ANOS1* and *PROKR2* in KS and *FGFR1*, *GNRHR* and *TAC3R* in nCHH were the most mutated genes. Oligogenicity occurs in 25% of CHH probands with *DMLX2*, *FGFR1*, and *PNPLA6* being significantly involved in gene pairings. Almost 10% of CHH patients without genetic diagnosis carried rare variants in CPHD genes (*e.g. DCHS2*, *FAT2* and *CDON* in KS as well as *ROBO1, FAT2*, *DCHS2* and *KCNQ1* in nCHH). Additionally, CHH genes (*e.g. FGFR1*, CHD7 and *FGF8*) were mutated in CPHD and syndromic GN deficiency.

Conclusion

Herein, we demonstrated: (i) clinical and genetic overlap between patients exhibiting GN deficiency; (ii) altered sense of smell and robust response to LHRH test in CPHD suggesting a dual defect (pituitary and hypothalamus); (iii) 25% of oligogenic inheritance in CHH; and (iv) novel putative CPHD genes (*ROBO1, DCHS2, FAT2* and *KCNQ1*) in CHH.

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P24

JOINT2710

The roles of PDLIM1 in silent corticotroph adenomas aggressiveness

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Objective

Recognised by aggressive behaviour, silent corticotroph adenomas (SCA) represent up to 15% of non-functioning pituitary neuroendocrine tumours (PitNETs). Clinical presentation is usually related to tumour volume without hypercortisolism-related symptoms. We have previously shown that gene and protein levels of PDZ and LIM domain 1 (PDLIM1) are significantly upregulated in SCA when compared with normal functioning corticotroph adenomas (FCA) [1]. PDLIM1 plays important roles in cellular homeostasis and cytoskeletal organization, affecting morphological changes and migration. Tumorigenesis-related role is divergent, being a contributor in gastric cancer, glioma, and breast cancer, but a protector in colorectal and hepatocellular carcinoma. We hypothesized that PDLIM1 is involved in the aggressiveness of SCA. We aimed to assess the roles of PDLIM1 in corticotroph adenomas' aggressiveness and identify the responsible mechanisms.

Methods

Clinical, biochemical and imaging characteristics were obtained from a cohort of 50 patients (17 SCA and 33 FCA). *PDLIM1* gene expression was measured by RT-qPCR in tumour tissue. AtT-20 mouse pituitary corticotroph tumour cells were transfected with pCMV6-Entry plasmid containing *Pdlim1,* and three clones with stable Pdlim1 overexpression were selected by western blotting, expanded and used in CCK-8 cell proliferation and transwell migration assays. Furthermore, quantitative label-free mass spectrometry (MS)–based proteomics analysis was performed on cell lysate of each clone and wild-type (WT) AtT-20.

Results

SCA was larger in size than FCA (max diameter mean 26 vs 7 mm, $P<0.005$). All of SCA were macroadenoma ($n=17$), whereas FCA were both macro- and microadenoma ($n=11$ and 22, respectively). SCA expressed higher *PDLIM1* expression as compared to FCA ($P<0.01$). All selected clones with stable *Pdlim1* overexpression showed morphological changes: each contained suspension cell clusters, floating or hanging with adherent groups. Some adherent parts exhibited string-like fibroblastic appearance. The clones showed increased proliferation and migration ($P<0.0001$) as compared to WT cells. Proteomics analyses showed upregulation of Pdlim1, Igfbp4, Itgb3, Pcsk1n and Stc1 in all clones ($P<0.05$, for all). Furthermore, two clones showed upregulation of Ctsb, Igfbp5, Mcam, and Plin2 ($q<0.05$, for all). Ctsb, Igfbp4/5, Itgb3, Mcam and Stc1 are known to be involved in migration, invasion, and proliferation in other tumours. Pathway analyses showed activation of regulation of Insulin-like growth factor transport whereas lipid metabolism by PPARalpha, cholesterol biosynthesis, and gene expression activation by SREBP were inhibited.

Conclusion

PDLIM1 is upregulated in SCA and seems to contribute to proliferation and migration of corticotroph tumour cells.

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P25

JOINT977

Severe hyponatraemia in Europe: insights into endocrinologists' clinical practices and perspectives

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Background
The European Society of Endocrinology (ESE) guidelines (2014) recommend a bolus-wise strategy using hypertonic saline (HTS) for treatment of severe symptomatic hyponatraemia. The aim of treatment is to raise serum sodium by $\leq$10 mmol/l in first 24 hours[(1)]. However, there are recent controversies regarding risk of overcorrection and osmotic demyelination syndrome (ODS)[(2)], leading to significant heterogeneity in practice[(3)].
Aim
To evaluate the clinical practices and perspectives of endocrinologists across Europe in managing severe symptomatic hyponatraemia.
Methods
A web-based anonymous cross-sectional survey, endorsed by ESE, was disseminated to ESE members between 28/06/24 and 31/12/24 via email, newsletter and social media. The survey consisted of 13 multiple-choice questions and was developed using REDCap®. Data was analysed using R-Studio (version 4.4.2).
Results
A total of 642 responses were received. After excluding incomplete and non-European responses, 422 responses form 36 countries were analysed. 79.4% (n=335) responses were from endocrinology followed by Internal Medicine (10.9%) and emergency medicine (6.2%). Most responses were received from university hospitals (70.9%) and by senior clinicians i.e. professors/consultants (66.8%). Most clinicians (32%) had experience using both bolus and continuous infusions in managing severe symptomatic hyponatraemia while sole bolus or continuous infusion therapy was preferred by 29.9% and 23.7%, respectively. For those with experience of bolus therapy (n=113), preferred volumes of infusions were 100 mL (26.8%) and 150 mL (19.2%), while 4.5% preferred a weight-based dosage. 24-hour target sodium rise was defined as $\leq$8 mmol/l and $\leq$10 mmol/l by 38% and 37.8% of the respondents, respectively. In absence of seizures, most (83.9%) clinicians preferred one bolus infusion followed by a blood test before repeating a second, while 85.8% had at least some experience with using venous blood gas sodium with HTS use. 34.3% respondents had encountered $\geqq$1patient with suspected or confirmed ODS in their practice, while 54.9% reported association of ODS with sodium overcorrection.
Conclusion
This is the first European survey on severe symptomatic hyponatraemia management, offering insights into real-life practice. Our survey underlines that **first**, there is significant variation in practice, **second,** most clinicians prefer a more cautious approach than recommended by guidelines, and **third**, 1/3rd of clinicians have encountered ODS in their clinical practice. The survey results call for future research and an evidence-based review of ESE guidelines.
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P823

JOINT1520
Piperonyl butoxide: a putative novel endocrine disruptor causing Cushing Syndrome
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Introduction
Cushing's syndrome (CS) is a clinical condition due to exposure to high endogenous or exogenous glucocorticoids (GC). Chronic exposure to exogenous GC is generally associated with a more rapid onset of CS clinical signs as compared to endogenous hypercortisolism, but they share signs and symptoms. 10% of the total annual diagnoses of CS concerns children and the predominant cause are GC used to treat various clinical conditions. Indeed, the use of oral, inhaled, injected, or topical (e.g. creams and ointments) drugs containing GC is the most common cause of exogenous CS. In addition, some "unsuspected" natural formulations may contain GC or compounds with GC-like activity. Therefore, it is fundamental to investigate the use of these products in patients with CS. A 15-year-old girl referred to us for a suspected CS. Adrenocortical axis was suppressed but she denied any previous steroid consumption, and reported a 1-year head-application of an anti-lice spray. The clinical course showed a complete functional recovery after the product's withdrawal. The purpose of this study is to investigate whether the anti-lice product contains compounds with GC-like activity. Anti-lice products are widely used in the pediatric population to treat and/or prevent head lice infestation.
Methods
LC-HRMS was performed to detect the spray components in patient's serum, pyrethrins and piperonyl butoxide (PBO). To evaluate PBO effects, alone or combined with Mifepristone (Mif), we incubated the GloResponse 9XGA-L4UAS-luc2P HEK293 cell line (GloHEK cell) using increasing compound concentrations (from 0,25 mM to 100 mM). The luminescence assay was performed using PBO 10 μM.
Results
PBO levels were high in patient's serum during anti-lice product exposure (~ 50-fold vs. in control). Six months after stopping product application PBO levels were similar to control. PBO did not affect cell number at the concentration employed in the luciferase assay. To verify a possible PBO GC-like activity, we evaluated luminescence emission: PBO significantly increased baseline luminescence by >7-fold ($P < 0.01$). On the other hand, Mif enhanced baseline luminescence by ~2-fold ($P < 0.01$) and potently hampered PBO-induced luminescence ($P < 0.05$).
Conclusions
PBO showed a GC-like activity, by a direct binding to the GR. The latter is demonstrated by the evidence that PBO effects are prevented by co-incubation with the GR antagonist. The prolonged exposure to the anti-lice spray was causing the CS-like appearance in this young girl.
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P824

JOINT756
The personality profile and neurostructural associations in patients with cushing's disease
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Objective
To explore the personality profile and behavior of patients with Cushing's disease (CD) and their neurostructural correlates.
Methods
This study included CD (n = 38) and control (n = 29) groups. Controls were selected from volunteers who applied to hospital for routine tests between 2021-2022. Volunteers with signs suggestive of CD, exposed to glucocorticoids, and had uncontrolled diabetes and/or hypertension were excluded. Group-matching was performed for age, sex, and education. Psychometric assessments included Temperament and Character Inventory (TCI), Symptom Checklist-90-Revised (SCL-90-R), Buss-Perry Aggression Questionnaire (BPAQ), and Apathy Scale. Cortical thickness was examined using 3T magnetic resonance imaging. Surface-based morphometry was employed using the CAT12 toolbox. Least Absolute Shrinkage and Selection Operator (LASSO) was used to identify predictors of personality dimensions.
Results
Psychometric assessments revealed no differences in SCL-90-R (P >0.05 for all domains). TCI scores were similar between groups except for higher persistence in the CD group (6 [4–7] vs. 5 [3.5–6], P = 0.019). Total BPAQ scores were lower in the CD group (51 [46–60.5] vs. 66 [50–80.5], P = 0.011), indicating decreased aggression. Radiological analyses revealed cortical thinning in frontal and parietal regions in CD group. In left hemisphere, the largest cluster (P = 0.039, size = 3,418 voxels) showed thinning predominantly in rostral middle frontal (32%), precentral (14%), postcentral (10%), and superior frontal (10%) cortices. Thinning in this cluster was negatively correlated with cortisol (r=-0.528, P = 0.024), adrenocorticotropic hormone (ACTH) (r=-0.641, P = 0.004), and urinary free cortisol (UFC) (r=-0.546, P = 0.022). In right hemisphere, two clusters were identified. Cluster 1 (P = 0.026, size=6,098 voxels) predominantly involved the rostral middle frontal (23%) and superior frontal (19%) regions. Right Cluster 1 thinning was negatively correlated with cortisol (r=-0.538, P = 0.021), ACTH (r=-0.604, P = 0.008), and UFC (r=-0.474, P = 0.047). Right Cluster 2 (P = 0.037, size=5,481 voxels) exhibited thinning in the inferior parietal (22%), superior parietal (20%), and precuneus (16%) cortices. Thinning in right Cluster 2 correlated negatively with serum cortisol (r=-0.581, P = 0.011) and ACTH (r=-0.721, $P < 0.001$). LASSO analysis identified the CD, older age, and cortical thinning in Cluster 1 as

predictors of reduced aggression. Thinning Cluster 1 emerged as the strongest predictor of lower aggression.
Conclusion
CD might promote persistence and suppress aggression. Neuroimaging revealed thinning in bilateral frontal and right parietal cortex in CD group. Neurostructural changes became more evident with higher cortisol levels. Thinning in the right rostral middle frontal, superior frontal, and precentral gyri emerged as determinants of aggression, highlighting the role of neurostructural changes in shaping behavior in CD.

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P825

JOINT1671

Using genomics to characterize features of aggressiveness in PitNETs

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PitNETs aggressiveness is currently assessed based on clinical and histological criteria, leading to regularly updated classifications. The role of molecular criteria has yet to be defined. Multi-omics analyses show the importance of lineage as the main driver of unsupervised classifications. Aggressive PitNETs appear to be scattered according to their lineage without forming a distinct molecular group.
Aim
Identify genomic features associated with PitNETs aggressiveness.
Methods
• Five features of aggressiveness were explored: post radiotherapy progression, rapid tumor progression speed, Ki67 $\geqslant$ 10%, cavernous invasion and sphenoid invasion. A cohort of 155 tumors with or without these features were analysed by transcriptome, methylome, SNP array and NGS sequencing.
• Transcriptome and methylome signatures associated with features of aggressiveness were established by logistic regression stratified by lineage.
• Response to temozolomide was evaluated on 17 samples collected before temozolomide treatment, following RECIST criteria. Transcriptome signatures of temozolomide response were assessed with a differential gene expression analysis.
Results
Post radiotherapy progression, rapid tumor progression speed, and Ki67 $\geqslant$ 10% were associated with distinct transcriptome signatures linked to RNA metabolism in TPIT lineage, and to proliferation and cell motility in PIT-1 lineage. Post radiotherapy progression and rapid progression speed were associated with tumor hypermethylation. The latter was not associated with any specific location related to gene structures. Post radiotherapy progression, rapid tumor progression speed, and Ki67 $\geqslant$ 10% were associated with a group of tumors cumulating pathogenic somatic variants, including *TP53, CDKN2A/B, DAXX, MEN1,* and *PTEN*. Reversely, *USP8* and *GNAS* mutations weren't associated with any feature of aggressiveness, in TPIT and in PIT1 lineages, respectively. Cavernous and sphenoid invasion were not associated with any molecular signature. Response to temozolomide was associated with a leukocyte migration and differentiation transcriptome signature. O-6-methylguanine-DNA methyltransferase gene (*MGMT*), which promoter methylation and expression was proved to be predictive of temozolomide response in gliomas, was found underexpressed in responders compared to non-responders through transcriptome analysis. Longitudinal samples omics highlight genomic alterations already present in the earliest samples of tumor progressions. Alteration evolution also shows chromosomal rearrangements generating new aggressive clones.
Conclusion
PitNETs accumulating features of aggressiveness are associated with specific genomic markers. The prognostic value of these potential markers remains to be confirmed in an independent cohort.

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P826

JOINT935

Short-term efficacy of Stanozolol or recombinant human Growth hormone in CPP or EFP boys with excessive growth deceleration during GnRHa treatment

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Background
Gonadotropin-releasing hormone analogue (GnRHa) being the standard treatment for boys with central precocious puberty (CPP) or early fast puberty (EFP), but a considerable proportion will experience significant growth deceleration. Although combining growth hormone (GH) can counteract it, studies in boys are limited. Stanozolol (ST) offers a promising alternative, yet its efficacy remains understudied. We evaluate the short-term efficacy of GH or ST in CPP or EFP boys experiencing growth deceleration during GnRHa treatment.
Methods
Boys diagnosed with CPP or EFP who experienced excessive decline in growth velocity (GV, $<$ 5 cm/year) after receiving standard GnRHa treatment at the First Affiliated Hospital of Sun Yat-sen University (2000-2024) were included. Eighty-four boys were divided into three groups base on the therapy thereafter: GnRHa monotherapy (Group 1, $n = 40$), GH combined with GnRHa (Group2, $n = 25$), and ST combined with GnRHa (Group 3, $n = 19$). We assessed growth velocity (GV), predicted adult height (PAH), bone age (BA), IGF-1 levels, gonadal axis parameters, and glucose-lipid metabolism at baseline and at the sixth month.
Results
After six months, GV significantly increased in Group 2 [from 3.6 (1.2) to 7.2 (2.9) cm/year] and Group 3 [from 3.6 (1.7) cm/year to 7.1 (2.5) cm/year] compared to the Group 1 [from 4.4 (1.2) cm/year to 4.7 (1.8) cm/year] ($P < 0.001$ for all comparisons). PAH also significantly increased in Group 2 and 3 compared to the Group 1 ($\triangle$PAH, Group 1: 1.4 $\pm$ 1.9 cm, Group 2: 3.7 $\pm$ 2.7 cm, Group 3: 3.3 $\pm$ 2.0 cm; $P < 0.001$ for all comparisons). There was no significant difference in change of GV or PAH between the Group 2 and 3 ($P = 0.930$ for GV, $P = 0.577$ for PAH). Changes in GV were not correlated with changes in serum IGF-1 or sex hormone levels. The changes in BA in three groups were all 0.0 (0.3) years ($P = 0.895$). The Group 2 showed increased fasting insulin (from 9.8 $\pm$ 4.2 to 12.8 $\pm$ 6.4 uU/mL, $P = 0.021$) and HOMA-IR (from 2.1 $\pm$ 0.9 to 2.8 $\pm$ 1.5, $P = 0.026$), while Group 3 showed decreased HDL-C levels (from 1.4 $\pm$ 0.4 to 1.2 $\pm$ 0.3 mmol/l, $P = 0.042$).
Conclusion
Both rhGH and ST effectively reversed growth deceleration and improved PAH without accelerating BA in CPP or EFP boys with excessive growth deceleration during GnRHa treatment, but may differentially impact glucose or lipid metabolism. Further researches are needed to follow up to their adult final height.

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P827

JOINT1283

Phenotype and genotype of 23 patients with hypopituitarism and pathogenic GLI2 variants

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Aim
The objective of this study is to analyze the phenotype and genotype of patients diagnosed with congenital hypopituitarism and pathogenic *GLI2* variants.

Methods
A large cohort of patients with hypopituitarism was screened for *GLI2* variants using a next-generation sequencing panel. Genotype-phenotype correlations were then assessed using GENHYPOPIT phenotypic data.
Results
Pathogenic or likely pathogenic variants in *GLI2* were identified in 17 out of 59 mutations reported from 717 index cases. *GLI2* mutations were identified exclusively in patients with associated pituitary stalk interruption syndrome or extrapituitary signs ($n = 440$), representing the most frequent identified genetic cause in patients with syndromic pituitary deficiency. *GLI2* variants were the most frequent identified genetic cause in patients with syndromic hypopituitarism (68%): 88% (15/17) of mutations were truncating variants, and 45% were *de novo*. Most patients with a *GLI2* variant (21/23, 91%) had hypopituitarism, including 21.7% (5/23) presenting isolated growth hormone deficiency. Two patients had Kallman syndrome. Pituitary morphological abnormalities were present in 84% of the patients with pathogenic *GLI2* variants (index cases and affected relatives). The remaining signs included neurocognitive disorders (38%), hexadactyly (27%), cardiac septal defects and renal/vesical abnormalities. A possible digenic origin (*GLI2*/*HESX1*) is proposed in one family.
Conclusion
GLI2 has been identified as the most frequent genetic cause in congenital pituitary deficiency with pituitary stalk disruption syndrome or extrapituitary clinical feature. In addition to the commonly associated polydactyly and neurodevelopmental disorder, cardiac and renal abnormalities were frequently observed in these patients and should be investigated further. The variable expression of GLI2-associated phenotypes justifies further research in this area.

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P828

JOINT1789

[18F]Fluorethyltyrosine positron emission tomography for localisation of corticotroph pituitary adenomas in the initial evaluation of Cushing's disease

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Introduction
The preoperative localisation of ACTH-producing pituitary adenomas remains challenging. Magnetic resonance imaging correctly visualize up to 75% of ACTH-producing adenomas. In many patients, pituitary exploration has to be performed, with a risk of unnecessarily extensive resection, increasing the risk of postoperative pituitary insufficiency, or incomplete tumor removal, resulting in persistent disease. We therefore aimed to evaluate the potential of [^{18}F]Fluorethyltyrosine positron emission tomography ([^{18}F]FET PET/CT) in localising ACTH-producing pituitary adenomas in patients with first diagnosis of Cushing's disease.
Methods
[^{18}F]FET PET/CT was conducted in all consecutive patients with a primary diagnosis of Cushing's disease at LMU Hospital between June and December 2024 in addition to a preoperative MRI and inferior petrosal sinus sampling. Dynamic PET images were acquired 0-40 min after injection with a mean injected dose of 173 MBq. Maximal tumor-to-background ratios (TBR_{max}) were determined comparing maximum standardized uptake values of pituitary adenomas to mean standardized uptake values of the right frontal and temporal lobe. Numeric values were reported with median (interquartile range).
Results
A total of 10 patients were included, 5 with microadenoma, 2 with macroadenoma, 3 with no visible lesion on MRI. All patients had inferior petrosal sinus sampling confirming a pituitary origin of ACTH excess. The median preoperative ACTH level was 55.5 pg/mL (50.3-89.0), the median preoperative basal cortisol was 23.6 µg/dl (13.7-29.7). In all patients, dynamic [^{18}F]FET PET/CT revealed a focal intrasellar hotspot indicating a pituitary adenoma (median TBR_{max} 3.2; 2.4-3.6). 6/10 patients underwent transsphenoidal surgery until January 2025. In all operated patients, the focal intrasellar hotspot was consistent with the histopathologically proven corticotroph adenoma. 2 patients are still awaiting surgery, 1 patient refused surgery, 1 patient postponed surgery due to hospitalisation for severe depression. All operated patients showed a postoperative remission with a median basal ACTH of 6.0 pg/mL (4.5-20) and basal cortisol of 1.1 µg/dl (0.4-3.1). No patient experienced a postoperative anterior pituitary insufficiency.
Conclusion
Functional imaging with [^{18}F]FET PET/CT can be effective in localising ACTH-producing pituitary adenomas and can add valuable information to MRI and inferior petrosal sinus sampling.

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P829

JOINT1570

Overphosphorylation of the LKB1 signalling pathway proteins in sparsely granulated somatotropinomas

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Background
Somatotropinomas are histopathologically divided into sparsely (SG) and densely granulated (DG). SG exhibits aggressive clinical behaviour (presentation at a younger age, high proportion of invasiveness, resistance to treatments and recurrence (inspite of complete removal) as compared to DG. Dysregulation of LKB1-AMPK pathway can support tumour survival and growth by promoting autophagy and providing an adaptive response to a nutrient-poor microenvironment.
Method
High-throughput label-free quantitative mass spectrometry-based (Orbitrap Exploris mass spectrometer, Thermo Scientific) phosphoproteomics analysis was performed on SG ($n = 4$) and DG ($n = 4$) tumours in triplicates. Candidates of significantly enriched pathways (cut-off = 1.5fold-change) were considered for validation by immunohistochemistry ($n = 32$; SG = 24, DG = 8) on tissue microarray in separate group of samples.
Results and Discussion
In our data (total = 10418) 835 over and 4246 under phosphorylated proteins were detected. There was significant over-phosphorylation of 85 proteins in the LKB1-AMPK pathway (fold enrichment = 1.8, $P = 2.2E-09$) in SG tumours. Commercially available antibody guided the selection of four candidates TSC1 Ser1080, AMPKβ Ser108, MAPT Thr548, and ULK1 Ser638 for IHC. Over-phosphorylation of AMPKβ Ser108 (6.0-fold, $P = 0.01$) suggests metabolic adaptation to energy stress. Increase in TSC1 Ser1080 phosphorylation (9.5-fold, $P = 0.01$) implies inhibition of the TSC complex, potentially activating mTOR signalling and promoting anabolic processes in SG tumours. Over-phosphorylation of MAPT at Thr548 (3.8-fold, $P = 0.02$) suggests enhanced cytoskeletal dynamics, which can potentially facilitate invasion. ULK1 Ser638 phosphorylation showed increase (1.8-fold) phosphorylation. Ratio of Phosphorylated ULK1 Ser638 to Total ULK1 was significantly increased in SG tumours ($P = 0.01$). This trend may indicate autophagic adaptation to metabolic stress. Upstream analysis identified PRKAA1 and GSK3β as regulators of AMPKβ Ser108 and MAPT Thr548, respectively, mTOR phosphorylates TSC1 Ser1080 and ULK1 Ser638. IHC confirmed increase in mTOR expression in SG tumours (2.66-fold $P = 0.003$) compared to DG, underscoring mTOR's role in SG tumours. We observed significant correlation of AMPKβ Ser108 phosphorylation with MAPT Thr548 ($r = 0.7$, $P = 0.0001$) and TSC1 Ser1080 ($r = 0.59$, $P = 0.002$) phosphorylation. ULK1 Ser638 phosphorylation levels significantly correlated ($r = 0.5$, $P = 0.01$) with mTOR levels. Age was found to be inversely correlated with MAPT Thr548 (r = -0.5, $P = 0.01$) and ULK1 Ser638 (r = -0.4, $P = 0.02$). Maximum tumour diameter showed significant positive correlation with ULK1 Ser638 ($r = 0.5$, $P = 0.01$) and mTOR expression (0.4, $P = 0.03$) levels while tumour volume was found to be correlated with mTOR expression only ($r = 0.6$, $P = 0.02$).
Conclusions
Our results reveal a coordinated network of mTOR signalling complemented by PRKAA1-mediated AMPK activation and GSK3β-driven cytoskeletal remodelling in SG tumours.

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P830

JOINT1064

The endowatch – developing an 'external hypothalamus' to support patients (and their parents) with hypothalamic dysfunction

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Background

Children and adults with a suprasellar (hypothalamic) brain tumor often have excellent survival, but poor outcome due to hypothalamic dysfunction (HD). The hypothalamus, as the key regulator of the body, regulates the anterior pituitary gland, core body temperature, circadian rhythm, sodium and energy balance. Patients with HD experience chronic fatigue, recurrent headaches and inactivity due to hypothalamic imbalances. Patients and families urge us to find a solution because they are overwhelmed by the effort to detect and prevent these imbalances early, as if they were the patient's "external hypothalamus". In this project, we aim to develop a smart wearable that can act as an "external hypothalamus" for patients with HD. This wearable must be available 24/7 and continuously monitor body temperature, stress, sleep, daily activity in order to offer support to patients and their families in the management of HD. The aim is to improve outcomes and self-management, and to relieve caregivers.

Methods

By a multidisciplinary team from the Princess Máxima Center, Eindhoven University of Technology and Corsano Health B.V., the Corsano EndoWatch was developed. The EndoWatch consists of a smart wristband that communicates with a phone application via Bluetooth, visualizing measurements to enable continuous health-monitoring. Between June – August 2024, a first pilot study was performed with 10 patients with HD ($n = 8$ <18 y.o, $n = 2 \geq 18$ y.o), evaluating the adherence (% of hours per day the device was worn by the patient). Usability and desirability of the device were measured by questionnaire and a semi-structured interview.

Results

Adherence was shown to be satisfactory. The device was worn >80% of hours per day by 8/10 patients. Usability and desirability of the device were positively assessed. All families reported that they desire to use this device in the future, provided that certain adjustments are made. The most frequently reported suggestion for improvement was to enable remote monitoring for caregivers on a second interface.

Conclusion

Patients and parents appreciate the development of the EndoWatch that may serve as "external hypothalamus". We will open a second clinical study in May 2025, including 50 patients ($n = 40$ <18 y.o, $n = 10 \geq 18$ y.o) with HD, incorporating the suggested approvements that were reported in the pilot study. The primary outcomes of this study are patient reported experiences (PREs) assessed by mid-study (3 months) and end-study questionnaires (6 months). The PREs will play a central role in the further development and certification process of the EndoWatch.

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P831

JOINT607

Survival in patients with pituitary carcinoma

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Introduction

Pituitary carcinoma (PC) is defined as the presence of metastasis (craniospinal or systemic) from a pituitary tumor. Given the rarity of PC, limited information regarding survival and factors which may influence survival is available in literature.

Aim

To assess overall survival following detection of metastatic disease in patients with PC and to determine factors associated with clinical outcomes in these patients.

Methods

All patients with PC diagnosed between 1997 and 2024 were identified using the Mayo Data Explorer. Information regarding patient demographics, tumor characteristics, management, and outcomes was extracted.

Results

25 patients (56% male) were included; mean age at initial pituitary adenoma (PA) diagnosis was 50 $\pm$ 11.9 years. PA size at initial diagnosis was 2.1 $\pm$1.3 cm, 18 (72%) of which were functioning tumors. Surgery was the initial treatment in 24 (96%) patients. Radiation therapy (RT) was used in 25 (100%) cases with a median time to RT of 12 months (range 0-239). Median time to metastasis diagnosis was 6 (range 1-32) years, mean age of 59 $\pm$10.6 years. The most common site of metastasis was bone in 13 (52%) patients, followed by central nervous system (CNS) and spine in 12 (48%). Systemic therapy alone (temozolomide, CVD [cyclophosphamide, vincristine, dacarbazine], etoposide/-cisplatin, pembrolizumab or lutetium Lu 177 dotatate) was used in 6 (24%) patients, local treatment alone (radiotherapy, cryoablation or metastasectomy) was used in 9 (36%) of patients, combination treatment (locoregional and systemic therapy) in 8 (32%), and no additional treatment in 2 (8%). Median follow-up was 1.7 years (range 0.1-15.5). At last follow-up, 11 (44%) patients were alive, 11 (44%) died of PC, and 3 (12%) died from othercauses. The median survival time of patients from the identification of metastasis was 4 years. The 1-, 5- and 11-year survival rates were 70%, 37% and 13%, respectively. No difference in survival was seen according to metastasis site (CNS vs distant metastasis), corticotroph vs other PC cell type or treatment before or after 2010. Improved survival correlated with temozolomide (TMZ) treatment ($n = 9$) compared to those not treated with TMZ ($P=0.048$) and in nonfunctional compared ($n = 7$) to functional tumors ($P=0.048$).

Conclusion

This study demonstrates that survival among patients with PC is higher among those who received temozolomide and if the tumor was nonfunctioning. Despite current treatment modalities 5-year survival was poor (37%). Additionally, there is a lag between PA and PC diagnosis (6 years) emphasizing the importance of long-term follow-up.

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P832

JOINT1258

A mouse luteinizing hormone-blocking monoclonal antibody; development and in vivo proof of blocking capacity

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Introduction

To examine the effect of blocking Luteinizing hormone (LH) in several endocrine disorders, a mouse monoclonal antibody against the β-subunit of LH was developed. Here, the *in vitro* and *in vivo* validation of the LHβ-specific antibody is presented.

Materials and Methods

The LHβ-specific antibody was generated by immunizing mice using a recombinant protein fragment corresponding to amino acids S21-L141aa of mouse LH. For *in vitro* validation of the LHβ-antibody we used enzyme-linked immunosorbent assay (ELISA) and immunohistochemistry (IHC). For *in vivo* validation of the blocking capacity of the LHβ-antibody, male mice were treated with vehicle, GnRH agonist (Leuprorelin, 1.5 mg/kg), or co-treated with GnRH agonist + LHβ antibody (0.2 mg). The GnRH agonist were injection on day 2 and 4, whereas the LHβ antibody was injected on day 1-4 or 1+3. LH levels were measured on day 2, 4 and 5 with ELISA and testosterone levels were measured on day 2 and 5 with liquid chromatography– tandem mass spectrometry (LC-MS/MS). To examine whether the LHβ antibody was also efficient in blocking high LH levels, ovariectomized (OVX) mice were treated with vehicle or LHβ antibody on day 1-4 (0.2 mg). Blood samples were taken on day 2,4, and 5.

Results

The LHβ-antibody bound the LH peptide fragment (S21-L141aa) in an ELISA where a goat anti-mouse IgG was used to detect the bound complexes. Additionally, the antibody against the LHβ-subunit specifically stained the gonadotropic cells in the mouse pituitary. To prove the blocking capacity *in vivo*, i.e., whether the LHβ-subunit antibody can block LH-signaling we utilized the fact that a GnRH agonist in male mice initially induces high LH levels and subsequently high testosterone levels. Treatment with LHβ antibody completely reduced LH in all groups at all timepoints. At day 5, LH and testosterone was induced with the GnRH agonist alone compared with vehicle (2.3 vs 0.2 ng/ml

and 64 vs. 7 nmol/l, respectively). Compared with the GnRH agonist alone co-treatment with the LHβ antibody on day 1-4 completely abolished LH and testosterone levels on day 5 (2.3 vs 0.02 ng/ml and 64 vs 1.3 nmol/l, respectively). The LHβ antibody was also efficient in blocking the high LH levels in OVX mice (vehicle = 17.3 vs. LHβ antibody = 0.1 ng/ml).
Conclusion
A specific LH-blocking antibody was successfully generated, and its blocking capacity was demonstrated *in vivo*. In subsequent studies the possible non-gonadal effects of LH will be investigated using this LH-blocking antibody.
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P833

JOINT2219

Understanding the developmental down-regulation of mkrn3 at puberty through bioinformatics and experimental approaches

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Makorin Ring Finger Protein 3 (MKRN3) loss-of-function mutations are the most common genetic cause of central precocious puberty. Its expression levels in the brain drop significantly towards puberty, suggesting effects in repressing the central control of reproduction and its role as a childhood "pubertal brake". However, both the nature of this repression and the factors responsible for the drop in MKRN3 levels have remained unclear. To investigate these regulatory pathways, we performed bioinformatic analyses of several developmental RNA-seq datasets from rat and mouse brain, and from rat mediobasal hypothalamus (MBH). We identified genes whose expression levels correlate with those of *Mkrn3* and change specifically across the pubertal transition, potentially encoding regulators of its expression, downstream effectors, or co-regulated genes. In order to detect its up-stream regulators, we filtered this group of *Mkrn3*-correlated genes for those linked to both puberty and signaling. Notably, these included *Acvr1c*, whose expression was strongly negatively correlated with *Mkrn3* in all of the datasets and whose knockout was shown previously to delay puberty in mice. Analysis of single-cell RNA-seq data from mice hypothalamic neurons during development indicated that *Mkrn3* and *Acvr1c* are not expressed simultaneously in the same cell. In experimental models, we demonstrated that activation of Acvr1c in GnRH neuronal cells suppresses *Mkrn3* mRNA levels, and that this is mediated through Smad2/3 signaling. This repression involves recruitment also of the Kap1 transcription factor, and a marked shift from activating to repressive histone modifications at the gene locus. These findings provide a mechanistic explanation for the reduction in Mkrn3 arising from the developmental increase in expression of this receptor which can be activated by various available ligands. Our study highlights the value of integrating high-throughput gene expression data analysis with experimental studies to uncover novel regulatory networks, and have revealed here a new player in the regulation of pubertal onset.
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P834

JOINT1102

ß-arrestin 2 protein expression correlated with non-functioning pituitary neuroendocrine tumors (NF-PitNETs) *in vitro* responsiveness to dopamine agonists

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Non-functioning pituitary neuroendocrine tumors (NF-PitNETs) represent the most common subtype of PitNETs after prolactin-secreting ones and are still orphan of an effective pharmacological approach for persistent or recurrent cases. Lot of attention was given to dopamine receptor type 2 (DRD2) agonists (DAs), based on high DRD2 expression levels in NF-PitNETs, but their use in clinic is still controversial, since they efficacy on tumor growth's control is not well demonstrated. β-arrestin2 has been recently identified as possible molecular determinant predicting DAs responsiveness in NF-PitNETs. In fact, its fundamental role in regulating DRD2 inhibitory effects on AKT phosphorylation and cell proliferation in NF-PitNETs has been unveiled, since it has been demonstrated that β-arrestin2 lack prevents the inhibitory effect of DRD2 on AKT pathway activation with a consequent resistance to the antimitotic action of DAs. The aim of this study was to investigate β-arrestin2 expression at both protein and transcript level in human NF-PitNETs, correlating it with their *in vitro* responsiveness to DAs in terms of cell proliferation inhibition. 65 primary cultured NF-PitNET cells have been treated for 72h with 100nM DAs and cell proliferation assay was performed. DAs treatment determined a significative inhibition of cell proliferation (-27.7(20.14),$P < 0.001$) in 26 samples (considered 'responsive' NF-PitNET, using a cut-off of at least 15% of cell proliferation inhibition). Then, RNA and proteins from NF-PitNETs frozen tissues have been extracted ($n = 56$ and $n = 48$ for proteins, respectively) have been extracted. β-arrestin2 relative expression of 23 NF-PitNET samples *in vitro* responsive to DAs treatment and 33 resistant ones has been evaluated by real-time PCR (qPCR). Our data revealed that there was no significative difference between the median of expression between the two groups (0.0037(0.0032) responsive vs 0.0033(0.0031) resistant). Moreover, β-arrestin2 protein expression was analysed in 24 responsive and 24 resistant NF-PitNETs by western blot. Our analysis revealed that the 83% of NF-PitNETs responsive to DAs were positive for β-arrestin2 expression, while only the 20% of resistant ones expressed it ($P < 0.001$). In addition, significative correlation ($P < 0.05$) between β-arrestin2 protein expression and DA responsiveness of NF-PitNET samples tested has been highlighted. β-arrestin2 mRNA levels were not correlated to protein expression nor with NF-PitNET cell proliferation inhibition after DAs treatment. In conclusion, our analysis demonstrated that β-arrestin2 protein expression positively correlated with NF-PitNETs *in vitro* sensitivity to DAs, paving the way for a potential role of β-arrestin2 as a biomarker predicting responsiveness to pharmacological treatment with DAs for NF-PitNETs.
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P835

JOINT903

Validation of the PANOMEN-3 predictive model for tumor recurrence and progression in pituitary tumors. a real-world spanish multicenter study

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Background
the aim of our study was to validate the classification proposed by the PANOMEN-3 group for the prediction of tumor recurrence and or progression in pituitary tumors (PTs).
Methods
Multicenter national case-control study of patients with PTs followed for at least 5 years. Kaplan-Meier curves were used to assess the time to tumor recurrence/progression. Uni- and multivariate Cox regression analyses were used to estimate the hazard ratio [HR] and prognostic capacity of the classification proposed by the PANOMEN-3 group.
Findings
One thousand patients were included, 500 were males and 500 females. The mean age at diagnosis was 51.7 ± 15.7 years. Pituitary surgery was performed in 809

patients and the remaining 191 patients were followed with active-surveillance or medical treatment. After a median follow-up of 8.3 (range 5-30) years, there were 244 (24.4%) patients who experienced tumor recurrence or biochemical/radiologic progression; and were thus classified as cases (231 in the surgical group and 13 in the conservative/medical treatment group). Of the 231 cases, 37 had tumor recurrence after surgical cure, 175 had significant tumor growth and 42 functioning PTs had experienced significant biochemical progression. The other 756 patients remained stable and thus, were classified as controls. The median recurrence-free survival was 16.5 years [95% CI: 14.9 to 18.7], indicating that 50% of patients experienced a recurrence within this period of time. At the last follow-up, 39 patients had died; 6 of 244 (2.5%) in the case group and 33 of 756 (4.4%) in the control group ($P = 0.18$). The diagnostic accuracy of the PANOMEN-3 model to predict recurrence/progression was 77.8% (95% CI 0.734-0.822). Residual tumor (HR 2.67, $P < 0.001$), hereditary syndrome (HR 12.62, $P = 0.015$) and active secretory status (HR 1.82, $P = 0.028$) were the most important variables in this model. There was a significantly positive tendency to increase the incidence of recurrence as the PANOMEN-3 grade increased (Mantel-Haenszel Test for linear Trend: Chi2 = 34.17, $P < 0.001$). The differences in survival were evident when comparing the four grades (PANOMEN 0, 1, 2 and 3), especially between grade 0 and 1 compared to 2 and 3 (0% in grade 0; 12% in grade 1, 32% in grade 2 and 35% in grade 3; $P < 0.001$).
Interpretation
The predictive model proposed by the PANOMEN-3 group may be useful to guide the prognosis and therapy of PTs in the Spanish population since it offers a good accuracy to predict tumoral/biochemical recurrence and/or progression in operated and non-operated patients.

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P836

JOINT640

Urea-stimulated copeptin: a novel diagnostic approach in polyuria polydipsia syndrome

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Background and Objectives
The differential diagnosis between arginine vasopressin (AVP) deficiency and primary polydipsia remains challenging. The method with the highest diagnostic accuracy is osmotically stimulated copeptin using hypertonic saline infusion. However, this method is limited to experienced hospitals, requires close monitoring, and may be cumbersome for patients. Therefore, an alternative simplified osmotic stimulation test would be highly desirable. Intravenous urea has been shown to stimulate AVP secretion. However, no study investigated the effects of oral urea on copeptin levels.
Methods
Twenty-two healthy adults were included in a randomized double-blind placebo-controlled cross-over trial. Participants underwent two visits after an overnight food fasting and two-hour fluid fasting period. They received a single weight-adapted dose of urea (0.5 g/kg body weight; minimum 30g, maximum 45 g) and placebo in random order. Serum copeptin was measured at baseline, 30, 60, 90, 120, and 150 minutes. In a second step, 13 patients with AVP-deficiency and 13 patients with primary polydipsia were included in a single arm, open label pilot study, receiving urea only. The primary endpoint was the maximum increase in copeptin within 150 minutes after ingestion of the study drink.
Results
In healthy adults, median [IQR] copeptin significantly increased from 4.6 [3.0 – 5.7] pmol/l at baseline to a maximum of 10.1 [7.2 – 11.6] pmol/l at 120 minutes after ingestion of urea, while it remained stable at 3.8 [2.9 – 6.6] pmol/l during placebo ($P < 0.001$). In patients with AVP-deficiency, copeptin remained below detection limit throughout the test, while in patients with primary polydipsia the peak was seen 150 minutes after ingestion of urea at 7.4 pmol/l [4.3, 10.3]. The best copeptin cut-off for differentiating AVP-deficiency from primary polydipsia was 3.5 pmol/l after 120 minutes, with a sensitivity and specificity of 92%, respectively.
Conclusion
Oral urea stimulates copeptin levels in healthy adults and patients with primary polydipsia, but not in patients with AVP-deficiency, establishing the first oral copeptin-based test in differentiating primary polydipsia from AVP-deficiency.

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P837

JOINT1383

Prognostic study of suspected dual CHH patients treated with gonadotropins

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Objective
This study aimed to investigate the treatment outcomes and predictive indicators in suspected dual congenital hypogonadotropic hypogonadism (CHH) patients treated with GnRH or hCG/hMG.
Methods
A total of 37 male dual CHH patients who received GnRH or hCG/hMG treatment from January 1, 2010 to the present were included. Clinical data including age, height, weight, LH, FSH, T, AMH, and INHB were collected from the medical records. Based on their treatment response, patients were divided into two groups: typical response ($n = 20$) and atypical response ($n = 17$). The diagnostic criteria for dual CHH are as follows:1) Testosterone (T) levels remain below 100 ng/dl after an hCG prolongation test. 2) T levels remain below 100 ng/dl after six months of GnRH treatment (5-10 mg/90 min, 16 pulses/day). Patients in the atypical response group had serum T levels below 200 ng/dl within six months of treatment or did not produce sperm during the treatment period. Patients not meeting these criteria were classified as having a typical response.
Results
1. Compared with the typical response group, the atypical response group had a higher incidence of cryptorchidism (40.0% vs 76.5%, $P = 0.065$), lower baseline ultrasound-measured testicular volume (TV) (0.43 ± 0.34 vs 0.18 ± 0.09 ml, $P = 0.046$), lower AMH level (15.39 ± 5.60 vs 6.84 ± 4.62 ng/ml, $P = 0.000$), and lower T level after hCG prolongation test (70.52 ± 20.21 vs 28.80 ± 19.30 ng/dl, $P = 0.000$).
2. The AUC for predicting typical response in suspected dual HH patients was as follows: AMH: 0.950 ± 0.055, with a cut-off of 10.65 ng/ml (sensitivity 80%, specificity 100%); T after hCG prolongation test: 0.883 ± 0.088, with a cut-off of 66.65 ng/dl (sensitivity 66.7%, specificity 100%); Combined AMH and T after hCG prolongation test: 1.0 (sensitivity 93.3%, specificity 100%).
4. For cumulative doses of HCG (24,000-40,000 units), HMG (0-3,375 U), and GnRH (4-4.8 mg), the AUC for T was 0.918 ± 0.058, with a cut-off of 135.8 ng/dl (sensitivity 80%, specificity 100%). The combined prediction of T and TV had an AUC of 0.945 ± 0.056 (sensitivity 90%, specificity 100%).
Conclusion
Gonadotropin therapy promotes testicular development and sperm production in patients suspected of having dual CHH. Patients with AMH levels below 10.65 ng/ml and T levels below 66.65 ng/dl after an hCG prolongation test may be considered for a diagnosis of dual CHH.

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P838

JOINT122

Omentin-1 as a new regulator of porcine pituitary function: *in vitro* effect on global proteome, endocrinology, and signaling pathways

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Omentin-1 has significant implications for metabolism and insulin sensitivity, especially in obesity, metabolic syndrome, and inflammatory diseases. Also, expression of omentin-1 has been observed in reproductive cells including the ovary, placenta, and anterior pituitary (AP). Moreover, omentin-1 regulates steroid hormone secretion through the upregulation of steroidogenesis-related proteins. This highlights its significant role in the regulation of female

reproductive hormones. The objective of the present study is to examine the *in vitro* effects of omentin-1 on the global proteome and its role in the regulation of tropic hormone levels and signaling pathways in porcine AP cells. To investigate this, AP cells were isolated from Large White (LW; normal body weight) and Meishan pigs (MS; genetically obese) during the mid-luteal phase of estrous. We conducted liquid chromatography-tandem mass spectrometry with tandem mass tag labeling following a 24-hour treatment with omentin-1 (50 ng/mL). Functional analyses were performed to investigate dose-dependent of omentin-1 (10, 50, 100 ng/mL) alone and in combination with GnRH (100 ng/mL), CRH (1000 nM), TRH (1000 nM), and GHRH (100 nM) on the expression and secretion of LH, FSH, ACTH, TSH, PRL, GH, and their respective hypothalamic receptors in AP cells (using RT-qPCR and ELISA). We also explored the role of OMNT1 on gonadotropins secretion via extracellular signal-regulated kinases 1 and 2 (ERK1/2), protein kinase C, and insulin receptor signaling pathways (using ELISA). Statistical analysis used two-way ANOVA, and Tukey's post-hoc test ($n = 4$ at least). Proteomic analysis identified ~7,000 proteins, 34 differentially expressed in LW pigs, and 198 in MS, (cutoff 1.2-fold, $P < 0.05$). Bioinformatics using the DAVID, Panther, and Reactome platforms highlighted the involvement of omentin-1 in gonadotropin regulation, insulin receptor recycling, immune response, and transport to the Golgi and subsequent modification, homeostasis, and metabolism. In MS, proteins upregulated included LHβ, VDAC3, and cathepsin D, while SARM1 and ERK1/2 were downregulated. In LW, RRAGD was downregulated, and in both breeds, SIX1 was down-regulated. Functional experiments have revealed that omentin-1 plays a modulatory role in the expression and secretion of tropic hormones. Additionally, it is involved in key signaling pathways, including ERK1/2, and protein kinase C suggesting its significant impact on cellular signaling and endocrine regulation in AP cells. The description of the molecular mechanism of omentin-1 action creates new opportunities for research into targeted therapy and improvement of efficiency of livestock production through modulation of hormonal functions.

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P839

JOINT616

Insulin-like growth factor 1 as a diagnostic marker to differentiate progressive central precocious puberty from non-progressive precocious puberty: a prospective study

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Background
Central precocious puberty (CPP) results from early activation of the hypothalamic-pituitary-gonadal axis. Its diagnosis often requires GnRH stimulation tests, which are invasive and costly. Serum insulin-like growth factor 1 (IGF1) and IGF1-SDS levels have emerged as potential markers to differentiate CPP from non-progressive forms of CPP (NP-CPP), as isolated thelarche (IT).
Methods
Prospective study (June 2022-December 2024) including 82 girls under 8 years. Participants were divided into CPP ($n = 39$), non-progressive puberty (NP-CPP and IT, $n = 26$), and control groups ($n = 17$). Anthropometric measurements, Tanner staging, bone age, pelvic ultrasound and serum IGF1 and IGF1-SDS levels were performed. GnRH stimulation tests confirmed CPP cases.
Results
Mean serum IGF1 and IGF1-SDS levels were significantly higher in CPP patients (270.15 ng/mL; 1.943 SDS) compared to NP-CPP (174.12 ng/mL; 0.788 SDS) and controls (139.28 ng/mL; 0.208 SDS) ($P < 0.001$). Multivariate analysis confirmed IGF1 (OR = 1.025, 95%CI: 1.010-1.040) and IGF1-SDS (OR = 8.721, 95%CI: 2.624-28.986) as significant predictors of CPP. ROC analysis revealed an AUC of 0.837 for IGF1 (95%CI: 0.738-0.935) and 0.862 for IGF1-SDS (95%CI:0.771-0.953). Cut-off values of 231 ng/mL for IGF1 (71.8% sensitivity, 96.2% specificity) and 1.71 for IGF1-SDS (64.1% sensitivity, 96.2% specificity) demonstrated good accuracy (82.2% and 77.8%, respectively).
Conclusions
Serum IGF1 and IGF1-SDS are promising as effective non-invasive markers to distinguish CPP from non-progressive precocious puberty. Values below 231 ng/mL or 1.71 SDS may significantly reduce the likelihood of CPP, potentially avoiding invasive GnRH stimulation tests. These findings may support the integration of IGF1 measurements into the initial diagnostic approach for girls presenting with early pubertal signs.

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P840

JOINT2345

It is quite stressful to be a stem cell

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The stress response is an adaptive mechanism that results in the release of glucocorticoids from the adrenal cortex, in order to regulate metabolic, immune and inflammatory related processes of the body. The intensity and duration of this response is tightly regulated by the Hypothalamic Pituitary Adrenal (HPA) axis and a pivotal component of this axis is the negative feedback of glucocorticoids. Central to this process, the pituitary gland modulates glucocorticoid levels by adjusting adrenocorticotropic hormone (ACTH) secretion in response to corticotrophin releasing hormone (CRH) from the hypothalamus and glucocorticoid feedback from the bloodstream. Our studies are centred around the response of HPA axis stem cells in mouse under physiological and stress conditions. We present here that SOX2+ anterior pituitary stem cells (PSCs) are responsive to glucocorticoids, activate glucocorticoid receptor (GR) signalling and are implicated in the stress response. To determine the role of GR signalling in PSCs, we generated *Sox2CreER/+;GRfl/fl* mice, where the GR receptor can be deleted specifically in the stem cells upon administration of a drug, tamoxifen. Combining in vivo and *in vitro* analyses, we show that PSCs activate GR during an acute stress model, leading to upregulated expression and secretion of cytokines, able to influence neighbouring cells. *in vitro* data using mouse corticotroph tumour AtT-20 cells and *in vivo* data from the mouse model, support that GR-dependent signalling regulates the *Pomc* promoter, in a dose-dependent manner. Together, these data indicate a functional role for GR signalling in SOX2+ pituitary stem cells implicating these cells in paracrine signalling during the stress response.

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P841

JOINT1887

Development and validation of rapidly progressive central precocious puberty diagnostic prediction models in girls

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Objective
This study aims to develop a diagnostic prediction model for girls with rapidly progressive central precocious puberty (CPP) using machine learning algorithms.
Methods
CPP girls admitted to the department of endocrinology, genetics and metabolism of the hospital without treatment intervention for a follow-up period of more than 3 months from June 2017 to June 2023 were included retrospectively. These girls were randomly divided into training (70%), validation (15%), and test set (15%). The training set data were used to screen the predictors based on Lasso regression. Validation set data assisted the training set data to adjust the model parameters to establish the rapidly progressive CPP girl diagnosis prediction model based on five machine learning algorithms including Logistic regression, support vector machine, random forest, limit gradient lifting and artificial neural network, and carried out internal validation. The test set data were used for model external validation.

Results
A total of 277 CPP girls were analyzed, of whom 141 (50.9%) were diagnosed with rapidly progressive CPP and 136 (49.1%) were diagnosed with slowly progressive CPP. Lasso regression included five predictors: BMI (kg/m^2), group of basal luteinising hormone (LH) (LH $<$ 0.20 IU/l, 0.20 IU/l $\leq$ LH $<$ 0.52 IU/l, LH $\geq$ 0.52 IU/l), group of insulin like growth factor 1 (IGF-1) SDS (IGF-1 SDS $<$ 0.35, IGF-1 SDS $\geq$ 0.35), and advanced bone age (y). Five machine learning algorithm prediction models were developed. The artificial neural network model has the best performance, with AUC vulues of 0.774 in internal validation and 0.725 in external testing cohort, and the accuracy rate was 76.2% and 69.1%, respectively. When the prediction probability was greater than 0.80 as the diagnostic threshold of rapidly progressive CPP, the specificity of the model in the validation and the test set data were 100.0% and 95.5%. When using a prediction probability less than or equal to 0.30 as the diagnostic threshold for slowly progressive CPP, the model demonstrated sensitivities of 96.2% and 95.5% in the validation and test set, respectively.
Conclusion
This study developed prediction models based on machine learning algorithm for the typing of CPP girls. Internal validation and external testing ensured a good degree of discrimination and calibration of the models, which could assist in the diagnosis of rapidly progressive CPP on the basic of clinical data.
Key words
central precocious puberty, girl, machine learning, prediction model.
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P842

JOINT2551
Impact of pasireotide LAR on lipid and glucose metabolism in patients with acromegaly: a systematic review and meta-analysis
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Background
Pasireotide long-acting release (PasiLAR) is a somatostatin multireceptor ligand commonly used as a second-line medical treatment in patients with acromegaly resistant to first-generation somatostatin receptor ligands (fg-SRLs). PasiLAR is more effective in achieving biochemical control and its tolerability is similar to the fg-SRLs, with the exception of a greater incidence and severity of hyperglycemia. A comprehensive assessment of the metabolic effects of PasiLAR in patients with acromegaly has however not been performed to date. This systematic review and meta-analysis aims to synthesize evidence on PasiLAR effects on lipid and glucose metabolism in patients with acromegaly.
Methods
A comprehensive search was conducted in MEDLINE, Embase, Cochrane Library, and Web of Science for studies published between 2000 and 2024 and retrieved 3441 records. Studies assessing lipid and glucose metabolism in patients with acromegaly on treatment with PasiLAR for at least 6 months were included. Two reviewers screened eligible publications, extracted outcomes, and assessed risk of bias. This systematic review followed Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines and was registered in PROSPERO in May 2024 (registration number: CRD42024544686).
Results
We included a total of 19 studies (18 only PasiLAR, 1 PasiLAR plus PegV), involving 896 patients with acromegaly. Nine studies were retrospective (47%) and ten were prospective randomized controlled trials (53%). A majority of patients included in the meta-analysis were male (58%). Median age (IQR) was 45.8 (43.0 to 47.8) years. PasiLAR treatment was associated with a significantly higher levels of high-density lipoprotein cholesterol (HDL-C) (mean difference [MD] 6.2 mg/dl; 95% confidence interval [CI] 1.4-10.9) and no significant changes in triglycerides, total cholesterol, or low-density lipoprotein cholesterol compared to baseline. PasiLAR treatment was associated with increased fasting plasma glucose (FPG) (MD 23.4 mg/dl; 95% CI 18.8-28.1) and glycosylated hemoglobin (HbA1c) (MD 0.5%; 95% CI, 0.4-0.7). Diabetes frequency was higher after treatment (58.6%) compared to baseline (30.9%), with an odds ratio of 3.7 (95% CI 2.9-4.7).
Conclusions
This systematic review and meta-analysis is the first comprehensive evaluation of the effects of PasiLAR treatment on both lipid and glucose metabolism in patients with acromegaly. Treatment with PasiLAR for at least 6 months was associated with increased HDL-C, FPG, HbA1c, and frequency of diabetes mellitus in patients with acromegaly. These findings are novel and emphasize the importance of a personalized approach to the treatment of acromegaly with a careful examination of metabolic status, to prevent impairment of lipid and glucose metabolism.
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P843

JOINT2725
The role of functional imaging with 11C-methionine and 11F-tyrosine in patients with cushing's disease
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Background
Transsphenoidal surgery is the first treatment option for Cushing's Disease (CD). Unfortunately, conventional dedicated pituitary MRI – the current golden standard – fails to detect the culprit lesion in approximately 30-50% of patients. Novel imaging techniques using positron emission tomography (PET) with specific radioactive tracers and co-registration with MR images have been used in patients with pituitary adenomas and might improve the surgical outcomes of corticotroph adenomas.
Aim/Objective
To assess functional imaging-guided diagnostic and surgical accuracy of ^{11}C-methionine PET-CT co-registered with MRI (^{11}C-MET-PET/MRI), and ^{18}F-fluoroethyl-l-tyrosine PET/CT co-registered with MRI (^{18}F-FET-PET/MRI) for patients with CD with an inconclusive MRI and high treatment need.
Methods
This cohort study included 31 patients with CD undergoing ^{11}C-MET-PET/MRI or ^{18}F-FET-PET/MRI in the diagnostic trajectory followed by surgery (2017-2024). Indication for functional imaging was determined by an experienced multidisciplinary team. Some patients underwent two functional imaging scans followed by surgery, resulting in a total of 36 evaluable functional imaging-treatment episodes. Outcomes were evaluated using histopathological confirmation and biochemical remission 6 months postoperatively.
Results
26 patients were female (71.0%), and mean age was 48 (11-73) years. Functional imaging was performed (^{18}F-FET-PET/MRI $n = 15$ and ^{11}C-MET-PET/MRI $n = 21$) mainly because of an unclear remnant lesion following prior surgery (24/36, 66.7%), or uncertain invasion/extension following surgery in 10/36 cases (27.8%). At the time of functional imaging, clinical severity of symptomatology was mild in 50% of patients, whereas the other 50% of patients had moderate or severe symptomatology. 32/36 cases (88.9%) had undergone previous surgery, only 4 patients were treatment-naïve. Functional imaging resulted in a positive "PET-signal" in 30/36 cases (83.3%), of which solely 10 (33.3%) could be related a lesion on the simultaneous MRI nor retrospectively on previous MRIs. Of the PET-positive lesions, confirmation was obtained by histopathology in 11/30 (36.7%), biochemical remission in 17/30 (56.7%), or either in 21/30 cases (70.0%). Regarding the entire cohort without clear surgical target, biochemical remission was obtained in 21/36 cases (58.3%). For repeat surgery, remission rates were 72.7% (16/22 cases) for patients with unclear remnants, and 40.0% (4/10 cases) for patients with unclear invasion/extension. In treatment-naïve patients, 1/4 cases (25.0%) achieved remission.
Conclusion
Functional imaging with ^{18}F-FET-PET/MRI and ^{11}C-MET-PET/MRI in complex patients lacking surgical target on conventional MRI showed a PET-positive lesion in 89%, which could be surgically confirmed in 70%, and yielded a remission rate of 60%, particularly in patients undergoing repeat surgery. Therefore, functional imaging should be considered in complex patients with CD.
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P844

JOINT3484
Natural history of non-functioning pituitary microadenomas in clinically diagnosed MEN 1 syndrome
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Introduction
Pituitary adenomas (PAs) represent one of the three main characteristic endocrine tumors associated with multiple endocrine neoplasia type 1 (MEN1) syndrome and are presumed to have a more aggressive behavior compared to incidentally found PAs. In this study, we aim to emphasize the long-term evolution of non-functioning pituitary microadenomas (micro-NFPAs) in MEN1 patients.
Methods
We conducted a retrospective cohort study that included all adult index patients with a clinical diagnosis of MEN1 syndrome and micro-NFPAs, that were evaluated in our clinic at the Romanian National Institute of Endocrinology, C.I.Parhon'', between January 1st 2018 and 31st December 2024. We sought to investigate the evolution of micro-NFPAs with a focus on tumor growth and pituitary function. We defined tumor growth or regression as a minimum 20% change in size compared to baseline.
Results
We identified 68 MEN1 patients that associated PAs, 18 macroadenomas and 50 microadenomas, of which 39 (78%) were non-functioning. 76.9% were females, with a mean age at diagnosis of 52.1 $\pm$ 13.2 years. The maximum tumor diameter at baseline was 5.1 $\pm$ 1.7 mm, without differences between sexes. No cystic lesions, hypopituitarism or visual field deficit were observed at baseline. Micro-NFPAs were associated with hyperparathyroidism or entero-pancreatic tumors in 69.2% and 15.4% of cases, respectively, all three classical, P''s being accounted for in 15.4% of patients. Micro-NFPAs were the first MEN1 component diagnosed in only 12.8% of cases, more frequently being discovered ensuing MEN1 screening, following hyperparathyroidism (51.3%) or entero-pancreatic neuroendocrine tumors (NETs) (30.8%) diagnosis. More than half of patients (53.8%) were reassessed through imaging and pituitary function testing. Over a median follow-up duration of 6 years (interquartile range: 3.9-9), only 1 patient (2.6%) had significant tumor enlargement, while 28.2% regressed and 23.1% were stable. None developed new pituitary insufficiency. No predictors were identified for tumor growth. Patients with tumor reduction were older ($P = 0.06$), had larger tumor diameters at diagnosis ($P = 0.038$) and pathogenic MEN1 gene mutations on genetic tests (mostly Sanger sequencing, $P = 0.014$) compared to those whose tumors were stable or progressed. However, logistic regression found none of these factors to be significant predictors of tumor shrinkage.
Conclusion
Micro-NFPAs in MEN1 syndrome are generally discovered through screening following the diagnosis of hyperparathyroidism or entero-pancreatic NETs and have a benign course over long follow-up intervals.

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P845

JOINT706

High risk of psychiatric morbidity in patients with acromegaly: a cohort study and meta-analysis

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Introduction
Psychiatric morbidity in acromegaly is increasingly recognized. However, current studies are limited by small sample sizes and divergent Results We aimed to evaluate the risk of psychiatric morbidity in a retrospective cohort study comparing acromegaly with non-functioning pituitary adenomas (NFPAs) combined with a meta-analysis of the existing literature.
Methods
The cohort study included data from medical records analysed using Chi2-, t-tests and log-binomial regression. The meta-analysis included studies retrieved from PubMed, Embase and PsycINFO that reported risk of psychopathology in acromegaly compared to NFPA or healthy controls using a random effects model.
Results
105 acromegaly and 211 NFPA patients were identified in the cohort study. They had similar sex distributions. Patients with acromegaly presented with smaller pituitary adenomas (17.9 $\pm$9.9 mm vs. 22.9 $\pm$10.6 mm, $P < 0.001$), more frequent pituitary surgery (89.1% vs. 60.2%, $P < 0.001$) and hormone replacement therapy (25.7% vs. 16.1%, $P = 0.042$). Acromegaly patients had higher risk of depression (RR: 1.9, CI95% [1.2;3.2], $P = 0.009$), and increased need of admissions to the psychiatric ward (5.7% vs. 0.5%, $P = 0.006$). Daily opioid use was higher in acromegaly patients with psychiatric morbidity and was associated with a diagnosis of arthropathy ($P = 0.009$). The risk of anxiety was indifferent with a CI95% of [0.5;4.4]. The meta-analysis (8 studies, 1,387 patients) revealed increased risks of both depression (RR: 1.8, CI95% [1.3;2.5]) and anxiety (RR: 1.9, CI95% [1.1;3.2]) in acromegaly compared to NFPAs. Likewise, the risk of depression was increased compared to healthy controls (RR: 2.5, CI95% [1.8;3.5]).
Conclusion
This study reveals a higher risk of depression and anxiety in acromegaly. This warrants increased psychiatric awareness in these patients.

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P846

JOINT3697

Involvement of menin, p27 and pakt in prolactinoma development. sexual differences

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Menin is a fundamental protein for regulating the cell cycle and proliferation in the pituitary gland, specifically in lactotroph function due to its ability to regulate p27Kip1 and the AKT signalling pathway. In this work, we focused on the involvement of menin on prolactinoma development, using two murine models of prolactinoma. One model is characterised by overexpressing the β subunit of the human chorionic gonadotropic hormone (hCGβ+) and the other by being knock-out for the dopamine receptor type 2 (Drd2KO). In both models, only females develop lactotroph hyperplasia and hyperprolactinemia from three months of age. In the hCGβ+ murine model, but not in the Drd2KO, we observed, by RTqPCR, higher levels of expression of the MEN1 gene in the pituitary gland of males than in females, without genotypic differences. We performed double confocal immunofluorescence to analyse the expression of proteins of interest specifically in lactotrophs (colocalization). Although no differences were detected between sexes or genotypes in the percentage of menin+ lactotrophs, important changes were observed in the subcellular localisation of menin. In WT male and female lactotrophs, menin is found in both, cytoplasm and nucleus. However, in transgenic females from both models (prolactinomas), nuclear expression of menin is completely lost. This lack of nuclear menin correlates with a decrease in the percentage of p27+ lactotrophs, accompanied by a marked increase in the levels of pAKT expression and a lower level of PTEN expression in the tumoral pituitary glands of both models compared to WT females. These alterations were not observed in males whose pituitary glands retained stable expression of nuclear menin and high levels of PTEN. We conclude that the loss of the nuclear menin in lactotrophs from transgenic females and the lower expression of PTEN contribute to the decreased expression of p27 and the elevated levels of pAKT respectively, favouring the development of a prolactinoma.

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P847

JOINT737

Multicentre 30-year data on the 4-mg intravenous dexamethasone suppression test in the diagnosis of cushing's syndrome

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Objective
Differentiating Cushing's syndrome (CS) from Pseudo-Cushing's (Low Probability of Cushing's [LPC]) may be difficult. We evaluated the 4-mg intravenous dexamethasone suppression test (IVDST) to differentiate CS from normal subjects and LPC, and to define responses in CS of various causes.

Design
Data from 140 patients with surgically confirmed Cushing's Disease (CD) who underwent IVDST(s) before their first pituitary operation, five with ectopic ACTH syndrome (EAS), 28 with adrenal Cushing's (AC), and 111 with LPC, from four tertiary hospitals between 1995 to 2024 were retrospectively evaluated. Thirty-two control subjects (normal and overweight/obese participants with or without type 2 diabetes) were previously studied. Dexamethasone was infused at 1 mg/h for 4h. Plasma cortisol and ACTH were measured at -60 min (baseline), -5 min, +3h, +4h, +5h and at +23h and +23.5h on Day 2.
Results
The cortisol at baseline, +5h and mean of Day 2 levels are shown in the table. Day 2 cortisol level of >130 nmol/l diagnosed CS with 95% sensitivity and 87% specificity. In the CD group, a partial suppression of cortisol at +5h to less than 70% of the baseline was demonstrated in 97%, with rebound hypercortisolism on Day 2 in 91% of patients. Day 2 cortisol levels were >130 nmol/l in 100% of EAS and 93% of AC. In 19 of 111 patients with LPC, Day 2 cortisol overlapped with CS. Control subjects showed marked suppression of cortisol which was maintained on Day 2.
Conclusion
IVDST has high sensitivity for diagnosis of CS. We suggest false negative results may occur when IVDST is performed during mild or subclinical disease or during quiescent phase. The specificity of 87% is lower than previously reported (96%), highlighting the importance of long-term follow-up of LPC. Because only five EAS were studied, the utility of IVDST in differential diagnosis of ACTH-dependent CS is uncertain.

	Cortisol (nmol/L) mean (range)		
	Baseline	+5h	Day 2 mean
CD	600 (226-1442)	182 (33-826)	476 (19-2177)
EAS	2403 (1120-3962)	2403 (841-3082)	2517 (1120-4089)
AC	507 (249-1453)	474 (95-1414)	501 (96-1807)
LPC	431 (94-1364)	97 (19-285)	82 (21-557)
Control	405 (252-651)	56 (23-108)	20 (7-48)

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P848

JOINT4025

Laterality of amygdalavolume of brain in different genders help predict individuals with ambiguous genitalia of disorders of sexual development

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Background
Human sex characteristics include genetic, anatomical structure, physiological function, neuropsychology and social identity. Patients who were born with ambiguous genitalia are in intersex conditions. Sex decisions of raising at their early years are significant and difficult. Hormones, chromosomes, and clinical phenotypes of genitalia are the major influences leading to decisions of sex, and they also guide sex differences in brain development. Individuals of 21-hydroxylase deficiency (21OHD) with chromosome of 46,XX offer a unique opportunity to address these issues. They have a 46,XX chromosome, high testorstorone and ambiguous genitalia of clitoridauxe.
Objective
Toexamine the asymmetry of the different zones volume of subcortical brain in normal girls and boys, build a classifier to predict the cases' sex and compare with their psychological sex.
Methods
11 children of CAH with 46,XX, 123 boys and 124 girls were included. T1-weighted anatomical data were collected using a magnetization-prepared rapid acquisition gradient-echo sequence. Pre-school activities investory (PSAI) was used to assessed the psychological sex in individuals below 5 years old, and children's sex role inventory (CSRI) was used in cases of and older than 5 years old.
Results
We found that laterality of Amygdala volume was significatly different between genders, showing a significant larger laterality of Amygdala volume in boys than that of girls ($T=2.335280$, $p=0.021$). Based on the laterality, we built a classifier to vertify the brain sex of the 11 cases. The brain sex of all the cases was identical with their psychological sex assessed by the questionnaries.
Conclusions
The findings further revealed the gender differences in brain, and we do use diversified ways to predict gender of individuals of disorders of sexual development (DSD). It is equally important to raise gender in accordance with neuropsychological needs and to obtain social acceptance as to maintain a status consistent with genetic, anatomical, and endocrine physiological functions.

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P849

JOINT1616

Musculoskeletal disorders in acromegaly: a national, registry-based cohort study

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Objective
Acromegaly is associated with multiple musculoskeletal complications that affect quality of life and work ability. No nationwide studies on these debilitating complications exist. We aimed to examine the risk of osteoarthritis, musculoskeletal surgery (incl. JOINT replacement), osteoporosis, fractures, and analgesic consumption in a national cohort of acromegaly patients.
Design
National, registry-based cohort study.
Methods
All validated incident and prevalent cases of acromegaly in the period 1977-2021 ($n = 844$) were included and matched 1:100 with healthy controls on sex and birth year. Outcomes were retrieved from the Danish Healthcare registries and identified using diagnosis, surgical procedure and medication codes. Time-to-event analyses in the form of Cox regression and Kaplan-Meier plots were applied.
Results
Patients were at significantly increased risk of osteoarthritis of the shoulder (HR: 5.25 [3.05; 9.06]), hip (HR: 3.15 [2.57; 3.87]) and knee (HR: 2.25 [1.85; 2.72]), and osteoporosis (HR: 2.13 [1.64; 2.78]) even before the acromegaly diagnosis. The risk of JOINT replacement surgery of the shoulder (HR: 4.60 [2.57; 8.25]), hip (HR: 3.32 [2.67; 4.12]) and knee (HR: 2.52 [1.89; 3.36]) was increased in acromegaly patients, as was the risk of being prescribed weak analgesics (HR: 1.22 [1.04; 1.44]) or opioids (HR: 1.58 [1.38; 1.82]). Furthermore, patients had a higher risk of being diagnosed with degenerative spinal disorders, such as spondylosis (HR: 2.04 [1.50; 2.77]), spinal stenosis (HR: 2.12 [1.56; 2.88]) and intervertebral disc herniation (HR: 1.79 [1.21; 2.66]). Surgical complications (HR: 2.19 [1.59; 3.03]) and repeat hip surgery (HR: 3.64 [2.09; 6.34]) also exhibited increased risk in patients.
Conclusion
In acromegaly, severe osteoarthritis involving multiple JOINTs develops even before acromegaly diagnosis and continues to progress over time, despite acromegaly-specific treatment and biochemical disease control. Furthermore, acromegaly imposes an increased risk of osteoporosis, musculoskeletal surgery - particularly JOINT replacement surgery -, surgical complications and necessity of strong analgesic medication. Our findings warrant further research into the management of musculoskeletal disease in acromegaly.

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P850

JOINT574

Thromboprophylaxis of venous thromboembolism in endogenous cushing's syndrome: recommendations from a delphi panel consensus position statement

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Background
Patients with Cushing's syndrome (CS) are at markedly increased risk of thromboembolic events. However, despite recognised risk, no guidance on thromboprophylaxis for CS has been established, and practices remain variable across clinical settings.
Aim
To provide recommendations for thromboprophylaxis, perioperative management, and treatment of VTE in patients with endogenous CS. To unify care practices and improve patient outcomes by mitigating the risk of venous thromboembolic events (VTE) in this population.
Methods
This was a Delphi method involving four iterative rounds of voting and subsequent discussions. The expert panel comprised 18 international specialists from 11 countries across 4 continents. Consensus was achieved with a threshold of $\geq$75% agreement. The recommendations were categorised into thromboprophylaxis, perioperative management, and treatment of VTE.
Results
Consensus was achieved on 14 recommendations. Thromboprophylaxis should be initiated at time of diagnosis and continued for at least three months after biochemical remission, provided there are no contraindications. Hospitalised patients with active CS should routinely receive thromboprophylaxis unless contraindicated. Patients with CS who are biochemically controlled on medical therapy and do not have additional risk factors may not require thromboprophylaxis. Low-molecular-weight heparin (LMWH), at standard weight-based prophylactic doses, is the preferred agent due to its known safety and efficacy. For perioperative management, LMWH should be administered until 24 hours before surgery and resumed 24 hours postoperatively, continuing for at least three months after achievement of biochemical remission. For patients undergoing inferior petrosal sinus sampling (IPSS), thromboprophylaxis should be reconsidered if it has not already been initiated. Prophylactic LMWH should be continued. Patients on direct oral anticoagulants (DOACs) should discontinue them 24–72 hours prior to IPSS and resume 48 hours after the procedure with interim prophylactic LMWH. The panel did not find sufficient evidence to recommend routine pre- or postoperative haemostatic testing to guide clinical decisions. Antiembolic stockings are not recommended due to limited efficacy and potential complications. Future research priorities include evaluating the use of DOACs in CS and determining the optimal duration of thromboprophylaxis post-remission.
Conclusion
These Delphi consensus recommendations aim to unify care practices and improve outcomes in CS by offering clear guidance on thromboprophylaxis, including its initiation, duration across different disease stages, and preferred treatment options. Key gaps for future research include the role of DOACs in CS, the optimal duration of thromboprophylaxis after remission, and refining criteria for thromboprophylaxis in patients with mild CS and mild autonomous cortisol secretion (MACS).

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P851

JOINT884

Safety and effectiveness of >8 years of osilodrostat treatment in patients with cushing's disease: findings from the LINC rollover open-label, multicentre study

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Introduction
The LINC clinical trial programme demonstrated that osilodrostat is effective and well tolerated in patients with Cushing's disease (CD); however, lifelong treatment is often required. The open-label, multicentre LINC rollover (NCT03606408) study evaluated the long-term safety and effectiveness of osilodrostat in patients with CD.
Methods
The study was planned to be open for ~5 years (or until 31/12/2023 in the UK). Participants benefitting from osilodrostat (investigator judged) after completing either the LINC 2, 3 or 4 trial extension phases were eligible for inclusion. Participants continued in the rollover until osilodrostat no longer provided clinical benefit, became commercially available in their country, or one of the protocol-defined discontinuation criteria was met. Participants attended quarterly visits for safety/clinical benefit assessments. The primary objective was to evaluate the long-term safety of osilodrostat, assessed by frequency of adverse events (AEs)/serious AEs (SAEs). Cumulative data are reported from parent study baseline to rollover end, unless otherwise stated.
Results
127 participants entered the rollover study (mean [SD] age: 41.3 years [12.4]; female: 74.8%). Median (min–max) osilodrostat exposure and dose was 5.0 (1.7–8.6) years and 4.9 (1.0–46.0) mg/day. All patients experienced $\geq$1 AE; 86.6% (n = 110) were considered treatment related, most commonly ($\geq$25% of patients) nausea (30.7%, n = 39), adrenal insufficiency (AI; 28.3%, n = 36) and fatigue (28.3%, n = 36). SAEs were reported in 44.9% (n = 57) of participants; 8.7% (n = 11) were considered treatment related, most commonly AI (4.7%, n = 6). AEs related to accumulation of adrenal hormone precursors were reported in 65.4% (n = 83), hypocortisolism in 55.9% (n = 71), pituitary tumour enlargement in 8.7% (n = 11), and arrhythmogenic potential and QT prolongation in 5.5% (n = 7). During the rollover, 22.0% (n = 28) discontinued osilodrostat; 3.9% (n = 5) discontinued because of treatment-related AEs, most commonly AI (n = 3). Adrenocorticotropic hormone, testosterone, 11-deoxycortisol and 11-deoxycorticosterone levels initially increased from baseline but generally stabilised during long-term treatment. Tumour volume generally decreased during the study, although inter-individual variability was high. At the end of osilodrostat treatment, 78.0% (n = 99) continued to receive clinical benefit. Mean urinary free cortisol levels decreased from 561.5 (4.1 x upper limit of normal [ULN]) at baseline to 85.0 nmol/24 h (0.6 x ULN) at week 12 of the parent studies and generally remained $\leq$ULN throughout treatment.
Conclusions
The LINC rollover study complements existing evidence demonstrating that osilodrostat is well tolerated and provides sustained effects in patients with CD during long-term treatment (for $\leq$8.6 years); no new safety signals were identified.

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P852

JOINT1213

Testosterone vs gonadotropin therapy for induction of puberty in boys with congenital hypogonadotropic hypogonadism

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Introduction
Congenital hypogonadotropic hypogonadism (CHH) is a rare endocrine disorder caused by impaired gonadotropin secretion or action, disrupting pubertal development and reproductive function. Testosterone therapy induces secondary sexual characteristics but does not promote gonadal maturation, whereas gonadotropin therapy supports both testicular growth and function.
Aims and Methods
This study aimed to retrospectively compare auxological and pubertal outcomes in 39 male patients with isolated CHH treated with either testosterone or gonadotropins. Outcomes were assessed at four time points: T0 (treatment initiation), T1 (6–12 months), T2 (18–24 months), and T3 (attainment of adult height and after 6 months after treatment end). Testicular volume (TV) was used as a marker of gonadal maturation. Testosterone therapy was titrated to a final dose of 250 mg/month intramuscularly (or 40–60 mg/day transdermally) over two years. Gonadotropin therapy included rFSH (75 IU twice weekly) and hCG (1000–2000 IU twice weekly), with treatment durations ranging from 6 to 46 months (median: 12 months).
Results
Among the 39 patients, 16 were treated with gonadotropins, and 23 received testosterone. The median age at puberty induction was 16.2 ± 1.5 years for the gonadotropin group and 16.7 ± 1.8 years for the testosterone group. At each time point, gonadotropin-treated patients consistently showed a significantly higher median TV than the testosterone group. This difference, already significant at T1, increased at T2 and persisted at T3 (9.0 mL vs. 4.0 mL; $P < 0.0001$), confirming a sustained effect of gonadotropin therapy. Half of the gonadotropin-treated patients transitioned to testosterone after pubertal induction. In this subset, the difference in TV remained significant (11.0 mL vs. 4.0 mL; $P = 0.0002$). Auxological analysis revealed better adult height corrected for mid-parental height (MPH) in the gonadotropin group (SDS: 0.19 vs. -0.57; $P = 0.04$), indicating these patients achieved an adult height closer to their genetic potential. No significant differences were observed in other parameters.
Discussion and Conclusion
Gonadotropin therapy led to greater and sustained increases in TV compared to testosterone, even after transitioning to testosterone. This underscores its ability to promote gonadal maturation and enhance fertility potential. Additionally, patients treated with gonadotropins achieved final heights closer to their genetic potential, likely due to the more physiologically pubertal progression, which avoids premature epiphyseal closure often associated with faster initial growth seen with testosterone. Nevertheless, further studies are needed to confirm these results and explore the long-term implications, particularly for fertility outcomes.

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P853

JOINT2256

Delayed puberty and intellectual disability: in a boy with a 15q11.2-q13. interstitial duplication including MKRN3 gene

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Background
The 15q11.2-q13 duplication syndrome is a rare genetic condition caused by the duplication of a chromosomal segment that is particularly prone to genetic rearrangements and subject to imprinting. It presents with a highly variable phenotype, including neurodevelopmental disorders and distinct craniofacial anomalies. This region includes the *MKRN3* gene, which is maternally imprinted and plays a critical role in regulating pubertal timing by inhibiting GnRH release. Paternally inherited loss of function mutation of *MKRN3* can lead to altered neuroendocrine signaling, impacting the onset of puberty and in particular causing central precocious puberty. Duplications of this chromosomal region have not been previously associated with alterations in pubertal timing to date.
Case Presentation
We report the case of a 16-year-old male with severe short stature, delayed pubertal development (Tanner stage 2, bilateral testicular volume of 8 mL with pubertal development arrest for two years, LH 1.6 IU/l, FSH 2.3 IU/l, Testosterone 95 ng/dl), and intellectual disability.
Materials and Methods
The patient's DNA was initially analyzed using Array – Comparative Genomic Hybridization (Array-CGH). To further characterize the identified duplication, MS-MLPA was performed to assess copy number variations and methylation status of the 15q11 region in genomic DNA extracted from peripheral whole blood samples (SALSA MLPA Probemix ME028-D1 Prader-Willi/Angelman, MRC Holland). Furthermore, to assess the impact of the 15q11-q13 microduplication on *MKRN3* expression in the patient's blood, quantitative real-time RT-PCR was conducted using the 2-ΔΔCT method.
Results
Genetic analysis identified a paternally inherited heterozygous interstitial duplication of the 15q11 region, spanning chromosomal positions 22,812,154 to 27,845,031, encompassing the *NIPA1*, *MKRN3*, and *OCA2* genes. Molecular analysis revealed a 67% reduction in methylation, consistent with paternal inheritance of the duplication. Quantitative analysis of *MKRN3* expression also showed an increase of over 2-fold compared to a healthy control.
Conclusion
The increased gene dosage of *MKRN3*, combined with reduced methylation, may enhance its inhibitory effect on the hypothalamic-pituitary-gonadal axis, delaying the pulsatile release of GnRH and contributing to the delayed sexual maturation observed in our patient. This observation, within the context of a structural genomic rearrangement, adds a novel contribution to the literature, expanding the spectrum of clinical manifestations associated with 15q11.2-q13 duplications.

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P854

JOINT1043

Genetic characterization of pituitary neuroendocrine tumours in the maltese population

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Pituitary neuroendocrine tumours (PitNETs) have a prevalence of 75.7/100,000 within the Maltese population. These tumours present a wide range of clinical behaviours, from hormone overproduction to local effects secondary to compression of adjacent structures, making them a significant public health concern. Despite their prevalence, the genetic factors contributing to sporadic PitNETs, which account for 95% of all cases, remain poorly understood. The primary aim of this study was to identify genetic variants associated with PitNETs in Maltese patients using germline whole exome sequencing, thereby contributing to the global understanding of the genetic aetiology of these tumours. The study cohort consisted of 44 Maltese patients diagnosed with PitNETs, selected based on comprehensive clinical evaluations and atypical phenotypic presentation. Germline DNA was extracted from blood samples, and whole exome sequencing was performed. Bioinformatic analysis was conducted using an in-house pipeline, incorporating variant calling, annotation, and filtering through a curated 75-gene panel associated with PitNET tumorigenesis, which was constructed using a PRISMA systematic review. Identified variants underwent functional prediction and pathogenicity assessment through in silico tools and structural modelling to predict the impact of missense variants on protein function. The study identified significant variants in five genes: *SDHA, CABLES1, CDK8, CDH23*, and *NGDN*. These genetic alterations were correlated with clinical data, revealing potential genotype-phenotype associations that could inform personalized treatment strategies. Each variant was validated through Sanger sequencing. This research provides novel insights into the genetic basis of PitNETs in the Maltese population and highlights unique characterisation of Maltese genetics and the importance of considering ethnic-specific genetic profiles in disease research. The findings underscore the potential for genetic screening in the clinical management

of PitNETs. Future work will focus on supporting these findings through functional assays, and exploring multi-omic approaches to further elucidate the molecular mechanisms thus improving diagnostic and therapeutic strategies.

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P855

JOINT2141

Pasireotide induces long-term cystic degeneration of somatotrophic pituitary neuroendocrine tumors (PitNETs)

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Background
Pasireotide LAR is a long-acting somatostatin analog with potential antitumor activity, as demonstrated by treatment induced increased MRI T2-signal intensity of somatotrophic PitNETs (1), but long-term follow-up data are lacking.
Aim
To investigate pasireotide's long-term antitumor effect and the impact on clinical outcomes in acromegaly patients.
Methods
We included participants from the previously published PAPE study (2) and evaluated clinical outcomes, medication use, and PitNET characteristics on MRI over the past 10 years. T2-weighted MRI signals of the PitNETs using grey matter as a reference were quantified and PitNET volumes and T2-intensity ratios (IRs) were calculated for each scan.
Results
Forty-four patients, 43 % female, median (IQR) age 52 (15 years) were included. Median treatment duration was 31.0 months. The median IR of the PitNETs increased between baseline and MRI at 7 years (1.09 vs. 1.57, $P < 0.001$), indicating cystic degeneration. In addition, a reduction in PitNET volume was observed between baseline and each subsequent follow-up MRI, with a more than twofold reduction in median volume between baseline and MRI at 7 years (1607 vs. 762 mm^3, $P = 0.03$). In 12 patients (27.3%), acromegaly treatment was reduced based on decreasing IGF-1 levels without presence of surgery or radiotherapy.
Conclusion
Pasireotide induces a long-term cystic degeneration process in somatotrophic PitNETs that persists for several years after treatment discontinuation. This phenomenon expands pasireotide's therapeutic applications by utilizing it as a potential preoperative treatment to enhance surgical outcomes.
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P856

JOINT1609

Acromegaly management beyond primary surgery: efficacy and safety of repeat surgery and radiotherapy

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Introduction
Re-intervention, either repeat surgery or radiotherapy, is suggested in patients with acromegaly if primary transsphenoidal surgery does not lead to remission. However, the evidence for re-intervention is weak. Our aim was to assess efficacy and safety of re-intervention.
Methods
Patients diagnosed with acromegaly at Oslo University Hospital between 2005 and 2021, and with two or more interventions were included in the study cohort. Re-interventions included repeat surgery and/or radiotherapy after primary surgery. Remission was defined as IGF-1 below the upper limit of reference range without concurrent medical therapy. Adenoma size was classified as micro- (<1 cm) or macroadenoma (≥ 1 cm) and invasiveness after the Knosp-Steiner criteria. Assessed complications were pituitary deficiency, cerebrospinal fluid leakage, meningitis, vascular injury, postoperative hematoma and venous thromboembolism.
Results
Of 223 patients diagnosed with acromegaly, 42 patients were included in the study cohort. At baseline, median age was 38 (IQR 29-48) years, 41 had macroadenomas and one had a microadenoma. After re-intervention, 23 patients (55 %) were in remission and eleven patients (26%) could reduce the dosage of medical therapy (table 1). Seventeen were in remission after repeat surgery and six after radiotherapy. Of the 19 patients not in remission, seven had undergone surgery with the goal of debulking and thus not remission. After re-intervention, seven patients acquired new hormone deficiencies, five after repeat surgery and two after radiotherapy. Two patients acquired corticotroph deficiency, one after repeat surgery and one after radiotherapy. One patient had cerebrospinal fluid leakage and meningitis after repeat surgery; The patient recovered, and his acromegaly was in remission. There was no incidences vascular injury, postoperative hematoma or venous thromboembolism after repeat surgery.
Conclusion
In this single center study, re-intervention was safe and resulted in remission or substantial improvement in most patients. Re-intervention should be considered for patients who would otherwise require lifelong medical treatment.
Key words

Table 1

	Frequency (%)	Remission	Reduced med	No remission
1 surgery + radiotherapy	12 (29%)	3	7	2
2 surgeries	22 (52%)	17	2	3
2 surgeries + radiotherapy	7 (17%)	2	2	3
3 surgeries + radiotherapy	1 (2%)	1	0	0
Total n	**42**	**23**	**11**	**8**

Total frequency of interventions in the study cohort including primary surgery.

acromegaly; re-intervention; somatotroph adenoma; transsphenoidal surgery; pituitary deficiency; radiotherapy; repeat surgery.

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P857

JOINT1947

Impact of compressive neuropathy on peripapillary retinal nerve fiber layer thickness in pediatric patients after craniopharyngioma surgery

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Purpose
The present study aims to evaluate alterations in the peripapillary retinal nerve fiber layer (RNFL) thickness in pediatric patients following surgical resection of childhood-onset craniopharyngioma (CP) and to identify tumor characteristics factors influencing these alterations, including changes in the lesion's location.
Methods
A retrospective analysis was conducted on 73 eyes from 38 patients with CP and 64 eyes from 32 age- and sex-matched healthy controls. The mean age of the CP patients was 10,5 $\pm$ 4,1 years (range 4–17), while the control group had a mean age of 10,1 $\pm$ 4,2 years (range 4–17). Optical coherence tomography (OCT) was used to assess the peripapillary RNFL thickness in the study and control groups. RNFL thickness was analyzed in the superior, inferior, and average sectors and across eight optic nerve sectors. Tumor characteristics and endocrine and

neurological complications were evaluated to determine their correlation with changes in RNFL thickness.
Results
Postoperative thickness of peripapillary RNFL and individual sectors was significantly reduced in the CP group compared to healthy controls. Tumor maximum diameter and volume, calcification, presence of Rosenthal fibers, total resection, recurrence, progression, and ventriculoperitoneal shunt correlated with damage of RNFL.
Conclusions
CP is associated with significant reductions in RNFL thickness, reflecting the impact of the tumor on optic nerve fibers. OCT is a valuable tool for monitoring visual pathway impairment and postoperative outcomes. Regular RNFL evaluation should be integrated into the long-term care of CP patients to optimize visual prognosis and detect progressive or residual damage.

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P858

JOINT3853

Prognostic factors of the level of cognitive functioning in children after craniopharyngioma treatment

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Introduction
Craniopharyngioma (CP) is a rare intracranial embryonal malformations of the sellar region. Treatment complications, besides hormonal deficits, include disturbances in the patient's emotional and cognitive functioning. Previous studies of cognitive functions indicate overall typical intellectual performance with reduced scores in several areas. In contrast, there is still no consensus about the specific patterns of cognitive functioning, which also depend on the tumor's particular traits and the treatment used.
Aim
Analyze children's cognitive functioning level after CP treatment and assess the relationship between the course of the disease and treatment and the occurrence of cognitive deficits.
Material and Methods
A study enrolled 40 patients aged 6-18 (the average age at the time of examination was 12.9 years, 25 boys and 15 girls) treated for CP in IP CZD. The Stanford-Binet Intelligence Scales: 5th Edition (SB5), Rey's Complex Figure Test, and Benton's Visual Retention Test were used.
Results
The mean age at diagnosis was 9.3 years +/- 3,8 (min. 1.9 max. 16.0). All patients were diagnosed with adamantinomatous CP, and most of the tumor was solid-cystic type. (75%). Calcifications were confirmed in 87,5% of patients. Median tumor size was 41 mm (IQR: 31-52). According to the classification that assesses the position of the tumor in the hypothalamus (Puget's grading system), most tumors were grade 2 - 63.2% (grade 1 - 26,3%, grade 0 - 10,5%). 12 (30%) children underwent reoperation, 8 (20 %) required ventriculoperitoneal shunt implantation due to hydrocephalus, and 22 (55%) required radiotherapy. The study group scored lower than the normative group in general intellectual potential and memory. Several factors were observed that seem to be associated with better performance in some cognitive tests: cystic tumor, no calcifications, tumor diameter less than 4 cm, 0 and 1 grade of the Puget's grading system, endonasal surgery, no radiation therapy. Valve implantation seems to be a variable of particular importance - the children who required a ventriculo-peritoneal shunt received lower scores in almost all tests performed.
Conclusions
Children's general level of cognitive functioning after CP treatment is lower than that of the general population but remains within normal limits. However, a significant reduction in memory function is observed. Factors related to the morphology and location of the tumor, as well as the treatment administered, may reduce the risk of cognitive deficits. Understanding the long-term cognitive sequelae of CP and its treatment requires a broad, interdisciplinary perspective.

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P859

JOINT3447

The natural course of macroincidentalomas: a retrospective study of a single reference center

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Introduction
Pituitary incidentalomas are incidental findings in the pituitary gland, detected on imaging performed for unrelated reasons and are present in approximately 10–38.5% of imaging studies. Nevertheless, the majority are microincidentalomas (<1.0 cm), while macroincidentalomas (≥ 1.0 cm) have a prevalence of approximately 0.16% on magnetic resonance imaging (MRI) and 0.2% on computed tomography (CT). Current guidelines recommend screening for hypopituitarism in lesions ≥ 6.0 mm and MRI monitoring due to their potential for slow growth and symptomatic progression. However, the limited long-term follow-up studies of macroincidentalomas compromise a full understanding of their natural progression.
Objetives
We aim to study patients diagnosed with pituitary macroincidentalomas followed at our referral center, focusing on their clinical characteristics, therapeutic approach, and clinical outcomes.
Methods
We retrospectively reviewed all macroincidentalomas (pituitary adenomas ≥ 1.0 cm diagnosed in an imaging study requested for a reason not related with the adenoma) followed at our center (Instituto Estadual do Cérebro Paulo Niemeyer). Demographical, clinical, biochemical and radiological data at diagnosis were collected. The frequency of tumor growth, vision impairment, apoplexy and new anterior pituitary deficit was evaluated in the follow-up.
Results
A total of 57 patients were included [(56% females, median age at diagnosis 70 years-old (38 – 85)]. Median maximal tumor diameter and tumor volume at diagnosis were 2.1 cm (1.0 – 4.0 cm) and 2.97 cm^3 (0.22 – 18.62), respectively. Any anterior pituitary deficiency was observed in 28% of the patients at diagnosis, the most frequent being hypogonadism, that was observed in 21% of the cases. Median follow-up was 4 years (1 – 9 years) and tumor growth was observed in 18% of the tumors while apoplexy occurred in 5% of the tumors. Tumor growth was observed after a median of 24 months (3-48). Vision impairment was observed in 21% of the patients during follow-up. Surgery was performed in 19 patients (33%) due to compression of the optic chiasm with or without vision loss or tumor growth. New pituitary deficiency was diagnosed in six (11%) patients. There was no difference in median age, maximal tumor diameter or tumor volume at diagnosis between tumors that grew and those that remained stable.
Conclusions
Macroincidentalomas are rarer than microincidentalomas but require close follow-up as approximately 18% will present clinically significant growth and one-third will require surgical treatment. Nevertheless, apoplexy is not frequent. Hypopituitarism is present in about 30% at diagnosis and should be evaluated in all patients upon diagnosis.

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P860

JOINT590

Immunohistochemical biomarkers in acromegaly: predicting treatment response and associations with tumor characteristics

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Background
Although surgery is widely accepted as the first-line treatment for acromegaly, its success rate remains variable. Pharmacologic therapy with first-generation somatostatin receptor ligands (fgSRLs) is frequently employed for patients with persistent acromegaly after surgery. However, resistance to these agents is common, highlighting the need for biomarkers that predict treatment response. We aimed to analyze the roles of known immunohistochemical (IHC) biomarkers and a novel marker, the cytoskeleton protein Filamin A (FLNA), in predicting treatment response and their associations with tumor characteristics.
Materials and Methods
We conducted an IHC study to evaluate the expression of somatostatin receptor subtypes (SSTR2 and SSTR5), cytokeratin granulation patterns (densely vs sparsely granulated), E-Cadherin, and FLNA in tissue samples from acromegaly patients who underwent surgery. Paraffin-embedded tumor samples were analyzed, and clinical data were retrospectively collected from patient files. This included information on surgical outcomes, pharmacological treatment response, and imaging data regarding tumor size and invasiveness.
Results
30 patients were included, with fgSRL treatment response data available for 21 patients. Resistance to fgSRLs was more frequently observed in patients with sparsely granulated tumors and lower IHC expression of SSTR2 and E-Cadherin. Positive correlations were identified between IGF-1 decrease after six months of fgSRL treatment and the expression of SSTR2 ($P = 0.024$, $r = 0.49$) and E-Cadherin ($P = 0.009$, $r = 0.64$). No correlation was found for SSTR5 expression. ROC curve analysis identified E-Cadherin as the best predictor of fgSRL response, achieving 100% sensitivity and specificity, surpassing SSTR2 and granulation patterns. FLNA expression was positive in all tumor samples, and higher FLNA expression was significantly associated with SSTR5 expression and suprasellar invasion.
Conclusions
IHC analysis of SSTR2 and E-Cadherin provides valuable insights for predicting fgSRL treatment responses in acromegaly. Densely granulated tumors with positive SSTR2 and E-Cadherin expression are associated with favorable outcomes, with E-Cadherin emerging as the most reliable predictive marker. The associations we observed between FLNA and SSTR5, as well as FLNA and tumor invasiveness warrant further investigation to clarify the predictive and prognostic role of FLNA in pituitary tumors. Incorporating IHC evaluation of these biomarkers in clinical practice may enable a more personalized therapeutic approach for patients with acromegaly.
Keyword(s)
pituitary, acromegaly, Immunohistochemistry, Filamin A, biomarkers.
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P861

JOINT768

Neurophysin I: a reliable, novel, and robust biomarker for oxytocin an analysis of a double-blind placebo-controlled cross-over trial

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Background
Oxytocin (OXT) deficiency is a recently identified new neuroendocrine entity associated with anxiety and reduced prosocial behavior. However, diagnosis and clinical progress have been hindered by challenges in reliably measuring OXT due to its instability and short half-life. Neurophysin I (NP-I), an equimolarly co-released cleavage product of the OXT precursor peptide, offers a promising alternative biomarker due to its stability and longer half-life, though it requires validation.
Methods
Analysis of a double-blind, placebo-controlled, cross-over study including 15 patients with hypothalamic-posterior-pituitary dysfunction and 15 matched healthy controls (according to age (+/-3), sex, body mass index [BMI] (+/-2), and menopause/hormonal contraceptives). Participants received a single oral of the strong OXT stimulator 3,4-methylenedioxymethamphetamine (MDMA, 100mg) and placebo, separated by two weeks. NP-I and OXT levels were measured at six time points over five hours. Subjective drug effects were assessed using visual analog scales. The area under the curve (AUC) in plasma NP-I from 0 to 300 minutes between both groups was analyzed using linear mixed-effects regression model. The AUC in receiver-operating characteristics curve (ROC) was assessed for MDMA-stimulated NP-I and OXT in differentiating patients from healthy controls.
Results
The median age was 34 years [IQR 25-46] in patients and 35 years [IQR 26-48] in controls, with both groups consisting of 53% ($n = 8$) females. In healthy controls, MDMA induced an 8-fold increase in OXT (peak: 624 pM [235-959]) and a 20-fold increase in NP-I (peak: 1508 pM [911-2233]). In contrast, in patients, no notable increase in OXT (peak: 92 pM [79-110]) and only a mild increase in NP-I (peak: 263 pM [140-300]). The AUC of NP-I after MDMA was 2279 pM•5h [1087-3696] in healthy controls and 97 pM•5h [50-241] in patients, with a significant difference of 2340 pM•5h (95%-CI [1462-3218]; $P < 0.0001$). NP-I strongly correlated with OXT ($r = 0.92$) and increases in subjective effects, e.g., 'liking effect,' 'feeling high,' 'trust,' and 'fear reduction' (all $R > 0.5$). MDMA-stimulated NP-1 demonstrated strong diagnostic performance in differentiating patients with OXT deficiency from healthy controls with a ROC-AUC of 100%.
Conclusion
These results validate NP-I as a biomarker for endogenous OXT secretion, addressing long-standing challenges in direct OXT measurement. NP-I offers novel opportunities for research in conditions where reduced OXT levels or disruptions in signaling are implicated, such as autism spectrum disorder, anxiety, and depression.
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P863

JOINT3588

Clinical presentation and outcomes of pituitary apoplexy in patients with PitNETs: an Italian multicentric study

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Purpose
To assess the clinical presentation and outcomes of pituitary apoplexy in a large cohort of patients with PitNETs.
Methods
Retrospective multicenter study, including 162 patients (100 males, median age 51 years) from ten Italian referral centers for PitNETs. All patients >18 years old with a diagnosis of pituitary apoplexy based on clinical and radiological features were eligible. Clinical and biochemical assessment was performed at the time of apoplexy and after at least 12 months of follow-up.
Results
At the time of apoplexy, patients with macroadenomas had a higher frequency of headache (81.7% vs 45.5%, $P = 0.011$), visual field defects (57.7% vs 18.2%, $P = 0.012$), diplopia (39.4% vs 9.1%, $P = 0.039$) and hypopituitarism (64.8% vs 27.3%, $P = 0.017$) compared to those with microadenomas. Men were more likely to have secondary adrenal insufficiency (59.6% vs. 40.3%; $P = 0.017$) and central hypogonadism (61.2% vs. 36.1%, $P = 0.002$) and were more likely to undergo surgery (78.0% vs. 58.1%, $P = 0.007$) compared to women. In terms of outcomes, no differences were observed between patients who underwent surgery and those who did not, except for hypothyroidism, which was more prevalent in surgically treated patients (62.8% vs 45.8%, $P = 0.034$). Nevertheless, 67.7%

of the surgically treated patients (48 out of 71) had a pre-existing diagnosis of central hypothyroidism at the time of apoplexy.
Conclusion
The size of the adenoma and the male se, have been demonstrated to influence the clinical presentation of the apoplectic event, while the management, surgical or conservative, does not appear to affect the long-term outcomes.

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P865

JOINT567

Generation and interrogation of a consensus multi-omics atlas for pituitary gland research

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Despite the widespread adoption of single-cell profiling for transcriptome and chromatin accessibility in the pituitary gland, there is still little agreement on cell type markers and cell population annotation. This lack of consensus stems from the disparate processing and downstream analysis methods used and arbitrary parameter and naming choices. To this end, we set out to generate a uniformly pre-processed and analysed consensus pituitary atlas (CPA), using all published single-cell profiled datasets to date (180 samples). Curation uncovered 8 out of 34 peer-reviewed publications to have either erroneously described barcoding kits or mouse samples with incorrectly assigned sexes. With these issues fixed, the atlas enables querying 750,000 cells, 10-times more than previous efforts, increasing the power of these analyses. We present the identification of novel consensus cell type markers for accurate cell typing, and markers associated with cell fate decisions. Mapping of isoform gene variants, reveals differential isoform preference across cell types. Leveraging the metadata associated with samples enabled dissection of sexual dimorphism at the cellular level. Notably, somatotrophs, lactotrophs, gonadotrophs and stem cells are dimorphic both at the gene expression and chromatin levels. Transcription factor motif enrichment suggested that these changes were driven by estrogen and androgen receptor activity in females and males respectively. We then extracted the most consistently predicted ligand-receptor interactions across all non-genetically modified (wild-type) transcriptomic samples ($n = 84$) using 5 different algorithms and present these for the different cell types. In stem cells, top interactions included SLIT2 signalling to Lactotrophs and Thyrotrophs, autocrine FGF signalling, as well as high expression of *Erbb4* receptor (targeted by NRG3 from melanotrophs). To increase reproducibility and data availability, we developed an online platform called *epitome*, where researchers can explore and download analysis results and processed samples associated with the CPA. This platform will allow the CPA to be continuously updated and maintained as more datasets become available, making it a useful resource for the community.

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P866

JOINT2593

Preliminary results from the core registry-gender incongruence module: current insights and future directions

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Objective
Healthcare for transgender and gender-diverse (TGD) adolescents varies across countries, and there are very few prospective and long-term outcome data. Therefore, a specific module dedicated to gender incongruence (GI) within the Core Registry (EuRRECa project) was developed to collect demographic and numerosity data while promoting the harmonization of care. Additionally, this project aims to facilitate longitudinal data collection through international, multicenter collaborations with the ultimate scope of fostering clinical research and refining current guidelines.
Methods
The module consists of five sections covering general information, including the presence of mental health comorbidities, as well as specific information on gonadal hormone suppression (GHS), gender-affirming hormone (GAH) therapy, fertility preservation, and gender-affirming surgery (GAS).
Results
As of December 2024, six centers from five European countries (Belgium, France, Poland, Switzerland, and the Netherlands) had actively joined the project. A total of 310 patients have been registered so far (Ghent 119, Katowice 81, Nijmegen 39, Lausanne 36, Amsterdam 27, Angers 8). The interest of patients in being contacted for research purposes, accessing the registry, and receiving the newsletter was investigated. If the vast majority of patients agreed to be contacted for research purpose by their responsible clinician, less than 40% gave consent to be contacted directly through the registry for outcome collection. The preliminary findings highlighted the existence of differences among centers, for example in protocols for the initiation of GHS and GAH, where variations in the age at the start of treatments and the choice of alternative formulations suggest the existence of differences in national regulations and healthcare policies, e.g. reimbursement criteria. Importantly, mental health comorbidities were commonly reported among TGD adolescents from all centers, emphasizing the need for comprehensive psychological assessment and targeted psychological care.
Conclusion
Despite being preliminary, the data collected so far highlight the importance of multicenter data collection in advancing knowledge on the care of TGD adolescents. Expanding this registry and fostering international collaboration will be crucial in standardizing protocols, improving care, and guiding evidence-based recommendations for TGD youth.

Key-words
transgender, adolescent, minor, Core Registry, EuRRECa.
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P867

JOINT368

Worldwide secular changes in limits for age at thelarche: an updated systematic review and meta-analysis

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Background
The mean age at thelarche has declined worldwide in recent decades. However, it is unclear whether this trend in the onset of puberty persists. Additionally, it remains unknown if there have been corresponding shifts in the upper and lower age limits (± 2 standard deviations [SDs]) of pubertal onset.
Objective
To update published data on the secular trend in mean age at pubertal onset in girls and to evaluate the upper and lower age limits of pubertal onset over time.

Methods
This systematic review and meta-analysis updated a previous review from our research group(1) of 38 publications (1977–2019) by conducting an extended literature search in PubMed and Embase for original and peer-reviewed studies published between 2019 and 2024. The current study included the 38 publications from the previous study in the meta-analysis, with minor data updates. Studies reporting the onset of breast stage 2 (B2, thelarche) in healthy girls examined by healthcare professionals were included. Study quality was assessed based on study design and statistical methods. Global trends were calculated using weighted regression analysis.
Results
A total of 44 publications (six new) met the inclusion criteria, representing 60 populations and approximately 246,000 girls. The mean age at thelarche decreased by 0.26 (95% CI: -0.43 to -0.09) years ($P = 0.002$), corresponding to 3.1 months per decade. In 30 of the 44 publications, data on SDs was available. The upper age limit of thelarche decreased by 0.29 (-0.53 to -0.04) years ($P = 0.02$), corresponding to 3.5 months per decade, while the lower age limit decreased by 0.12 (-0.41 to 0.16) years ($P = 0.40$), corresponding to 1.5 months per decade.
Conclusion
Our worldwide study confirmed that marked changes continue in the mean age at thelarche. Importantly, we found a downward trend in the upper age limit of pubertal onset in girls, while the trend did not reach statistical significance for the lower age limit of pubertal onset. Although our results may not directly inform revised age limits for normal pubertal timing in all countries, they provide a global overview of secular trends. Further investigation is needed to determine the clinical implications.
Reference
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P868

JOINT643
The role of caSR for gonadotropin release in male mice
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Introduction
A clinical study showed that calcium supplementation to prepubertal girls induced earlier puberty compared with placebo treatment. The calcium-sensing receptor (CaSR) is important for maintaining serum calcium concentrations within a narrow range. CaSR activity can be allosteric modulated by cinacalcet, commonly used in the clinic to treat hyperparathyroidism. CaSR has previously been identified in the pituitary gland of both humans and rodents, and we have found CaSR to be specifically expressed in α-glycoprotein subunit (αGSU)-positive cells in the anterior pituitary of mice. Gonadotropic cells of the anterior pituitary secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which promote e.g. pubertal onset, production of sex steroids, gametogenesis, and ovulation. The presence of CaSR in the pituitary suggest a direct regulatory role of calcium, which implies that the effect of calcium supplementation on pubertal timing, could potentially be caused by a direct effect of calcium on the pituitary. This study aims to elucidate the effect of CaSR modulation on pituitary function and male reproductive outcomes using pharmaceutical and genetic approaches.
Methods
Initially, the role of CaSR in pituitary function was examined by treating wildtype male mice of the reproductive age with cinacalcet (100 mg/kg) daily for two weeks. To explore further, a pituitary specific *Casr*-deficient mouse model was generated utilizing the Cre-LoxP system, and further validated through immunohistochemistry (IHC). The endocrine and reproductive phenotypes of both mouse models was examined through mass spectrometry and enzyme-linked immunosorbent assay (ELISA).
Results
Wildtype male mice treated with cinacalcet had a 64% decrease of LH serum levels compared with the control group ($p=0.039$). Furthermore, testosterone levels were reduced with 97% in mice treated with cinacalcet compared with vehicle-treated mice ($p=<0.0001$). The pituitary specific *Casr*-deficient mouse model was evaluated at 8-weeks of age, and there was a tendency towards higher LH serum levels.
Conclusion
Together, these preliminary findings suggest that modulation of CaSR activity can influence gonadotrophic cell function, thus highlighting a potential link between CaSR function and reproductive health. Further investigation of the phenotypic traits of the *Casr*-deficient mouse model is needed to fully understand the mechanisms underlying these observations.
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P869

JOINT2063
Calcium directly influences pituitary function in female mice through the calcium sensing receptor (CaSR)
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Introduction
In a previous randomized clinical trial (RCT), prepubertal children were given calcium supplementation or placebo. Girls in the intervention group entered puberty 5 months earlier than the placebo group, but no effect on pubertal timing were detected in the boys who participated in the RCT. CaSR is the main receptor for systemic calcium homeostasis, and its presence has been established in the anterior pituitary. The aim of this study was to investigate if the effect of calcium on pubertal timing seen in the RCT was due to a direct effect on pituitary function through CaSR.
Methods
A mouse model was generated using the Cre-LoxP method, to introduce a deletion of CaSR specifically in the anterior pituitary. Female knock-down (KD) and control mice ($n = 13$, both groups) were sacrificed at 8 weeks and blood samples and reproductive organs were collected. Hormone levels were measured using both commercially available and in-house ELISAs. Collected organs were weighted and stored either at -80°C or was formalin and paraffin embedded.
Results
Female reproductive organs showed significantly lower weight when comparing CaSR knock-down to control mice (organ weight/total body weight%): This included ovary weight (0.02176 vs. 0,03534; $P = 0.0035$) and uterus weight (0.1788 vs. 0.3826; $P = 0.0023$). No difference in *Fsh* expression was detected between the two groups. However, a tendency towards lower *Lhbeta* levels was observed in the KD group with a relative expression level of 0.33 compared to control set to 1 ($P = 0.0544$). Accordingly, a trend toward lower serum LH was detected in the KD mice (0.7619 ng/mL) compared to control littermates (0.9887 ng/mL), however this was not statistically significant ($P = 0.0845$). There was no difference in serum AMH or Inhibin-B levels between the two groups.
Conclusion
Female mice with a KD of CaSR in the anterior pituitary have lower ovary and uterus weight compared to littermate controls. No change in AMH og Inhibin B levels between the groups, but a slight tendency towards lower LH serum levels and *Lhbeta* expression levels in the KD group. Further characterization of the phenotype in this mouse model is ongoing, and the evaluation of puberty timing in these mice are still pending. If CaSR proves to be important for the regulation of the Hypothalamic-Pituitary-Gonadal (HPG) axis, it has a clinical perspective since CaSR can be modulated by the drug Cinacalcet, an allosteric agonist of CaSR, already in clinical use.
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P870

JOINT1096
Osilodrostat prior and new use in patients with endogenous cushing's syndrome: 2-year interim analysis results (safety and effectiveness) from the real-world non-interventional LINC 6 study
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Introduction
The ongoing prospective, non-interventional LINC 6 (NCT05382156) study evaluates long-term safety and effectiveness of osilodrostat, a potent 11β-hydroxylase inhibitor, in routine clinical practice over 3 years in patients with Cushing's syndrome (CS). We report results from a prespecified 2-year interim analysis.
Methods
Adults with endogenous CS were enrolled in five countries (Europe/USA) where osilodrostat is approved and available. The primary objective is long-term safety and tolerability, evaluated by the rate of osilodrostat-related adverse events (AEs) and serious AEs (SAEs). Secondary effectiveness endpoints include change in mean urinary free cortisol (mUFC) and late-night salivary cortisol (LNSC). Outcomes were analysed in patients who were prior (any time before study entry) or new users of osilodrostat. AE/SAE data are reported up to data cut-off (July 2024) in the safety population ($\geq$1 dose, $n = 206$). Cortisol changes are reported in patients with assessments at baseline and month (M)6. All assessments are descriptive.
Results
Data were available for 205 patients: Cushing's disease, $n = 161$; adrenal adenoma, $n = 12$; adrenal carcinoma, $n = 2$; bilateral adrenal nodular disease, $n = 10$; ectopic adrenocorticotropic hormone secretion, $n = 17$; other, $n = 3$. Among prior ($n = 135$) and new ($n = 70$) users, 74.1% and 78.6% were female, and mean (SD) age was 54.1 (13.9) and 50.8 (15.1) years, respectively. Median (min–max) on-study osilodrostat exposure and dose were 10.4M (0.0–20.8) and 5.0 mg/day (0.5–80.0) in prior users and 4.2M (0.4–19.6) and 4.7 mg/day (1.6–69.3) in new users. Thirty-one prior and 12 new users reported 75 and 30 AEs considered treatment related, most commonly (>6.0% of events) adrenal insufficiency (13.3%, $n = 10/75$), dizziness (8.0%, $n = 6/75$), diarrhoea and fatigue (both 6.7%, $n = 5/75$) among prior users and adrenal insufficiency (16.7%, $n = 5/30$), gastrointestinal disorder, hypokalaemia, headache, and abnormal hair growth (all 6.7%, $n = 2/30$ each) among new users. Seven (six [4.4%] prior, one [1.4%] new user) patients discontinued because of 11 (10 in prior, one in new user) treatment-related AEs. SAEs occurred in 9.6% ($n = 13/135$) of prior and 20.0% ($n = 14/70$) of new users; 7/21 (33.3%) and 4/24 (16.7%) SAEs were considered treatment related, respectively. At M6, mUFC and LNSC were normal in 67.6% ($n = 25/37$) and 35.3% ($n = 6/17$) of prior, and in 44.4% ($n = 4/9$) and 16.7% ($n = 1/6$) of new, users, respectively.
Conclusions
LINC 6 2-year interim data show the clinical utility of osilodrostat in a real-world setting for the management of CS in both prior and new users with differing aetiologies. AEs were as expected; few led to treatment discontinuation.

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P871

JOINT2778

Hypogonadotropic hypogonadism diagnosis in boys under one year of age based on gonadotrophins, testosterone, antimullerian hormone (AMH) and inhibin B (INHB) measurements

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Context
Congenital hypogonadotropic hypogonadism (CHH) in infant boys is a rare disorder that can manifest as micropenis and/or cryptorchidism. Mini puberty is considered a window of opportunity for CHH diagnosis and treatment. The lack of testosterone increase during this period is the gold standard for CHH diagnosis, but hormonal evaluation is not always available at this time. No cutoff values for the hypothalamic-pituitary-gonadal (HPG) hormones have been proposed before one year of age.
Objectives
The aim was to compare inhibin B (INHB), anti-Mullerian hormone (AMH), testosterone, LH, and FSH between infant boys (1 to 365 days) with micropenis and/or cryptorchidism due to isolated CHH (iCHH), CHH as part of combined pituitary hormone deficiency (CPHD), or of idiopathic origin (controls), and to determine discriminating cutoffs for CHH diagnosis based on sensitivity (Se) and specificity (Sp).
Methods
This multicenter study from seven University Hospitals in France included 132 boys aged 0 to 12 months with FSH $< +2$ SD scores (58 with iCHH, including 27 with a positive molecular diagnosis, 32 with CPHD, and 42 controls). Three periods of interest were studied: between 1 to 4 days, 15 to 65 days (mini puberty), and 66 to 365 days (after the testosterone peak of mini puberty).
Results
The best-discriminating hormone was INHB between 1-4 days (Se/Sp were 100%/83% at 150 pg/mL, and 89%/100% at 85 pg/mL), testosterone between 15-65 days (Se/Sp 100%/100% at 2.3 nmol/l), and INHB and AMH after 65 days (INHB, Se/Sp 100%/85% at 170 pg/mL and 88%/100% at 120 pg/mL)(AMH, Se/Sp 100%/71% at 800 pmol/l, and 60%/100% at 400 pmol/l).
Conclusion
Inhibin B $<$ 85 pg/mL between 1-4 days, testosterone $<$ 2.3 mmol/l between 15 65 days, and INHB $<$ 120 pg/mL and AMH $<$ 400 pmol/l between 66-365 days are associated with a high risk of CHH when FSH levels are low.

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P872

JOINT2718

Long-term outcome after craniopharyngioma in childhood: the role of treatment in specialized centers

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Background
Craniopharyngioma is a rare non-malignant tumor of the suprasellar region associated with poor outcomes, particularly severe hypothalamic obesity. The aim of this retrospective study was to compare the outcome of patients treated in two specialized university hospitals (surgery & long-term care) with the overall outcome in Germany documented in the German Craniopharyngioma Registry. The primary endpoint was BMI at the last follow-up in pediatric care.
Methods
All patients with craniopharyngioma undergoing surgery between 2000 and 2020 were identified from two specialized pediatric centers (SC). Data from the German craniopharyngioma registry (REG), collected in the same period, served as a comparison. Age and BMI at surgery, number and type of surgeries, radiotherapy, and age and BMI at last follow-up were recorded. Patients with follow-up $<$12 months were excluded. Each BMI was calculated as a percentage of the P95 value corresponding to age and sex (%BMI_{P95}), a measure that correlates better with fat mass in severely obese children than SDS-LMS. Data are given as median and quartiles. The Mann-Whitney U test was applied for statistical analysis.

Results
A total of 54 SC and 187 REG patients were analyzed. The cohorts (SC vs REG) were comparable in terms of age (9.7 y (6.1-13.2) vs 10.5 y (7.2-13.7)), sex (43 vs 52% female), and %BMI_{P95} (81.5 (70.0-92.2) vs 82.8 (71.8-96.1)) at surgery. Pre-treatment obesity (BMI >P97) was observed in 7.7% of SC patients compared to 11.7% in REG patients. Treatment modalities differed, with higher transsphenoidal surgery rates at SC (37.7 vs 19.3%) and lower radiotherapy rates at SC (31.5 vs 50.5%). Occurrence of relapse surgery (35.2 vs 32.0 %) and the number of relapses (mean of 0.54 vs 0.41) were comparable. The follow-up time was 7.8 y (5.3-10.5) in SC and 6.2 y (3.2-9.0) in REG, with last follow-up age of 18.6 y (15.5-20.2) in SC and 17.3 y (13.8-19.7) in REG. Height SDS at last follow-up was not different; -0,06 (-1,01 – 0.73) in SC and -0.05 (-0.89 – 0.79) in REG. In contrast, at last follow-up 37.0% of the patients were obese in SC, but 56.1 % in REG. Notably, %BMI_{P95} was 92.8 (77.8-118.4) in SC, but 106.5 (89.6-130.8) in REG, with a significantly higher post-surgical increase of %BMI_{P95} in REG ($P = 0.024$).
Conclusions
Data of this study clearly suggest that *children* with craniopharyngioma benefit significantly from treatment in specialized centers. The observed outcome speaks in favor of centralized care treatment.

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P873

JOINT4005

Outcome of hypercortisolism screening tests and morning plasma ACTH in the differential diagnosis of ACTH-dependent cushing's syndrome: results from a large European multicenter study

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Background
The limited availability of CRH in many countries poses a challenge in differentiating ACTH-dependent Cushing's syndrome (CS). While elevated ACTH and cortisol levels are frequently linked to ectopic CS (ECS), the diagnostic accuracy of standard CS screening tests (CSST) in distinguishing ECS from Cushing's disease (CD) remains uncertain.
Objective
To evaluate the diagnostic performance of morning plasma ACTH and CSST in differentiating CD from ECS in a large cohort of patients with confirmed ACTH-dependent CS.
Methods
We conducted a retrospective, multicenter study across six European centers. Inclusion criteria: (1) patients with overt ACTH-dependent CS and available morning plasma ACTH and CSST results at initial diagnosis; (2) confirmed diagnosis based on histopathology and/or biochemical findings. Cut-offs were determined using ROC analysis (ECS as reference) and the Youden Index. Results were expressed as multiples of the upper limit of normal (x ULN).
Results
A total of 542 patients (493 CD [91%]; 77% female; median age 43 years) were included. The optimal morning ACTH cut-off was 1.8x ULN (sensitivity 74%, specificity 77%, AUC=0.747 [95% CI 0.688-0.853]). Among CSST, 24-hour urinary free cortisol (24h-UFC) showed the best diagnostic performance (cut-off 5.9x ULN, sensitivity 81%, specificity 79%, AUC=0.869 [95% CI 0.816-0.923]), followed by late-night salivary cortisol (cut-off 6.5x ULN, sensitivity 84%, specificity 71%, AUC=0.855 [95% CI 0.768-0.942]) and the 1mg-dexamethasone suppression test (cut-off 9.9x ULN, sensitivity 83%, specificity 72%, AUC=0.823 [95% CI 0.740-0.906]). In 347 patients (313 CD [90%]) with morning ACTH and at least two CSST available, concordance among the majority of tests resulted in a sensitivity and specificity both of 85%, with a high negative predictive value (98%) but a low positive predictive value (37%). Of note, when test results were evenly discordant, results of CSST were prioritized over ACTH due to their higher AUC values.
Conclusion
While morning ACTH and individual CSST have limited accuracy in distinguishing ACTH-dependent CS subtypes, their combined evaluation can improve the noninvasive diagnostic approach. In particular, concordantly low CSST results strongly suggest the absence of ECS.

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P874

JOINT852

Immune-related hypophysitis and imaging: a distinct type of hypophysitis?

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Background
Immune checkpoint inhibitors (ICI) have transformed the prognosis of many solid malignancies. However, their use has also been associated with distinct endocrine immune-related adverse events (irAEs), hypophysitis being among the most common.
Purpose
To describe, in a real-world patient cohort, how ir-hypophysitis is depicted on a pituitary magnetic resonance imaging (MRI) and how these imaging findings are evolved overtime.
Methods
A retrospective analysis of pituitary MRI was conducted in cancer patients treated with ICI-based regimens who developed biochemically documented pituitary insufficiency from January 2016 to September 2024. The first MRI was performed at the time of diagnosis of ir-hypophysitis, and the second MRI during the follow-up. MRIs were evaluated by a central radiologist team blinded to the onset of ir-hypophysitis.
Results
Sixty-six ICI-treated cancer patients diagnosed with biochemically documented anterior pituitary deficiency were eligible for inclusion in our analysis. The majority of them received immunotherapy (70% anti-PD-1 or anti-PDL-1 ICI, and 19% anti-PD-1/anti-PD-L1 and anti-CTLA-4 combinations) for melanoma (90.9%), whereas 4.5% of cases for lung cancer, 1.5% colon cancer and 3% hepatocellular carcinoma. The initial pituitary MRI was available in 60 patients and performed at a median time of 2 weeks post-diagnosis of ir-hypophysitis. Abnormalities were found in 32 patients (53.3%), including enlargement (25%) or reduced enhancement of the pituitary gland (10%), empty sella turcica (8.3%), and less commonly heterogeneous enhancement (5%), reduced dimensions of the pituitary gland (3.3%) and slight deviation of the stalk (1.7%). A 2nd pituitary MRI assessment, after a median follow-up of 1.6 years, was available in 37 patients; 45% of them presented alteration of their initial abnormal MRI findings. Abnormalities were described in 62.2% of cases, including reduced dimensions (18.9%), enlargement of the pituitary gland (16.2%), a partially empty sella turcica (16.2%), heterogeneous enhancement of the pituitary gland (8.1%) and reduced enhancement (2.7%). No ICI-based regimen nor combination treatments were associated with a specific abnormal pituitary imaging or with the frequency of abnormal imaging findings at follow-up. Patients with multiple axes deficiencies presented an increased prevalence of MRI abnormalities compared to those with isolated corticotrope deficiency in both time assessments.
Conclusion
MRI pituitary abnormalities in patients with ir-hypophysitis were found in approximately half of them; were not specific to the underlying malignancy and the administered ICI; and persisted over time transforming their abnormal MRI imaging. The other half presented normal pituitary MRI in both assessments, keeping the challenge of imaging for this irAE.

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P875

JOINT642

Progression of potentially aggressive PitNETs after radiotherapy: risk factors, management, and outcomes

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Objective

Radiotherapy plays a relevant role in pituitary neuroendocrine tumors (PitNETs) uncontrolled by surgery and resistant to medical treatments. Radiotherapy controls tumor progression in most cases, but not always. Prognostic factors for tumor progression after radiotherapy remain poorly defined. The aim was to evaluate tumor progression after radiotherapy, to identify risk factors, and to report management and outcomes in a cohort of PitNETs with uncontrolled progression.

Design

Retrospective, single-center, observational study.

Methods

In total, 123 consecutive patients who underwent radiotherapy for PitNETs and were followed at Cochin Hospital between 2000 and 2022 were included. Radiotherapy was performed in the following situations: uncontrolled tumor progression (80%), adjuvant (9%), or uncontrolled secretion (11%). Median follow-up after radiotherapy was 10.0 years.

Results

Tumor progression after radiotherapy was observed in 28/123 (23%) patients. Progression-free survival was 95, 86 and 78% at 2, 5, and 10 years from radiotherapy, respectively. Higher risk of progression was associated with lactotroph and corticotroph tumor types (HR 12.0, 95%CI 1.2 to 117.1 and HR 9.3, 95%CI 1.3 to 69.6, respectively), male sex (HR 3.7, 95%CI 1.6 to 8.4), and evidence of necrotic-hemorrhagic changes before radiotherapy on MRI (HR 3.1, 95%CI 1.1 to 8.4). Surgery, temozolomide and re-irradiation were the most frequent treatments for the management of tumor progression after radiotherapy, used in 18/28 (64%), 16/28 (57%) and 8/28 (29%) cases, respectively. Other treatment approaches included immunotherapy, anti-VEGF antibodies, EGFR tyrosine kinase inhibitors, peptide radionuclide therapy, cisplatin, and enzalutamide. The most common complication of radiotherapy was the new onset of pituitary deficits, observed in 41% of cases; other complications, including radiation-induced neuroinflammation, cerebrovascular events, and second brain tumors, were rare (3%, 2%, 2%, respectively). Among the 8 patients who experienced re-irradiation, median progression-free survival was 1.4 years, with 2/8 patients maintaining tumor control in the long term (>5 years). The safety profile was acceptable, with only one case of optic neuropathy. Overall, 3 patients developed metastases, and 6 patients died because of tumor progression.

Conclusion

Radiotherapy is an effective and generally safe treatment for the achievement of tumor control in patients with PitNETs with aggressive potential. Tumor progression can still occur in some cases, and can pose challenges in clinical management. Histological tumor type, sex, and necrotic-hemorrhagic components at MRI hold a prognostic value in predicting tumor progression risk. Being all simple and available markers, they can be useful in clinical practice for optimizing therapeutic strategies and personalizing patient care.

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P876

JOINT2447

Clinical exome sequencing study of growth hormone secreting pituitary tumors

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The biological behaviour of growth hormone secreting pituitary tumors (GH-PitNETs) varies significantly and strongly influences prognosis. The tumor microenvironment (TME) may provide a useful framework for understanding this heterogeneous behaviour of GH-PitNETs, through the dynamic interplay between tumour cells and TME components. Despite the interest in TME in acromegaly has increased exponentially over the last few decades, there is limited elucidation of its mechanisms, particularly in relation to genes expression involved in TME regulation. GH-PitNETs may be associated with specific germline mutations, however the genetic and molecular landscape of GH-PitNETs has been partially explored. Therefore, the aim of this study was to investigate germline genetic variants in patients with acromegaly through clinical exome sequencing (CES) analysis and to explore a possible correlation with molecular and histological characteristics of GH-PitNETs, including TME immune cells. A retrospective, observational, single centre study was conducted. Forty-six patients diagnosed with acromegaly were included in this study. In this cohort 31 were females (67%) and mean age at diagnosis was 55 ($\pm$12.3) years. After DNA extraction, CES was performed and genomic alterations were detected, classified and filtered using a dedicated bioinformatics pipeline. We excluded benign and probably benign variants according to the ACMG criteria, and variants with a minor allele frequency of more than 0.05 in the international databases. The remaining variants were subjected to the ENSEMBL Impact classification. The Metascape database was employed to perform pathway enrichment analyses, based on Gene Ontology biological process and KEGG Pathway for the targets. In our cohort, CES analysis identified 5759 unique variants in patients with GH-PitNETs, but no predominant variants were found. However, our data suggested that 5 unique mutations in 5 different genes (KCNJ12, FANCD2, TRIOBP, SYN2, and TYRO3) may be correlated with some tumor characteristics, including ki67% (P-value $=$ 0.03), and invasiveness of GH-PitNETs (P-value $=$ 0.01), possibly through some implication in TME regulation. Moreover, this is the first study showing that genes (FANCD2, SPTA1, TYRO3, and ZNF335) of the "regulation of lymphocyte activation" pathway (GO:0051249) may regulate immune cells infiltration in GH-PitNETs. In particular, these gene alterations seemed to influence the number of CD68+ macrophages (P-value $=$ 0.015) and the ratio of CD68+ macrophages to CD8+ T-lymphocytes (P-value $=$ 0.014). In conclusion, this study provides, for the first time, a comprehensive analysis by CES of germline variants in a cohort of GH-PitNETs. These findings may contribute understanding of the genetic landscape of acromegaly.

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P877

JOINT2311

"Liver fibrosis and steatosis markers- FIB-4 and HSI in acromegaly: a single-center observational study"

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Acromegaly, characterized by excessive growth hormone (GH) and insulin-like growth factor 1 (IGF-1) secretion, is associated with significant metabolic alterations. This study investigates the relationships between IGF-1, liver fibrosis FIB-4 and hepatic steatosis HSI indexes, and other endocrine and metabolic parameters in patients with acromegaly to better understand the systemic impact of the disease. This retrospective study included 150 consecutive patients, 96 m*et all* criteria and complete data. FIB-4 ($Age \times AST/PLT \times ALT^{1/2}$) was used as a LF (liver fibrosis) predictor (<1.3 low risk [LR-LF], 1.3-2.67 intermediate risk [IR-LF], >2.67 high risk [HR-LF]). HSI [$8 \times (ALT / AST) + BMI + 2$ (if type 2 diabetes) $+$ 2 (if female)] score of $\geq$ 36 predicted the presence of hepatic steatosis. Patients were grouped by age (<40, 40-60, >60 years). Spearman's

correlation assessed relationships between IGF-1, endocrine markers, onset age, and tumor size with FIB-4 and HSI. Group comparisons used ANOVA, Kruskal-Wallis, t-tests, or Mann-Whitney U tests as appropriate. The cohort consisted of 42% males and 58% females, with a mean age of 47.67 $\pm$ 14.62 years. The mean FIB-4 score was 1.03 (SD = 0.62), while the mean HSI score was 38.3 (SD = 7.01). Notably, 21 patients presented with a FIB-4 score greater than 1.3, and 60 had an HSI score exceeding 36. Age-related differences were observed, with IGF-1 ($P = 0.0001$) decreasing with age. Patients with type 2 diabetes had higher FIB-4 (1.18 $\pm$ 0.51 vs. 1.0 $\pm$ 0.64, $P = 0.023$). A significant negative correlation was identified between IGF-1 and FIB-4 (ρ = -0.36, $P = 0.0004$). Additionally, age correlated positively with HSI ($\rho = 0.23$, $P = 0.0266$). TSH and PRL negatively correlated with FIB-4 (ρ = -0.23, $P = 0.0257$ and ρ = -0.27, $P = 0.0093$, respectively. This study underscores the complex interplay between IGF-1, liver fibrosis markers, metabolic factors, and endocrine dysfunction in acromegaly. Higher IGF-1 levels may have a protective role against fibrosis progression, warranting further investigation into its clinical significance. Additionally, increasing age is associated with a higher risk of liver steatosis, highlighting the need for age-related monitoring of liver health in this population. Further studies are needed to assess IGF-1 impact on the liver.

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P878

JOINT2513

The clinical course and the systemic inflammation biomarkers (SIBs) differ between giant and not-giant aggressive prolactinomas

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Introduction
Aggressive prolactinomas (APRL) constitute a subgroup of aggressive PitNets. Their distinguishing features constitute invasion (radiological/histological), high proliferation profile, resistance to standard medication, and an increased risk of early recurrence.
Objectives
To analyse the clinical course and the systemic inflammation biomarkers in aggressive prolactinomas.
Methods
Data concerning clinical course, radiological invasion, systemic inflammation biomarkers (SIBs), and treatment of APRL were analyzed.
Results
22 cases of APRL: 4 women (18.2%) and 18 men (81.2%), among which 14 constituted giant tumors (>4 cm) were analyzed. The most frequent symptoms included headaches 5/22 (68%) and vision disturbances 10/22 (45.5%). 50% of women noticed menstrual cycle alterations and galactorrhea. 4/18 (22.2%) of men reported libido loss. According to the MRI, in 15/22(68.2%), the tumor infiltrated the optic chiasm; in 20/22 (90.9%), the cavernous sinuses (in 17/22, infiltration included ICA). 52.4% (11/21) of tumors were grade 4 in the Knosp classification. In 9/22 (40.9%), we observed insufficiency of the gonadal, adrenal, and thyroid axis; in 10/22 (45.5%) - isolated gonadal axis dysfunction. All the patients were treated with dopamine agonists (predominantly cabergoline - 19/22 (86.4%), an average weekly dose of 2.5mg (max-4.5; min-1). In the group of giant tumors (G) the average dose of cabergoline was 2.5 mg/week, while in the non-giant (nG) group 2.25 mg/week. 5/22 (22.7%) patients undergone the surgery (2 patients more than one). One patient received radiotherapy. Other therapeutic options included temozolomide (1/22), pasireotide (1/22), and lanreotide (3/22). When comparing a G group with nG, we observed that the Neu/lymph ratio and Plt/lymph were higher in the G group (2.87 vs. 1.46, $P = 0.007$; 164.4 vs. 103.58, $P = 0.068$). Moreover, baseline prolactin level (upper normal limit (UNL)) was higher in the G (1232xUNL) vs nG group (141xUNL), $P = 0.059$. The average reduction in prolactin levels was less significant in the G group – 78.7% (0-99.7%) vs. 87.5% (39.4%-99.73%) in the nG group.
Conclusion
The clinical course of the disease and SIBs differ between giant and not-giant aggressive prolactinomas. Further studies are needed to understand the nature of this condition.
Keywords
Aggressive prolactinoma, prolactinoma, cabergoline, pasireotide.
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P879

JOINT1165

Acromegaly detection from facial images using machine learning

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Background
There is a substantial delay in the diagnosis of acromegaly contributing to increased morbidity and mortality. Machine learning-based analysis of facial images has shown promising potential in identifying acromegaly. However, there is a need for further validation in large acromegaly cohorts, incorporating new methodological insights in machine learning development and using human expert assessment for comparison.
Methods
Video recordings from 155 patients with acromegaly and 153 matched controls at all seven Swedish University hospitals were collected using cellphones. Facial pictures from different angles were extracted. Clinical data regarding disease course and status were obtained. Four different deep neural network architectures were trained to distinguish photographs of patients with acromegaly from controls. These neural networks were pretrained on large image datasets including three networks trained on various image categories (ImageNet networks) and one on human faces [Facial Representation Learning (FaRL)]. The performance of these models was compared to that of 12 experienced endocrinologists.
Results
The FaRL based machine learning model presented higher sensitivity compared to the compound majority assessment (ensemble) of experienced endocrinologists (0.82 vs 0.66), with only marginally lower specificity (0.87 vs 0.93). The overall diagnostic performance was comparable for FaRL and the expert ensemble with ROC AUC 0.89 for both. However, the balanced accuracy of each individual endocrinologist was lower (range 0.72-0.79) than the FaRL model (0.80). Accuracy of the other neural networks were inferior to FaRL. The classification agreement between the top-performing models and human experts was high for true negatives (76%) but lower for true positives (55%). Both the machine learning models and human experts showed greater sensitivity in accurately classifying males compared to females, but showed no significant difference in precision metrics between patients with active ($n = 33$) vs controlled acromegaly ($n = 122$).
Conclusions
A FaRL-based machine learning model shows comparable accuracy to expert endocrinologists in acromegaly identification by face photographs, but with the advantage of higher sensitivity. This supports that digital face analysis can be useful in acromegaly detection. Further research is required to validate its performance and explore its applicability in clinical practice.

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P880

JOINT2008

Hyponatremia correction is associated with increased brain-derived neurotrophic factor levels (BDNF) – subanalysis of a randomized, double-blind, placebo-controlled, crossover trial

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Background
Hyponatremia is the most common electrolyte disorder in clinical practice and is associated with cognitive impairment. We have recently shown that correction of sodium levels can improve cognitive function[1]. Growing evidence suggests that serum brain-derived neurotrophic factor (BDNF) correlates with cognitive performance, playing a crucial role in learning, memory, and development of neurocognitive diseases, like dementia and depression. There is currently no data on serum BDNF levels in the context of hyponatremia.
Aim
The primary objective of this study was to investigate the effect of hyponatremia correction on serum BDNF levels.
Design and Methods
Secondary analysis of a prospective randomized, double-blind, crossover, placebo-controlled trial of 4-week empagliflozin 25mg/d vs placebo treatment in patients with syndrome of inappropriate antidiuresis (SIAD), conducted at the University Hospital Basel, Switzerland, from December 2017 to August 2021. Serum BDNF levels were assessed by quantitative enzyme-linked immunosorbent assay (ELISA). Statistical analyses were performed using R version 4.4.2.
Results
A total of fourteen patients were included in the analysis (50% female, median age 72 years [65–77]. At baseline, the median sodium in the empagliflozin group was 131 mmol/l [128–132], which increased to 134 mmol/l [131–136] after treatment ($P = 0{,}008$). In the placebo group, median sodium was 131 mmol/l [130–132] at baseline and remained stable at 131 mmol/l [128–132] after treatment. In the total cohort, an increase in sodium was significantly associated with an increase in BDNF levels (1 mmol/l sodium increase led to a 0.3 ng/ml increase in BDNF levels, $P = 0.04$), which was more profound after empagliflozin treatment ($P = 0.004$, compared to placebo $P = 0.3$). However, in the multivariant model the treatment arm was no independent predictor of BDNF change. In the patients without an increase in sodium, the median BDNF was 11,4ng/ml [10,2–18] at baseline compared to 10,9 ng/ml [8,7–15,7] after treatment. In patients with an increase in sodium, baseline median BDNF was 12,3 ng/ml [9,6–14,7] and increased to 15,2 ng/ml [11,8–19,3] after the treatment period. No association was observed between Montreal Cognitive Assessment (MoCA) scores and BDNF levels, regardless of treatment group.
Conclusion
Our findings indicate that hyponatremia correction increases the serum cognitive marker BDNF, highlighting the importance of hyponatremia correction in cognitive health. Further studies are needed to confirm the role of BDNF upon hyponatremia treatment.
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P881

JOINT1397

Perception and psychological effects of central precocious puberty or early normal puberty, and its treatment among girls and their caregivers

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Background
There is limited data regarding the perception and psychological effects of central precocious puberty and early normal puberty (CPP/EP) among girls and their caregivers, particularly given the differences in socio-cultural contexts among different ethnicities. This study aimed to evaluate the psychological effects of CPP/EP on Thai girls and their caregivers, and to explore their perceptions of CPP/EP and the treatment using gonadotropin-releasing hormone analog (GnRHa).
Methods
CPP/EP girls were enrolled. Questionnaires were administered to assess the perceptions and psychological effects of CPP/EP. Newly diagnosed patients were additionally evaluated for bullying, depression, anxiety and low self-esteem using standardized tools.
Results
Nine hundred and fifty-four participants (340 CPP, 140 EP, and 474 caregivers) were included. Thirty-eight out of 480 girls were newly diagnosed, and 442 girls had been followed, with 427 out of 442 patients having received GnRHa therapy. Their mean (SD) age was 9.9 (1.1) years at enrollment. The duration of GnRHa treatment was 1.8 (1.0) years. Regarding the perception of CPP/EP; breast buds, body odor and acne were perceived by the girls as the signs of puberty in 234 (49%), 174 (36%), and 162 (34%) girls, respectively. Two hundred and sixteen (45%) girls believed that some kinds of foods were the cause of CPP/EP. Furthermore, 379 (79%) girls and 374 (79%) caregivers appreciated that menarche contributed to a reduction in height gain, and 352 (73%) girls and 304 (64%) caregivers believed that height gain would continue increasing if menstruation stopped. On a 10-point anxiety scale for CPP/EP, caregivers reported a high score of 8.3 (1.7). The child's short final height was the most concern by caregivers ($n = 369$, 78%), followed by early menarche and side effects of GnRHa therapy. Among the 38 newly diagnosed girls, 8 (21%) reported being bullied, with experiences of verbal harassment about their breasts, breast grabbing, and social exclusion. Additionally, 4 (11%) girls were tested positive for depression, 9 (24%) for anxiety, and 5 (13%) for low self-esteem. Comparing CPP and EP girls, depression and anxiety were more prevalent in the CPP group (20% vs. 10% and 38% vs. 30%, respectively). Being bullied was significantly correlated with higher levels of depression, anxiety, and low self-esteem.
Conclusions
This study demonstrated that girls and their caregivers had inadequate knowledge about CPP/EP, highlighting the importance of providing accurate information. Given the psychological stress associated with CPP/EP, appropriate counseling and psychological support should be incorporated into its standard care.
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P882

JOINT3389

Hemodynamic changes in patients with idiopathic central precocious puberty treated with gonadotropin-releasing hormone (GnRH) analogue

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Objective
In this study, we aimed to evaluate the effects of leuprolide acetate on hemodynamic parameters, including blood pressure, arterial strain, and arterial stiffness, in patients diagnosed with idiopathic central precocious puberty (ICPP) through a prospective case-control study design.
Materials and Methods
This study included female patients diagnosed with ICPP and initiated on leuprolide acetate 11.25 mg/3 months therapy at our Pediatric Endocrinology Department, with no additional chronic illnesses. Ambulatory Blood Pressure Monitoring (ABPM) was performed at baseline, 3rd, and 6th months to obtain 24-hour blood pressure measurements. Simultaneously, carotid artery stiffness and strain parameters were assessed using Speckle Tracking Carotid Strain (STCS) ultrasonography.
Results
The study included 24 female patients diagnosed with ICPP with a mean age of 8.3 ± 1 years, bone age of 10.5 ± 1.4 years, height standard deviation (SD) of 1.3 ± 1.1, and BMI SD of 0.9 ± 1.1. Cranial MRI findings were normal in all cases, and routine biochemical and hematological tests were within normal ranges. According to ABPM data, baseline measurements showed a systolic blood pressure (SBP) SD of 0.8 ± 0.6, diastolic blood pressure (DBP) SD of 0.2 ± 0.6, mean arterial pressure (MAP) of 82.6 ± 6.2 mmHg, pulse wave velocity (PWV) of 4.3 ± 0.2, central SBP-SD of 0.2 ± 0.6, and central DBP-SD of 0.2 ± 0.7. The proportion of dipper patterns was 8.2 ± 4.3% for SBP and 13.2 ± 6.4% for DBP. At the 3-month follow-up, central DBP-SD increased to 0.4 ± 0.5 ($P = 0.017$). However, no significant differences were observed in SBP-SD, DBP-SD, central SBP-SD, PWV, or MAP when comparing the 3rd and 6th months. No significant change in the dipper pattern was observed when baseline, 3rd, and 6th-month data were compared. Similarly, arterial stiffness and strain parameters assessed via STCS ultrasonography showed no significant differences between baseline, 3rd, and 6th-month measurements.
Conclusion
While case reports in the literature have indicated a potential increase in blood pressure associated with GnRH analogue treatment, no prospective case-control studies have systematically examined this relationship. Our study is the first to investigate this association in a controlled prospective design. An increase in central DBP was observed at the 3rd month of GnRH analogue treatment. However, no significant differences were found in other blood pressure parameters, dipper pattern, arterial stiffness, or strain parameters in the 3rd and 6th-month evaluations.

Note
The study is still ongoing, and a preliminary analysis has been conducted based on 16 patients with completed 6-month data. The full dataset is expected to be completed by the time of the conference.

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P883

JOINT508

"Endocrine and genetic influences on neurodevelopment: insights from neuroimaging in turner syndrome"

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Background
Turner Syndrome (TS), a chromosomal disorder resulting from partial or complete monosomy of the X chromosome, affects multiple organ systems, including the brain. TS is characterized by distinct neurocognitive and structural abnormalities, including deficits in visuospatial abilities, social cognition, and memory, along with morphological changes in specific brain regions. Understanding these changes through neuroimaging is critical for improving diagnosis and targeted interventions.
Methods
A systematic review of 15 neuroimaging studies was conducted, encompassing 696 patients with TS, ranging from children to adults, and 641 matched controls. Studies utilized multimodal MRI techniques, including volumetric analysis, diffusion tensor imaging, and surface-based morphometry. Key outcomes assessed included regional brain volume, cortical thickness, white matter integrity, and functional connectivity.
Results
Neuroimaging studies consistently demonstrated structural and functional alterations in TS. Common findings included:.
• Amygdala and hippocampus: In 30 TS patients, increased left amygdala volume and reduced right hippocampal volume were observed, which correlated with social cognition and memory deficits.
• Parietal regions: Aberrant growth trajectories of white and gray matter were evident, especially in the left superior parietal regions, linked to visuospatial impairments.
• Cortical structure: Smaller cortical surface area and increased cortical thickness were predominant in TS patients, with regional differences in the pericalcarine, postcentral, and parietal areas.
• White matter networks: Reduced topological efficiency of hemispheric white matter connectivity was observed, particularly in the parietal modules, impairing working memory.
• Functional connectivity: Intrinsic connectivity disruptions in regions involved in math-related cognition and visuospatial processing were identified.
Across studies, the role of X chromosome haploinsufficiency, hormonal deficiencies (notably estrogen), and genomic imprinting were underscored as key contributors to these neurodevelopmental anomalies.
Discussion
These findings highlight the interplay of genetic and hormonal factors in shaping brain development in TS. The identified structural abnormalities have direct implications for neurocognitive deficits, particularly in visuospatial, social, and memory domains. The data suggest the importance of early diagnosis and tailored interventions, including hormonal replacement therapy, to mitigate neurodevelopmental challenges.
Conclusion
Consistent neuroimaging findings show that Turner Syndrome profoundly impacts brain structure and function. A comprehensive understanding of these alterations can guide improved therapeutic strategies, enhancing the quality of life for individuals with TS. Future research should focus on longitudinal studies to track developmental trajectories and the impact of interventions.

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P884

JOINT898

Spliceosome approach for the identification of diagnostic and prognostic biomarkers and therapeutic targets in paediatric brain tumors

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Brain tumors represent the second most common malignancy in children and adolescents and the leading cause of cancer-related mortality in this population. These tumors are characterized by their resistance to conventional therapies and the severe long-term side effects which involves hormonal imbalances and disruptions in the hypothalamic-pituitary axis. Despite some advances, the molecular causes underlying these tumors remain unclear, and tools for accurate diagnosis/prognosis, and treatment are very limited. Recent data from our group have identified the spliceosome (molecular machinery controlling the RNA splicing-process), as a critical player in the progression/aggressiveness of various endocrine-related cancers, including adult brain tumors. However, the alteration and role of the spliceosome in paediatric brain tumors remains largely unexplored. Herein, we initially analyzed the potential alteration of spliceosome components in seven independent cohorts of paediatric brain tumors (gliomas and medulloblastomas) using bioinformatics tools, identifying a significant over-expression of the spliceosome in tumor vs. non-tumor samples. Notably, some spliceosome alterations were associated with key clinical features, including tumor aggressiveness and survival outcomes. Notably, one spliceosome component (SF1) was found to be overexpressed in diffuse gliomas and medulloblastomas and its expression levels could discriminate between tumor and non-tumor samples. Moreover, higher *SF1* levels were associated to higher glioma grades and worse patient outcome (based on survival curves). Interestingly, enrichment analysis revealed a robust correlation between higher *SF1* expression levels and key oncogenic signalling-processes, such as MYC, mTOR, and p53 pathways. Functionally, we tested the therapeutic potential of Pladienolide-B, a inhibitor of the spliceosome activity, in different brain tumor cell-models [i.e. glioma (SF188 and KNS42) and medulloblastoma (DAOY) cells, as well as in primary patient-derived cell cultures], which revealed that Pladienolide-B significantly altered critical cancer hallmark features in all cell-models used, including the inhibition of cell proliferation, migration, and stem-like features, and an apoptosis induction. These effects could be mediated by disruptions in key pathways governing cell-cycle progression, cellular-differentiation, and metabolic-pathways signaling. Altogether, our results demonstrate a drastic splicing machinery-associated molecular dysregulation in paediatric brain tumors, which could potentially be considered as a source of novel diagnostic and prognostic biomarkers as well as therapeutic targets. Remarkably, the spliceosome component SF1 is directly associated with characteristics of tumor progression/aggressiveness and patient survival and represents, together with the use of inhibitors of the spliceosome activity, a novel potential therapeutic target/approach to tackle these devastating pathologies.

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P885

JOINT1942

Refining pituitary adenoma classification: the role of transcription factors in diagnosis and risk assessment

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Introduction
The new classification of pituitary tumors (WHO 2022) is based on transcription factors (TF) detected through immunohistochemistry (IHC) to determine tumor lineage. The aim of our study was to evaluate the usefulness of incorporating the WHO 2022 classification into the pathological study of pituitary adenomas (PA).
Materials and Methods
We retrospectively analyzed records of adults with PA who underwent surgery between January 2023 and December 2024. Clinical, radiological (tumor size, cavernous sinus invasion), and histopathological data were reviewed, including IHC for hormones and TF: SF1, Tpit, Pit1, GATA3, and Ki-67%. High-risk PAs were identified according to WHO 2022 criteria. Tumors were classified as invasive if they had Knosp grade III or IV.
Results
A total of 112 tumor samples were included. The majority belonged to the SF1 lineage (50%), followed by Pit1 (29%), TPIT (21%). With the incorporation of TF analysis, the diagnosis was modified in 19 patients:.

• 11 clinically non-functioning adenomas (CNFA) with negative hormonal IHC were reclassified as gonadotropinomas (SF1+; $n = 7$), 1 corticotropinoma (TPIT+) and 1 null cell.
• Only 2 CNFA were triple-negative but GATA3+.
• 5 patients with acromegaly were reclassified as: 1 immature, 1 mature Pit1 lineage tumor, 2 acidophil stem cell tumors, and 1 plurihormonal (Pit1 and SF1).
• 2 patients with thyrotropinoma were reclassified as immature and mature Pit1 lineage tumors.
• 1 CNFA with IHC for PRL and GH was re3.
• classified as plurihormonal (Pit1 and SF1).
• 43 gonadotropinomas, 2 corticotropinomas, 1 acidophil stem cell, 3 Pit-1, and a plurihormonal tumor were GATA3+.
• 31 patients with high-risk histological subtype tumors (7 reclassified with TF). These tumors were associated with invasiveness in 48% and Ki-67 $\geq$ 3% in 6.4%.
• 81 patients with low-risk histology: 38% were invasive, and 3.7% had Ki-67 $\geq$ 3%.

Conclusions
The addition of IHC for TF to routine diagnostics allows a more accurate classification of pituitary adenomas, particularly in cases with absent or low hormonal expression. IHC for GATA3 could be a useful marker for diagnosing gonadotropinomas and certain immature tumors. Diagnosing Pit1 adenomas presents challenges due to variability in hormonal expression, coexpression of transcription factors, and distinction between mature and immature types. The classification of tumors into high- and low-risk groups provides an additional parameter for individualized risk assessment, which should be considered along with clinical, radiological, and histopathological factors. These findings reinforce the need for molecular techniques to refine PitNET classification and enhance diagnostic precision.

Keywords
pituitary neoplasms, tumor classification, WHO 2022.

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P886

JOINT2845

Persistent HPG axis reactivation: a conundrum in transgender male adolescents on gender-affirming testosterone therapy

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Context
Transgender male adolescents undergoing gender-affirming hormone therapy (GAHT) often start with a combination of gonadotropin-releasing hormone analog (GnRHa) to suppress puberty and testosterone therapy to induce masculinizing changes. While GnRHa effectively suppresses the hypothalamic-pituitary-gonadal (HPG) axis, the degree of gonadotropin suppression achieved with testosterone monotherapy following GnRHa discontinuation remains unclear. Understanding the dynamics of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels during this transition is essential for optimizing treatment protocols and achieving desired clinical outcomes.

Aim
To investigate the degree of suppression of the HPG axis achieved by testosterone monotherapy in transgender male adolescents, as reflected by changes in LH and FSH levels following GnRHa discontinuation.

Methods
We conducted a retrospective cohort study from 2018 to 2023 at the Israeli Children and Adolescents Gender Clinic, Dana-Dwek Children's Hospital. The cohort consisted of 68 transgender male adolescents who started GAHT at Tanner stage 4–5. Outcome measures included changes in serum LH and FSH levels, as well as the LH/FSH ratio, assessed at baseline, during combined GnRHa and testosterone therapy, and during testosterone monotherapy.

Results
Baseline LH levels were within the normal range, followed by a significant decrease during combined GnRHa and testosterone treatment, and an increase during testosterone monotherapy (6.11 $\pm$ 5.06 vs. 0.32 $\pm$ 0.50 vs. 3.17 $\pm$ 2.97 IU/l, respectively; $P < 0.001$). Similarly, baseline FSH levels were within the normal range, followed by a marked decrease during combined GnRHa and testosterone treatment, and an increase during testosterone monotherapy (5.87 $\pm$ 2.77 vs. 1.46 $\pm$ 1.23 vs. 4.68 $\pm$ 3.14 IU/l, respectively; $P < 0.001$). Post hoc analysis revealed significant differences in LH, FSH, and LH/FSH ratios across the three treatment phases.

Conclusion
In transgender male adolescents, testosterone monotherapy following GnRHa discontinuation did not lead to full HPG axis suppression, with LH and FSH levels remaining within the normal range. These findings suggest that gender-affirming testosterone alone may not completely suppress gonadotropin secretion in transgender males. Future research is needed to explore the testosterone-mediated feedback mechanisms underlying incomplete LH and FSH suppression, which could have implications for optimizing hormone therapy in transgender male adolescents.

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P887

JOINT536

Expression of asprosin, furin and Olfr734 in the pituitary during the estrous cycle in control and obese mice. *in vitro* effect of asprosin on pituitary cell proliferation

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Background
Asprosin, a novel adipokine, is the result of a profibrillin (FBN1) cleavage by furin, which also generates the mature fibrillin-1. Asprosin binds to an olfactory receptor Olfr734, influencing glucose and lipid metabolism, ovarian, and cardiovascular functions. Crossing the blood-brain barrier, it acts as an orexigenic peptide - stimulates food intake *via* AgRP neurons in the hypothalamus and contributing to energy homeostasis. However, its role in pituitary function remains elusive. The aim of this study was to examine asprosin/furin/Olfr734 expression in the pituitary of control (CTRL) and diet-induced obese (DIO) female mice, and in LβT-2 mouse gonadotroph cell line. Furthermore, we investigated the *in vitro* effects of asprosin on pituitary cell viability and proliferation.

Materials and Methods
Female C57BL/6J mice were fed a control (CTRL, $n = 5$) or high-fat diet (DIO, $n = 5$) for 12 weeks. CTRL mice were analyzed during proestrus, estrus, and diestrus, while DIO mice were studied only in estrus. Asprosin/furin/Olfr734 mRNA and protein expression were analyzed in mouse pituitary and LβT-2 cells using RT-qPCR and Western blotting, respectively. Also, serum levels of asprosin, oestradiol (E2), progesterone (P4), FSH, LH, leptin, adiponectin, triglycerides, cholesterol, and glucose were measured by ELISA and enzymatic tests. LβT-2 cells were treated with recombinant mouse asprosin at doses 1-100 nM alone or with GnRH (50 nM) for 24 h. Cell viability was measured by AlamarBlue and proliferation using BrdU assay. Statistical analyses included one-way ANOVA and Pearson's correlation ($P < 0.05$).

Results
In the pituitary, asprosin/furin/Olfr734 expression varied along the estrous cycle with DIO mice exhibiting reduced expression vs CTRL. Moreover, we found that expression of asprosin and Olfr734 were negatively correlated with serum asprosin concentration and metabolic parameters, including glucose, LDL cholesterol, triglycerides, adiponectin, and leptin. Additionally, asprosin/furin/Olfr734 were detected in LβT-2 cells, where asprosin did not influence either basal or GnRH-induced viability or proliferation.

Conclusion
Our findings demonstrate that the expression of asprosin/furin/Olfr734 in the mouse pituitary is regulated by both the estrous cycle and animal metabolic status. Asprosin did not affect LβT-2 cell viability or proliferation, suggesting that its role in the pituitary may be more related to its secretory activity rather than direct cell regulation, ultimately linking metabolic changes to female reproduction. These results provide a foundation for further exploration of asprosin's mechanisms of action in the modulation of murine gonadotrophs like gonadotropin secretion.

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P888

JOINT1972

Impact of disease activity on cognitive and psychological outcomes in acromegaly: a prospective study

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Purpose
To investigate the cognitive and psychological aspects of acromegaly and to assess how disease activity may affect these outcomes.
Methods
This prospective study included patients with acromegaly between 18 and 65 years of age who consecutively admitted to Pituitary Center between June 2021 and July 2023. Cognitive functions were assessed using a series of standardized tests targeting memory, attention, executive function, verbal fluency, and visuospatial skills. Additionally, Beck Depression Inventory (BDI), Beck Anxiety Inventory, and Acromegaly Quality of Life Questionnaire (AcroQoL) assessments were conducted. These evaluations were performed preoperatively and at the 9th month postoperatively following transsphenoidal surgery (TSS) to assess the anticipated changes in neuropsychological functions based on disease activity.
Results
A total of 19 patients with acromegaly were included in the study. Remission was achieved through TSS alone in 9 patients, while 10 patients required postoperative somatostatin receptor ligands. Cognitive functions (Montreal Cognitive Assessment Test) were better in the remission phase compared to the initial active disease phase (23.36 ± 3.46 vs 24.93 ± 3.73; $p = 0.035$). Cognitive flexibility and selective attention (Stroop Test) were impaired during the active period of the disease (17.79 ± 12.31 vs 12.29 ± 8.23; $p = 0.016$). Memory functions (Wechsler Memory Scale-Logical Memory Test: immediate recall, delayed recall, recognition) showed improvement from the active phase to remission ($p = 0.016$, $p = 0.003$, $p = 0.008$; respectively). BDI scores were significantly higher in the active phase compared to remission (7.36 ± 3.48 vs 5.43 ± 3.03; $p = 0.009$). Additionally, AcroQoL scores were lower during the active disease phase than in the remission phase (76.21 ± 16.02 vs 92.86 ± 11.97; $p = 0.007$).
Conclusions
Acromegaly may impair cognitive and psychological functions, which appear to improve with effective treatment.

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P889

JOINT1447

Primary empty sella and pituitary insufficiency – a retrospective analysis

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Background
The number of incidental findings of primary empty sella (PES) is rising due to the increasing availability and quality of neuroradiological imaging. However, the clinical implications of PES diagnosis are not always clear, especially with respect to possible hypopituitarism at baseline and over time. The aim of this longitudinal study was to examine the emergence of potential hormone insufficiencies during follow-up and derive recommendations from that.
Methods
We conducted a retrospective, single-center analysis of patients with neuroradiologically confirmed empty sella. All patients with secondary genesis of empty sella, for example due to pituitary surgery, traumatic brain injury or radiation therapy were excluded from the study. Data regarding hormone levels, clinical presentation, pre-existing diseases and medication was analysed for the available follow-up period of each patient.
Results
97 patients were enrolled in the study (age $= 57.1 \pm 16.1$ years; female $= 54$ %; BMI $= 27.2 \pm 6.2$ kg/m^2), the diagnosis of PES was an incidental finding in 58.8 % of cases. At baseline, anterior total or partial pituitary insufficiency was diagnosed in 33 out of 97 patients, with 7 persons suffering from total anterior hypopituitarism. The most frequent finding was hypogonadism with 26 % followed by insufficiencies of the thyrotropic axis (25 %) and somatotropic axis (23 %). Adrenal deficiency was prevalent in 22 % of patients. Arginine vasopressin deficiency was found in 3 patients and hyperprolactinemia in 17 patients. Total pituitary insufficiency was not detected in any patient. Complete follow-up hormone levels were available for 44 patients. In patients with intact pituitary function at baseline, mean basal hormone levels remained stable over time, indicating resilient pituitary function in the majority of patients. 1 out of 44 patients who did not initially have an impairment of pituitary function developed an insufficiency of the corticotropic, somatotropic and gonadotropic axis during follow-up.
Conclusions
Our study shows that pituitary insufficiency is common among patients with primary empty sella. 34 % of patients had an impairment of one or more hormone axes at baseline. This emphasizes the urgent need of endocrinological assessments at diagnosis. Only one patient developed pituitary insufficiency during follow-up, indicating that worsening of pituitary function in patients with intact function at diagnosis is rare. Consequently, our data does not support regular follow-up investigations in asymptomatic PES patients with intact pituitary function at initial presentation.

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P890

JOINT1313

Long-term safety of pasireotide in patients with acromegaly: final results from a 10-year open-label phase iv rollover study (B2412)

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Introduction
B2412 (NCT01794793), an open-label, multicentre, Phase IV rollover study, evaluated the long-term safety of pasireotide (a second-generation, multireceptor-targeted somatostatin receptor ligand) in patients with rare endocrine diseases, including acromegaly and Cushing's disease (maximum study duration, 10 years). Here, we report data from the final analysis in patients with acromegaly who received pasireotide long-acting release (LAR) during the rollover.
Methods
Patients continuing to receive treatment benefit at the end of a previous pasireotide trial (investigator assessed) were eligible to enter the rollover and initially remained on the same pasireotide dose that they were receiving at the end of the parent study. Data are reported for patients with acromegaly who were treated with pasireotide LAR across five parent studies and received ≥ 1 pasireotide dose during the rollover. The primary objective of the B2412 study was to evaluate long-term pasireotide safety based on the frequency of adverse events (AEs) and serious AEs (SAEs). Data are reported from rollover start to end, unless otherwise stated.
Results
Overall, 221 patients with acromegaly from 24 countries entered the rollover to receive pasireotide LAR; 75.6% ($n = 167$) of patients completed treatment and 24.4% ($n = 54$) discontinued, most commonly because of patient consent withdrawal (5.9%, $n = 13$). Median (min–max) duration of pasireotide LAR exposure and average dose from parent study baseline to rollover end was 7.5 years (0.3–16.8) and 37.5 mg/month (6–68). AEs regardless of study drug relationship were reported in 77.8% ($n = 172$) of patients, most commonly (≥ 10% of patients) hyperglycaemia (12.7%, $n = 28$), COVID-19, headache (each 10.9%, $n = 24$) and hypertension (10.4%, $n = 23$). 65.6% ($n = 145$) of patients required additional therapy to manage AEs, most commonly for back pain, hypertension (each 9.0%, $n = 20$) and hyperglycaemia (7.7%, $n = 17$). 10.9% ($n = 24$) of patients required dose interruption/adjustment to manage AEs, most commonly for aspartate aminotransferase increased, COVID-19, SARS-CoV-2 test positive, diabetes mellitus, growth hormone deficiency, hyperglycaemia and insulin-like growth factor decreased (each 0.9%, $n = 2$). SAEs were reported in 22.6% ($n = 50$) of patients, most commonly COVID-19 (3.2%, $n = 7$). Three patients died during the

rollover (cardiac failure, $n = 2$; pulmonary embolism, $n = 1$). Overall, 15 patients (6.8%) discontinued because of AEs, most commonly hyperglycaemia (1.8%, $n = 4$). No new safety signals were identified.
Conclusion
Pasireotide is a well-tolerated long-term treatment option for patients with acromegaly, with patients having received treatment for ≤ 17 years from parent study entry. Hyperglycaemia was infrequent, and AEs, including hyperglycaemia, were mostly manageable without treatment discontinuation during the rollover.
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P891

JOINT1267
Endoscopic ultrasound-guided radiofrequency ablation is a safe and efficient treatment of symptomatic insulinomas – a single center experience of 14 patients
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Content
Insulinoma is the most common functional pancreatic neuroendocrine neoplasm. The vast majority are benign and less than 20 mm. Pancreatic surgery is considered standard treatment, but complications related to the surgical procedure are significant. Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) represents a novel and minimally invasive approach.
Aim
To evaluate efficacy of EUS-RFA in localized insulinomas.
Methods
We prospectively included patients diagnosed with insulinoma based on symptomatic hypoglycemia with inappropriate high levels of insulin. Lesions considered for RFA treatment were localized biopsy proven pNEN (Ki-67 $< 10\%$), size < 25 mm. The procedures were performed under general anesthesia. The patients were admitted for 24-hour observation after EUS-RFA. 3-6 months following EUS-RFA, efficacy was evaluated with EUS and 72-hours fasting test. 1 year after EUS-RFA, patients were re-evaluated for symptoms of hypoglycemia. In case of incomplete response, patients were eligible for a 2nd treatment.
Results
From 2022 to 2024, all 14 patients referred to our department with insulinoma underwent EUS-RFA. Mean age 60 (range 31–79) years. The average size was 15.4 (range 9.0–23.0) mm, 5 were in the head of pancreas, 7 in neck/body and 2 in the tail. No adverse events were observed during the procedure and all patients were discharged after uneventful hospitalization. One patient presented with acute necrotizing pancreatitis 13 days after the procedure and underwent EUS-guided drainage. Normoglycemia was observed in 13 out of 14 patients 1-6 months after EUS-RFA and in 6 out of 7 patients 1 year after EUS-RFA. In 3 patients a 2nd EUS-RFA procedure was needed, with complete remission in 2 patients and persistent hypoglycemia in the last patient.
Conclusion
EUS-RFA is an effective, minimally invasive treatment for localized insulinomas. The procedure seems to have a superior safety profile compared to conventional surgery, but long-term efficacy of EUS-RFA has yet to be evaluated.
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P892

JOINT1829
Changes in prevalence and incidence of pituitary neuroendocrine tumours: a 25-year population based study in malta
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Objective
Epidemiological data is essential for assessing disease health burden. The aim of the study was to explore longitudinal trends in incidence and prevalence of pituitary neuroendocrine tumours (PitNET) and analyse these variations.
Methods
Population based retrospective analysis on all patients diagnosed between 2000 and 2024 in a well-defined population, the Maltese islands. Main outcome measures: Prevalence Rate 2024; Standardised Incidence rates (SIR) 2000-2024 together with other relevant descriptive epidemiological statistics.
Results
From a total of 987 patients that were diagnosed with PitNETs, 880 patients were alive at end of 2024 giving an overall prevalence of 156.2/100,000 whilst 859 patients had presented between 2000 and 2024 providing an overall SIR of 7.04/100,000/year. Median age at presentation was 43 years (IQR 32-58). 28.2% had suprasellar extension with 19.3% having chiasmal compression. Cavernous sinus invasion was evident in 17.6% of patients. 7.8% of the cohort passed away. Interestingly, no evidence of increased mortality was observed in this cohort of patients when compared to the general population with a standardised mortality ratio (SMR) of 0.68 (95%CI 0.52-0.84). Non-functional PitNETs (NFPitNET) constituted 55.1% of the cohort, whilst 39.0% were prolactinomas, 7.1% were somatotropinomas and 2.7% were corticotropinomas giving rise to an overall SIR of 3.35, 3.01, 0.46, 0.20/100,000/year respectively. Males accounted for 37.3% of the entire cohort, giving rise to a SIR of 4.67/100,000/year compared to 9.72/100,000/year in females. Macroadenomas constituted 36.8% of the tumours with a SIR of 2.25/100,000/year. Furthermore 3.5% of the whole cohort were giant PitNETs (> 40 mm) resulting in a SIR of 0.20/100,000/year. On further analysis, there was an increase in the rate of all PitNETs from 4.26/100,000/year between 2000-2005 to a rate of 10.90/100,000/year in 2020-2024. In males SIR increased from 2.00/100,000/year to 8.16/100,000/year during the same time frame while in females it increased from 6.66/100,000/year to 14.36/100,000/year. The SIR for prolactinomas increased from 2.26/100,000/year to 3.98/100,000/year while for NFPitNETs from 1.58/100,000/year to 6.20/100,000/year for the same time periods. For PitNETs specifically greater than 30 mm in diameter at presentation, notably the SIR increase was relatively smaller, from 0.44 to 0.58/100,000/year when comparing the same time periods.
Conclusion
This study provides in depth and contemporary analysis of epidemiological trends of PitNETs in a well-defined population. Incidence rates appear to be increasing over time and in general, the survival outcomes of patients with these tumours appears to be quite favourable.
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P893

JOINT3711
Folliculo-stellate cells in a series of ACTH-secreting pituitary neuroendocrine tumors
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Introduction
Folliculo-stellate cells (FSCs) are nonsecretory cells located in the anterior pituitary gland, having a star-like appearance and the ability to form follicles. They represent a heterogeneous population in terms of both phenotype and function. FSCs form a support network and regulate endocrine cells activity by producing numerous paracrine factors. Furthermore, they might be involved in the pathogenesis of pituitary neuroendocrine tumors (PitNETs).
Materials and Methods
Eight patients with Cushing's disease were included in the study. The tumor specimens were obtained after transsphenoidal surgery. The preoperative diagnosis was supported by clinical features, hormonal assessment, and radiological evaluation (contrast-enhanced pituitary magnetic resonance imaging, MRI). The histopathological diagnosis was performed using hematoxylin eosin morphological staining. Reticulin staining was applied for reticulin fibers evaluation. Immunohistochemical (IHC) evaluation for anterior pituitary hormones (GH, PRL, ACTH, TSH, FSH, LH) and transcription factors (PIT1, TPIT, SF-1) were assessed to perform an adequate classification of the tumors. FSCs were analyzed using glial fibrillary acidic protein (GFAP).
Results
Histopathological evaluation revealed acidophilic tumor cells with a diffuse growth pattern. All cases had IHC positive reaction for ACTH and TPIT. In

addition, three cases showed positive IHC expression for GH and PIT1. According to current WHO classification, these were considered PitNETs with unusual IHC combination (TPIT/PIT1 positive). Morphologically FSCs were star shaped, with long cytoplasmic prolongations among the tumoral cells. GFAP positive cells were identified in all PitNETs, with high heterogeneity regarding the distribution pattern and intensity of the reaction. Two of the corticotropinomas presented only a few isolated positive FCSs with a low intensity of the IHC expression. Five of the cases showed GFAP positive cells distributed in small groups/nests among tumoral cells. In only one of the tumors, FSCs were organized in a wide and dense network. Moreover, the tumors classified as PitNETs with unusual IHC combination (TPIT/PIT1 lineage) presented GFAP positive cells located in the vicinity of blood vessels, having close contact with the endothelial cells.

Conclusion

FSCs represent non-secretory cells occupying approximately 5-10% of the anterior pituitary lobe. In our cases, they showed a wide variability regarding the distribution pattern and intensity of reaction. TPIT/PIT1 positive tumors presented a high density of FSCs. The strong connection between FSCs and blood vessels in TPIT/PIT1 positive PitNETs may contribute to the selection of two different cell lineages. Further studies are needed to establish the connection between these cells and PitNETs.

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P894

JOINT1126

Clinical, metabolic, bone and body composition characteristics of patients with various causes of childhood growth hormone deficiency (COGHD) in the transition period - a single center study

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Introduction

Patients with COGHD represent a heterogeneous group in many respects, and one of the most important points is the etiology of this hormone deficiency. In this regard, reported studies are inconsistent in relation to anthropometric characteristics, metabolic profile, body composition (BC) and bone mineral density (BMD) of these subjects.

Aim

To investigate the influence of the etiology of COGHD on the clinical characteristics of patients after completion of growth in transition period.

Patients and Methods

In a monocentric, observational, retrospective cross-sectional study spanning the last 20 years, we investigated 302 COGHD patients (16-25 years old, mean age 18.8 $\pm$ 2.1 years, 198 males) at first evaluation after transfer from pediatrics to the adult department. Sixty-two subjects experienced childhood-onset endocranial tumor (TUM, 22.5%). Other patients had congenital (CON, 59.2%) or idiopathic COGHD (IDI 18.3%). Cross-sectional analyisis of metabolic parameters, BC and BMD were performed in these patients.

Results

Persistent GHD was confirmed in 67% of patients after retesting at adult department. The three observed etiological groups did not differ according to body weight, body height, BMI and waist/hip ratio ($P > 0.05$). Insulin levels in the OGTT were significantly higher in the TUM group, than in IDI and CON patients, observing basal insulin, AUC (area under the curve) and peak insulin ($p<0.01$). TUM group showed significantly higher HbA1c levels, total cholesterol, LDL cholesterol and triglycerides compared to the two other groups ($p< 0.001$). BMD (g/cm^2) and Z score at spine was significantly lower in TUM patients compared to CON and IDI groups. Lean body mass did not differ between 3 investigated groups ($P >0.05$), while fat mass and percentage of fat were higher in TUM group ($p< 0.01$).

Conclusion

the cause of COGHD proved to be an extremely important parameter in metabolic characteristics, body composition and bone mass in the transition period. We have shown that tumor-induced GHD in childhood is a risk factor for increased insulin resistance, unfavorable lipid profile and body composition, with susceptibility to lower bone density and thus the risk of bone fractures.

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P895

JOINT805

The effect of MDMA on the anterior pituitary

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Background

3,4-Methylenendioxymethamphetamine (MDMA) has recently been suggested as a novel provocation test to evaluate hypothalamic-posterior pituitary function in suspected cases of oxytocin deficiency. Limited preliminary evidence also suggests that MDMA may stimulate anterior pituitary hormone secretion, potentially contributing to its cardiovascular and neuropsychological effects. However, its effects on the anterior pituitary have not yet been fully investigated. Therefore, this analysis aimed to investigate the effect of MDMA on anterior pituitary hormone axes in healthy adults.

Methods

This secondary analysis utilized data from a double-blind, placebo-controlled crossover randomized clinical trial conducted at the University Hospital Basel, Basel, Switzerland, between Feb 2021 and May 2022. Healthy participants received a single oral dose of MDMA (100 mg) or placebo in randomized order. Plasma hormone levels of the anterior pituitary (adrenocorticotropic hormone [ACTH], thyroid-stimulating hormone [TSH], luteinizing hormone [LH], prolactin, growth hormone [GH] and their peripheral endocrine glands (cortisol, free thyroxin [fT4], testosterone, estradiol) were measured at baseline and 120 minutes after drug-intake. Changes in plasma hormone levels following MDMA vs placebo were compared using paired Wilcoxon test.

Results

A total of 15 healthy participants (median [IQR] age: 35 years [26–48]; 53% female) with a mean (SD) BMI of 23.2 kg/m^2(2.1) were included. MDMA strongly stimulated the pituitary-adrenal axis, with plasma ACTH increasing from 12 ng/l [10.5, 14.9] at baseline to 35.5 ng/l [17.6, 58.9] at 120 minutes, resulting in a significant change of ACTH ($P = 0.0008$). This was accompanied by a cortisol increase from 347 nmol/l [252, 409] to 566 nmol/l [415, 701], resulting in a significant change of cortisol ($P = 0.025$). Prolactin showed a mild increase from 12 µg/l [7, 16] at baseline to 14 µg/l [10.4, 21.8] at 120 minutes, resulting in a non-significant change of prolactin ($P = 0.062$). No significant effects of MDMA were observed on GH, the pituitary-gonadotropin axis, or the pituitary-thyroid axis. Under placebo, no relevant hormonal changes occurred.

Conclusion

MDMA partially stimulates the anterior pituitary, strongly activating the pituitary-adrenal axis and mildly increasing prolactin levels. These findings suggest that MDMA may serve as a novel stimulation test for assessing multiple pituitary axes simultaneously. Further validation in larger patient populations is necessary.

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P896

JOINT1104

Exenatide for diagnosing endogenous hyperinsulinemic hypoglycaemia - a randomised placebo-controlled, double-blind, cross-over proof-of-principle study - fast study

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Background

The 72-hour fasting test, the gold standard for diagnosing endogenous hyperinsulinemic hypoglycaemia (EHH), is cumbersome and costly. This study evaluated exenatide, a GLP-1 receptor agonist, as a faster, less burdensome alternative diagnostic tool.

Methods

In this prospective, placebo-controlled, double-blind, randomised cross-over, proof-of-principle study, 14 patients with confirmed EHH in a 72-hour fasting test received in a randomized order 10 µg intravenous exenatide or placebo after at least 24 hours in between. Fourteen matched controls received 10 µg exenatide in an open-label design. Clinical monitoring and measurements of glucose, insulin, C-peptide, and proinsulin were performed for 4 hours. Follow-up included imaging and histological confirmation for EHH patients.

Findings
Exenatide induced diagnostic hypoglycaemia in 6 of 14 EHH patients (42%) compared to none with placebo ($P = 0•005$). In patients with EHH glucose nadir occurred earlier after exenatide (67 min [95% CI 50–142] vs. 210 min [95% CI 174–219], $P < 0•0001$) and at lower glucose levels (2•68 mmol/l [95% CI 2•26–3•02] vs. 3•2 mmol/l [95% CI 2•92–3•77], $P < 0•0001$) compared to placebo. Proinsulin levels at 120 minutes post-exenatide were higher in patients with EHH (69 pmol/l [95% CI 3•8–232]) compared to controls (9 pmol/l [95% CI 4•5–16•9], $P = 0•0001$). Compared to the fasting test, exenatide significantly shortened time to hypoglycaemia compared to the fasting test (1•38 hours [95% CI 0•67–2•99] vs. 12 hours [95% CI 1•44–36•1] respectively, $P = 0•032$). All patients preferred the exenatide test over the fasting test. Exenatide was well tolerated.
Interpretation
Intravenous exenatide is a promising, faster, less cumbersome and less expensive diagnostic tool for EHH compared to the fasting test. Larger trials are warranted to confirm its diagnostic utility.

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P897

JOINT1028

Changes in circulating levels of miR-30b during minipuberty and puberty in girls

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Background
Puberty is characterized by major physiological and psychological changes required for achieving sexual maturation and fertility. Pubertal timing is tightly controlled by the hypothalamic-pituitary-gonadal (HPG) axis, with the initiation of puberty driven by the pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus. Makorin RING finger protein 3 (MKRN3), encoded by the maternally imprinted gene *MKRN3*, acts as an inhibitor to suppress GnRH activity and delay pubertal onset. MicroRNA-30b (miR-30b) has been proposed to act as a direct regulator of hypothalamic *MKRN3* expression and circulating levels of miR-30b-5p increase in concert with a decrease in circulating levels of MKRN3 in pubertal boys. However, it has not been described whether this is also the case in girls.
Materials and Methods
Longitudinal serum samples from 18 female infants from The COPENHAGEN Minipuberty Study (median age 3.7 months and 8.4 months, representing peri- and post-minipuberty, respectively), 29 girls (Tanner stage B1, B2 and $\geq$ B3 representing prepuberty, peripuberty, and postpuberty, respectively), and 24 young women (median age 19.0 yrs, single sample) from The Copenhagen Puberty Study were included. Serum from 23 pregnant women from The Copenhagen Mother-Child Cohort (median age 29.9 yrs, single samples) were also included. miR-30b-5p was measured in serum by reverse transcription quantitative PCR. Additionally, miR-30-5p expression was assessed by miRNA *in situ* hybridization in ovarian tissue from eight adult women. Wilcoxon signed-rank test and Pearson's correlation coefficient were used to analyze the data.
Results
Circulating miR-30b-5p levels decreased significantly from the peri- to the post-minipubertal stage ($p = 0.048$). A significant increase in circulating levels of miR-30b-5p was observed in girls at the post-pubertal stage compared with girls at the pre- and the peri-pubertal stages ($p = 0.0022$ and $p = 0.0017$, respectively). Furthermore, the circulating levels of miR-30b-5p were significantly lower in pregnant women when compared to young women ($p < 0.001$). Supporting the findings from serum, the ovarian expression of miR-30b-5p increased during folliculogenesis with the highest expression in antral follicles.
Conclusion
In girls, circulating miR-30b-5p levels followed both the deactivation and reactivation of the HPG axis as observed during minipuberty and puberty, respectively. These findings support a regulatory role of miR-30b-5p on the HPG axis at the hypothalamic level in the onset of puberty in girls. We cannot deduce whether the dynamics of circulating levels of miR-30b-5p is a direct proxy of hypothalamic miR-30b-5p or also a product of ovarian activity.

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P898

JOINT2819

Depression, cognitive dysfunction and anxiety in illicit androgenic steroid users' years after cessation of usage

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Background and objectives
The use of anabolic androgenic steroids (AAS) among younger men has increased, giving rise to a public health concern. Despite this alarming trend, the long-term effects of AAS on mental health – particularly depression, cognitive function and anxiety remains poorly understood. The objective of this study was to assess these psychological and cognitive outcomes in former illicit users of AAS years after cessation and comparing them to current users and healthy age-matched never-users of AAS.
Methods
A cross-sectional study including men involved in recreational strength training grouped according to their history of AAS use. Three validated questionnaires were used to assess self-reported mental health participants: Major Depression Inventory (MDI), Cognitive complaints in bipolar disorder rating assessment (COBRA) and General Anxiety Disorder-7 (GAD-7). Higher scores indicate more pronounced symptoms in all three questionnaires.
Results
We initially recruited 79 previous and 193 current AAS users, as well as 57 healthy age-matched never-users. We excluded 14 previous and 31 current AAS users who had previously been diagnosed and treated for psychiatric disorders, our final study population consisted of 65 previous and 162 current AAS users. The mean (SD) age was 35 (9) years. Elapsed duration of cessation of AAS geometric mean (95 CI) was 1.9 (0.9-3.0) years in previous users. Previous AAS users consistently exhibited more pronounced symptoms of depression, cognitive dysfunction and anxiety compared to current AAS users and controls, expressed as a higher score in the MDI, COBRA and GAD-7, respectively (table). Using multiple linear regression models adjusted for age, duration of AAS use, and level of education, low serum testosterone was significantly associated with higher scores of depression ($P = 0.041$) and showed borderline associations with cognitive dysfunction ($P = 0.075$) and anxiety ($P = 0.07$).
Conclusions
Previous AAS users displayed increased levels of self-reported depression, cognitive dysfunction and anxiety compared to healthy age-matched non-users years after AAS cessation.

	Current AAS users	Former AAS users	Never-users	*P*-value
Age, years (mean ± SD)	34.5 ± 8.6	35.7 ± 9.8	35.7 ± 8.8	0.583
S-testosterone (median and IQR)	19.0 (11.9 - 28.6)	13.6 (10.7 - 16.9)	17.9 (14.8 - 16.9)	<0.001
MDI scorer (median and IQR)	11.0 (6.0 - 16.0)	13.5 (8.0 - 25.0)	5.0 (3.0 - 8.0)	<0.001
COBRA score (median and IQR)	10.0 (6.0 - 15.0)	15.0 (7.0 - 19.5)	7.0 (4.0 - 10.0)	<0.001
GAD-7 scores (median and IQR)	3.0 (1.0 - 7.0)	5.0 (3.0 - 7.0)	1.0 (0.0 - 3.0)	<0.001

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P899

JOINT2241

Hypothalamic-pituitary abnormalities in paediatric histiocytosis: preliminary retrospective data from a large cohort of a tertiary italian center

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Introduction
Histiocytosis is a rare hematologic condition involving tissue infiltration by dendritic cells, macrophages, or monocytes. Langerhans cell histiocytosis (LCH) has an estimated incidence of 2–9 cases per million children annually. Pituitary involvement, particularly diabetes insipidus (DI), affects 5–30% of cases, potentially leading to multiple pituitary hormone deficiencies (MPHD).
Patients and Methods
This retrospective study analysed 115 paediatric histiocytosis cases diagnosed from September 2004 to September 2024 at the Italian Referral Center for Histiocytosis in Florence, Italy. The median age at diagnosis was 7 years (IQR 10). Demographic, clinical and biological data were collected.
Results
The cohort included a total of 115 patients: 105 LCH, 3 Juvenile Xanthogranuloma, 3 mixed forms, 2 Rosai-Dorfman, 1 histiocytic sarcoma, and 1 indeterminate cell histiocytosis. A total of 36/115 (31%) patients had pituitary functional involvement: 33 LCH and 3 mixed forms. DI was diagnosed in 34/115 (29.5%) patients at a median age of 5,7 (IQR 3). It was the first manifestation in 17/34 (50%) and developed after a median of 4 years (IQR 3.25) in remaining cases. Growth hormone deficiency (GHD) was the second most common hormonal deficiency, affecting 11/115 (9.6%) patients, with an average onset of 8.6 years (IQR 4). In 1/11 (9%) cases, GHD was isolated; in 10/11 (91%) cases, it was associated with DI. Of these, 2/10 (20%) had GHD at disease onset, and 8/10 (80%) developed it after a median of 4.8 years (IQR 3.25) following DI onset. Central hypothyroidism occurred in 4/115 (3.5%) patients, all with DI. Hypogonadotropic hypogonadism affected 4/115 (3.5%), all with DI and one with hyperprolactinemia. Precocious puberty was observed in 1/115 (0.8%) male patient. Central adrenal insufficiency developed in 2/115 (1.7%), both with DI and GHD. MPHD occurred in 12/34 (35.2%) DI patients.
Conclusions
To the best of our knowledge, this represents one of the largest paediatric cohorts of endocrinopathies in histiocytosis. Hypothalamic-pituitary hormone deficiencies may be the first manifestation of histiocytosis or may complicate it during the course of disease. Thus, paediatric endocrinologists should screen and monitor these patients in close collaboration with hematologist-oncologist with expertise in histiocytosis.

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P900

JOINT2612

Aggressive pituitary adenomas and pituitary carcinomas

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Introduction
Aggressive pituitary tumors (APTs) are rare neoplasms defined as invasive and refractory to treatment, with early recurrences. Pituitary carcinomas (PCs) besides their aggressive behavior are diagnosed by the presence of metastases. However, the diagnostic criteria for APTs are not well-defined and there are several approaches for characterizing aggressiveness. The aim of this study is to find clinical features characteristic for patients with APTs and PCs.
Material and Methods
The study is a retrospective analysis of a series of 45 patients (14 women and 31 men) treated from the 2006 to 2024 by the endoscopic transsphenoidal surgeries for pituitary adenomas presenting aggressive clinical behavior. The mean age of the patients was 48.4 years (20-70 years), and the mean follow-up period was 10.4 years (0-18 years).
Results
In this group 3 patients were diagnosed with PCs (6.7%) and the rest with APTs (93.3%). Six patients died during follow-up period (13.3%). There were 91.1% macroadenomas, the tumors were invasive in 75.5% and functioning in 33.3% of the patients. The patients had 3.3 resections for APTs or PCs on average. The Knosp scale grade assessed preoperatively was III in 9 patients (20.0%), and IV in 8 patients (17.8%). Twenty-nine patients (64.4%) had radiotherapy, and 13 patients had pharmacotherapy (28.9%) as additional treatment methods. According to Lyon's classification the most numerous groups were 2a (35.6%) and 2b (28.9%). The gross total resection was accomplished in 17 cases (37.8%), the subtotal resection was achieved in 20 patients (44.4%), and in 6 cases (13.3%) only the partial resection was possible. Postoperatively 68.2% of the patients showed varying improvement in visual field defects and visual acuity. Transient diabetes insipidus (DI) was observed in 1 patient (2.2%), epistaxis in 4 patients (8.8%), and 2 patients (4.4%) had a postoperative oculomotor nerve paresis.
Conclusion
Surgical treatment of APTs and PCs is safe and associated with a low complication rate. The patients are younger and have more resections than in usual pituitary adenomas.

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P901

JOINT708 Validation of arginine-stimulated copeptin cut-offs for diagnosing AVP deficiency (central diabetes insipidus)

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Background
Distinguishing arginine vasopressin (AVP) deficiency (central diabetes insipidus) from primary polydipsia is challenging. While hypertonic saline-stimulated copeptin testing provides the highest diagnostic accuracy, it is often restricted to specialised centres, requiring close monitoring and potentially causing patient discomfort. Initially, arginine-stimulated copeptin was proposed as a simpler alternative, but a head-to-head comparison study found it less precise than hypertonic saline stimulation. However, the same study identified two new high sensitivity and specificity cut-offs for arginine-stimulated copeptin, though these cut-offs have yet to be validated.
Methods
This is a secondary analysis of the initial prospective multicentre study, including adult patients with confirmed AVP deficiency or primary polydipsia. Participants underwent the arginine stimulation test, with plasma copeptin measured at baseline and 60- and 90 minutes after infusion. The primary objective was to revisit the original study to validate the proposed arginine-stimulated copeptin cut-offs of >5.2pmol/l (high sensitivity cutoff with $>90\%$ sensitivity) and ≤ 3pmol/l (high specificity cutoff with $>90\%$ specificity).
Findings
In total, 96 patients were included between May 2013 and June 2018: $n=38$ [40%] with AVP deficiency and $n=58$ [60%] with primary polydipsia. At 60 minutes after arginine infusion, a copeptin level ≤ 3.0 pmol/l showed a specificity of 95% (95% CI: 0.88-1.00) for AVP deficiency, while a copeptin level >5.2 pmol/l demonstrated a sensitivity of 97% (95% CI: 0.92-1.00) for primary polydipsia. The ≤ 3.0 pmol/l cut-off accurately identified 71% ($n = 27/38$) of patients with AVP deficiency, and the >5.2 pmol/l cut-off correctly identified 69% ($n = 40/58$) of patients with primary polydipsia.
Interpretation
This analysis validates two new copeptin cut-offs of the arginine stimulation test to distinguish AVP deficiency from primary polydipsia: >5.2 pmol/l for high sensitivity in diagnosing primary polydipsia and ≤ 3.0 pmol/l for high specificity in diagnosing AVP deficiency. These thresholds might offer a practical initial alternative to hypertonic saline testing.

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P902

JOINT3861

Central diabetes insipidus and panhypopituitarism in acute myeloid leukemia

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Introduction
Acute myeloid leukemia (AML) is characterized by the rapid and uncontrolled proliferation of blasts in the bone marrow. Central diabetes insipidus (CDI) is an uncommon manifestation of AML.
Case Report
We report the case of a 68-year-old Tunisian patient with no significant medical history, admitted for evaluation of persistent dry mouth and dry eyes, associated with a polyuria-polydipsia syndrome in the context of a two-month history of general deterioration. Clinical examination revealed marked weight loss, a polyuria-polydipsia syndrome (fluid intake = 6L/day, urine output = 4.5L/day), dehydration, hypotension (B*P* = 90/50 mmHg), xerophthalmia, and xerostomia (grade III sialadenitis). Laboratory investigations showed: **Blood glucose** = 0.3 g/l; **Serum sodium** = 155 mmol/l; **Plasma osmolality** = 321 mosmol/l; **Urine osmolality** = 240 mosmol/l; **Hemoglobin** = 8 g/dl; **Mean corpuscular volume (MCV)** = 86 fL; **White blood cell count** = 7,000/mm^3; **Platelet count** = 100,000/mm^3; **Peripheral blood smear**: 20% circulating blasts. The diagnosis of AML was confirmed based on indings on bone marrow aspiration. Given the presence of polyuria-polydipsia syndrome, hypotension, and hypoglycemia, a global pituitary dysfunction was suspected and confirmed by: The absence of the posterior pituitary bright spot on MRI and evidence of panhypopituitarism (cortisol = 46 ng/mL, FT4 = 4 pmol/l, FSH = 2,58 mUI/l, testosterone = 0,35 ng/ml) Pituitary MRI revealed infiltration of the pituitary stalk and oss of T1 hyperintensity of the posterior pituitary. Cytogenetic analysis revealed monosomy 7. The patient was treated with desmopressin, hydrocortisone hemisuccinate, and L-thyroxine, leading to clinical improvement. Chemotherapy was subsequently initiated.
Conclusion
The associations between DI and AML remain enigmatic and the underlying cause of DI in patients with AML is likely multifactorial. It has been associated with chromosomal abnormalities involving chromosomes 3 or 7. Diagnosis remains challenging, but clinical improvement following chemotherapy supports this etiology.

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P903

JOINT868

GLP-1 agonist semaglutide for the treatment of acquired hypothalamic obesity in adolescents: efficacy, adverse effects and impact on quality of life and eating behaviours

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Background
Hypothalamic obesity (HO) is a complex disorder marked by rapid and excessive weight gain, following damage to key hypothalamic structures responsible for energy homeostasis and appetite. Traditional lifestyle intervention often fails to result in meaningful or sustained reduction in body mass index (BMI) for general obesity, and are even less efficacious with HO. Favourable outcomes have been reported with GLP-1 agonist semaglutide for obesity which suggest it could be beneficial for adolescents with HO.
Method
Prospective observational study of the off-label use of semaglutide in adolescents with acquired HO across two tertiary paediatric hospitals, according to a standardised treatment and monitoring protocol. Dose titrated to effect (appetite suppression and sustained weight loss without significant adverse effects) starting at 0.25mg/week with four weekly increases up to a maximum of 2mg/week by 16 weeks at the earliest if clinically indicated. We report efficacy, tolerability, safety, impact on quality of life (QOL) and eating behaviours.
Results
Ten adolescents (60% male, age 11.6-17.3 years) with acquired HO are receiving semaglutide plus lifestyle intervention. Primary diagnoses include craniopharyngioma ($n = 6$), pituitary adenoma ($n = 2$), pineal tumour ($n = 1$) and bilateral thalamic infarcts ($n = 1$). After 8 weeks of therapy, 9/10 participants had a reduction in BMI SDS (range 0.03 to 0.18 SD) and BMI expressed as a percentage of 95th percentile (range 2 to 35%). Five participants have completed 24 weeks of therapy thus far with 4/5 participants experiencing a reduction in BMI SDS (range 0.03 to 0.18 SD) and BMI expressed as a percentage of 95th percentile (range 1 to 13%). Two patients have achieved at least a 5% reduction in total body weight. Waist to height ratio has reduced in all cases (mean reduction 5.0%, range 1.5 to 9.8%). 24-week data for the remaining 5 participants is awaited. Appetite suppression was evident from the starting dose with gastrointestinal side effects (vomiting, nausea and loose stool) being the most common, primarily occurring at treatment initiation or following dose escalation. No serious adverse events or therapy discontinuation has occurred. Treatment was associated with increased satiety responsiveness and slower eating measured by the Child Eating Behaviour Checklist. QOL assessments identified baseline deficits in physical comfort and body esteem, which have demonstrated the greatest improvements following treatment.
Discussion
Semaglutide is a promising therapy for HO. Data suggests this is a safe and effective treatment, although individual responses have varied. Further evaluation of long-term efficacy and safety is required.

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P904

JOINT89

Repurposing dasatinib, an FDA-approved tyrosine kinase inhibitor, for the treatment of aggressive pituitary tumors

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Introduction
Pituitary tumors (PT) occasionally exhibit an aggressive behavior, being invasive and resistant to treatment, growing rapidly and presenting multiple recurrences. We conducted a transcriptomic analysis of 22 tumors from 11 patients, including both primary and recurrent tumors from the same individuals. We identified several differentially expressed genes that are involved in lipid-related pathways, such as the up-regulation of diacylglycerol kinase gamma (DGKG), also confirmed by immunofluorescence and rt-PCR in another cohort of PT. Moreover, with molecular docking and drug repurposing tools, we observed that dasatinib, a tyrosine kinase inhibitor (TKI) already approved by the FDA for chronic myelogenous leukemia, has DGKG as a potential therapeutic target. Additionally, a novel small molecule targeting kinases (KPG-04) was designed, and its ability to induce apoptosis and decrease cell proliferation was tested.
Methods
GH3 cells and primary PT cultures were exposed to dasatinib and KPG-04 at increasing concentrations and cell viability and apoptosis were assessed by means of flow cytometry. PT samples were obtained surgically and immediately disassociated enzymatically.
Results
Exposure of GH3 cells to dasatinib decreased cellular proliferation in a dose-dependent manner: 28% at 1 μM ($P = 0.0048$), 50% at 2.5 μM ($P = 0.003$) and 98% at 5 μM ($P = 0.0395$). Dasatinib also resulted in apoptosis induction at concentrations as low as 1 μM and increasing progressively with 2.5 μM and 5 μM ($P = 0.0001$). Significantly higher concentrations of KPG-04 were required to induce cell proliferation arrest (57.23% at 50 μM, $P = 0.0039$; 68.95% at 75

μM; and 74.58% at 100 μM) and had no effect on apoptosis. Similarly, preliminary results showed that exposure of PT primary cultures to dasatinib resulted in a reduction in cellular proliferation and apoptosis induction.
Conclusion
Dasatinib, but not KPG-04, induces apoptosis and decreases cell viability in a dose-dependent manner starting at very low, probably non-toxic concentrations in both, a murine mamosomatotrope cell line and in PT primary cultures. This opens a new perspective in the treatment of aggressive PT resistant to conventional multimodal therapy, but prospective clinical studies are needed to ascertain the efficacy and safety of this TKI. We are currently designing new small molecules capable of targeting kinases such as DGKG.

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P905

JOINT2946

Macroorchidism and elevated inhibin B levels as key indicators of an extremely rare manifestation of mccune-albright syndrome in boys

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Introduction
Precocious puberty is rare in boys with McCune-Albright syndrome (MAS). Cases of unilateral or bilateral macroorchidism, along with elevated inhibin B and anti-Müllerian hormone (AMH) levels but normal androgen levels, have been reported due to the autonomous hyperfunction of Sertoli cells. Management is challenging and focuses on suppressing gonadal steroidogenesis and mitigating the peripheral effects of androgens.
Case Report
Our patient first presented at age 5 years and 6 months with macroorchidism, increased height (135.8 cm, +1.82 SDS) and growth velocity (10.96 cm/year, +7.03 SDS), as well as accelerated bone age (+49 months). Tanner staging showed PH2, G2-3; testicular volumes were 8 mL and 10 mL, and penile length was 9.0 cm. Laboratory evaluation revealed normal basal and stimulated (Synacthen) androgen levels and a normal urine steroid profile. LH and FSH were at prepubertal levels. Alpha-fetoprotein and beta-HCG levels were normal. Inhibin B levels were markedly elevated (367 ng/l), while AMH was within the normal range (15 ng/l). Ultrasound imaging showed enlarged but homogeneous testes without microlithiasis. Genetic testing ruled out fragile X syndrome, and karyotyping confirmed a 46, XY genotype. Whole-exome (blood) sequencing did not reveal any pathogenic variants. The patient was lost to follow-up but presented again at 7 years and 4 months. After LH-RH stimulation, LH increased from <0.5 to 4.5 U/l, while FSH remained unchanged. We initiated treatment with leuprorelin acetate. However, pubertal signs and growth acceleration progressed, prompting us to perform a testicular biopsy. Genetic analysis of testicular tissue revealed somatic hypomethylation of all four GNAS differentially methylated regions (DMRs): exon A/B (GNAS-A/B: TSS DMR = A/B), GNAS antisense (GNAS-AS1: TSS DMR = AS1), extra-large stimulatory G protein (GNAS-XL: Ex1 DMR = XL), and neuroendocrine secretory protein 55 (GNAS-NESP: TSS DMR = NESP), compared to normal methylation results in DNA from blood sample of the same patient. No further mutation has been detected in both tissues. Following this diagnosis, we initiated combination therapy with spironolactone and anastrozole and discontinued leuprorelin acetate.
Conclusion
Precocious puberty in boys with McCune-Albright syndrome is rare and requires a testicular biopsy for diagnosis. Given the underlying etiology, GnRH agonists are ineffective; however, a combination of third-generation aromatase inhibitors and antiandrogens may be the preferred therapeutic approach. [1]Aversa T, Zirilli G, Corica D, De Luca F, Wasniewska M. Phenotypic testicular abnormalities and pubertal development in boys with McCune-Albright syndrome. Ital J Pediatr. 2018 Nov 19;44(1):136.

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P906

JOINT2102

Toward earlier diagnosis of childhood suprasellar brain tumors through improved growth monitoring

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Introduction
Childhood suprasellar brain tumors (SBT) may cause growth retardation with simultaneous weight gain due to hypothalamic dysfunction. Many parents experience delay in diagnosis, with in hindsight pre-existing slower growth and increase in BMI. Earlier detection of SBT could prevent additional complications, such as visual impairment.
Aim
To assess whether the current referral criteria in growth monitoring by youth health care services can timely detect SBT, and whether additional criteria can lead to earlier detection.
Methods
Data were analyzed from a cohort of children diagnosed with SBT at ages 3-18y (n = 139) and compared to controls (healthy children registered at the youth healthcare service). New referral criteria based on change of height standard deviation score (HSDS) and/or BMI SDS were assessed.
Results
In the SBT cohort, 22.6% (12/53) of children with childhood craniopharyngioma (cCP), 10.8% (7/65) with low-grade glioma (LGG), and 0% (0/21) with germ cell tumor (GCT) met the current referral criteria. Had the current referral criteria been strictly followed, 47.4% (9/19) of the SBT cohort could have been detected 1y earlier than their age of diagnosis. By extending the referral criteria with ΔHSDS < -1, an additional 11 children with SBT (6 cCP, 3 LGG and 2 GCT) would be identified. Of all SBT children meeting this criterion (n = 23), 52.2% (12/23) would have been referred at least one year earlier than their age of diagnosis. This new criterion would lead to referral of 7 months earlier than the current criteria. When extending the guideline with ΔHSDS < -0.75 and ΔBMI SDS > 0.5, 5 additional SBT children were identified compared to extension with ΔHSDS < -1.
Conclusion
Extending the current referral criteria for growth monitoring may enable earlier identification of children with SBT. However, even with the current criteria children seem to be diagnosed later than necessary. Raising awareness among parents and healthcare professionals about impaired growth as a potential early warning sign for SBT is crucial to effectively implement these criteria. Also, adding additional criteria, e.g. checking for neurological or visual symptoms in patients with growth faltering, may further lead to earlier diagnosis. The pending results from the control group will provide insight into the specificity of these new referral criteria.

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P907

JOINT1450

The association between gonadotropin-releasing hormone analogue use and body mass index in girls with idiopathic central precocious puberty or early puberty: a systematic review and meta-analysis

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Objective
The rising incidence of central precocious puberty (CPP) has led to increasing use of Gonadotropin-releasing hormone (GnRH)-analogues. There have been

inconsistent reports on the possible risk of increased adiposity with GnRH-analogue use. This study evaluated the association between GnRH-analogue use and adiposity change in females with idiopathic central precocious puberty or early puberty (EP).
Design
A PRISMA-compliant systematic review was conducted using the following databases: PubMed, Embase, Scopus, PsycInfo and Cochrane. Inclusion criteria were primary studies on females diagnosed with idiopathic CPP/EP who received GnRH-analogues, where quantitative measures of adiposity were reported. The JBI Critical Appraisal Tool for Observational Studies was used for quality assessment of individual studies. A meta-analysis was performed, with subgroup analyses based on baseline body mass index (BMI) status and GnRH-analogue type.
Results
Forty-six cohort studies with 3,606 females who received GnRH-analogues for CPP/EP were included. The mean age of the study participants at initiation of GnRH-analogue was 8.07 (1.19) years, while duration of treatment ranged from 6 months to $>$ 4 years. BMI-SDS had increased significantly within 2 years of therapy (0.17, 95% CI 0.12–0.23) and at the end of therapy (0.10, 95% CI 0.02–0.18). There was no significant change in BMI-SDS beyond 2 years of therapy (0.09, 95% CI -0.02–0.20) nor at final height (-0.10, 95% CI -0.24–0.05). Between the start to end of therapy, females with normal BMI at baseline experienced significant increase in BMI-SDS (0.32, 95% CI 0.22–0.42) compared to those with overweight or obesity (BMI-SDS -0.03, 95% CI -0.09–0.02). Leuprorelin use was associated with a mild but significant increase in BMI-SDS between the start and end of therapy (0.12, 95% CI 0.03–0.21), but this was not observed with triptorelin use.
Conclusions
GnRH-analogue use in females is associated with a transient increase in BMI-SDS during, but not beyond therapy. Females with normal BMI at baseline are at higher risk of significant BMI-SDS increase during therapy. These findings are clinically important to guide counselling and monitoring of individuals with CPP/EP who receive GnRH-analogue therapy.

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P908

JOINT22

Age-related differences in the clinical features and management of pituitary apoplexy: insights from a spanish cohort study

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Background
Pituitary apoplexy (PA) is a potentially life-threatening rare clinical syndrome. The objective of this study was to analyze the clinical presentation, treatment approaches, and outcomes of PA in patients younger than 65 years compared to those aged 65 years and older at PA diagnosis.
Methods
Retrospective, multicenter study including 301 patients diagnosed with PA from 2010 to 2023 across 18 medical centers in Spain. Patients were categorized into two groups based on age ($<$65 years and $\geq$65 years). Baseline characteristics, clinical presentation, treatment approaches (surgical vs. conservative), and outcomes were analyzed.
Results
Out of the 301 patients, 185 (61.5%) were younger than 65 years and 116 (38.5%), were 65 years or older. Older patients had a higher prevalence of comorbidities, such as diabetes (11.4 vs. 34.5%; $P < 0.01$), hypertension (29.7 vs. 79.3%; $P < 0.01$), dyslipemia (32.4 vs. 62.9%; $P < 0.01$) and cardiovascular disease (4.3 vs. 27.6%; $P < 0.01$). No significant differences were observed in clinical presentation, including Pituitary Apoplexy Score and radiological findings except for higher frequency of cranial nerve palsy (46.2 vs. 64.9%; $P = 0.02$) and decreased consciousness (12.0 vs. 20.7%; $P = 0.04$), that was higher in older patients. Regarding treatment approach, surgery was underwent in 209 and conservative approach in 92 patients without differences between age groups (29.9 vs. 32.8%; $P = 0.52$). In the histological study, necrosis was more frequent in older patients (66.7 vs. 80.6%; $P = 0.04$). Regardless of the treatment approach there were no statistically significant differences in outcomes. However, in patients managed conservatively, the percentage of spontaneous tumor shrinkage, was more pronounced in older patients (39.1 ± 38.7 vs. 58.7 ± 28.1%; $P = 0.03$).
Conclusions
While older patients with PA had higher rates of comorbidities and specific neurological symptoms, the clinical presentation and treatment approaches were largely similar across age groups. Older patients showed greater spontaneous tumor shrinkage with conservative management. These findings suggest that advanced age alone should not guide PA management, as outcomes appear comparable regardless of treatment approach across age groups. Given the higher frequency of necrosis observed in older patients, computed tomography imaging could underestimate the presence of apoplexy in this group, thus, the magnetic resonance imaging should be prioritized during the diagnostic workup for pituitary apoplexy in elderly individuals.

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P909

JOINT1884

Body mass index does not influence the gh response in the oral glucose tolerance test for the diagnosis of acromegaly

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Introduction
The most recent consensus on acromegaly, established by Giustina A *et al*., 2024, recommends adjusting nadir GH thresholds in the oral glucose tolerance test (OGTT) according to body mass index (BMI). This is because BMI influences GH suppression, with nadir levels being lower in obese than in lean individuals. Therefore, it is suggested to use BMI-specific thresholds to optimize the diagnosis and treatment of the disease.

Objective
To investigate differences in basal GH levels and in the GH response to the OGTT among acromegalic patients with obesity, overweight, and normal weight.
Methods
A retrospective study of 184 patients with acromegaly treated in 10 tertiary hospitals in Spain was carried out. BMI was calculated and baseline GH levels as well as GH response to OGTT were analyzed.
Results
A total of 184 patients with acromegaly were included (mean age 49 $\pm$ 14 years, 59% (n = 108) women). At baseline, 66 patients (36%) had obesity (median BMI: 33.3 kg/m^2 [32.0–37.4]), 82 (45%) were overweight (27.4 kg/m^2 [26.4–28.7]), and 35 (19%) had normal weight (23.6 kg/m^2 [22.3–24.6]). At diagnosis, ULN IGF-1 levels in patients with obesity, overweight and normal weight were 2.2 (1.7 – 3.1), 2.7 (1.9 – 3.7) and 2.0 (1.5 – 2.6), respectively (P = 0.011). Basal GH levels (ng/mL) at diagnosis in these three groups were 4.5 (1.9 – 7.2), 7.6 (3.1 – 11.7) and 12.1 (3.4 – 23.6), respectively (P = 0.002). In the OGTT, the reduction in GH levels from basal to nadir (ng/mL) in patients with obesity, overweight, and normal weight was 0.9 (0.4–1.7), 1.7 (0.3–3.3), and 3.5 (0.5–8.3) respectively (P = 0.016); Tukey P-values: normal weight vs overweight = 0.013, normal weight vs obesity = 0.052, overweight vs obesity = 0.868). BMI was not linearly associated with the absolute decrease from basal GH to nadir (P = 0.209), percentage decrease (P = 0.718) or nadir GH levels (P = 0.261). No significant differences in GH reduction during OGTT were observed between patients with and without type 2 diabetes (P = 0.721) and between patients with micro- and macroadenomas (P = 0.174).
Conclusion
In our cohort of patients with acromegaly, basal GH levels and GH response to the OGTT were similar across obese, overweight and normal-weight groups, regardless of whether they had type 2 diabetes or pituitary tumor size Therefore, BMI-based GH nadir cutoffs in the OGTT may not be necessary for acromegaly diagnosis.

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P910

JOINT1051

Sleep quality, depression and anxiety in patients with hypopituitarism – an international survey study

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Background
Pituitary dysfunction can significantly impact sleep quality, mental health, and fatigue, leading to a reduced quality of life. Despite these well-recognized issues, systematic assessments across different subtypes of pituitary dysfunction remain limited. Therefore, this survey was developed to address this gap by evaluating these symptoms in a large, diverse cohort of patients with pituitary conditions.
Methods
This cross-sectional, web-based, anonymous survey study was designed to capture patient-reported outcomes on sleep quality, mental health, and fatigue. Participants included adults with isolated anterior pituitary dysfunction (APD), isolated posterior pituitary dysfunction (arginine vasopressin deficiency, AVP-D), combined anterior and posterior pituitary dysfunction (PanHypo), and those with pituitary conditions but no hormone deficiency or excess (e.g., non-functioning pituitary adenomas) as clinical controls. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), mental health using the Patient Health Questionnaire-9 (PHQ-9) and the State-Trait Anxiety Inventory (STAI-T), fatigue levels using the Fatigue Severity Scale (FSS), insomnia levels using the Insomnia Severity Index (ISI), and daytime sleepiness using the Epworth Sleepiness Scale (ESS). Higher scores on the PSQI, FSS, ISI, ESS, PHQ-9 and STAI-T indicated worse outcomes. Total scores were compared across groups and adjusted for sex, age, and the Charlson Comorbidity Index.
Findings
Between September 2024 and November 2024, 451 patients participated in the survey. The median age was 52 years [42–60], with 80% female participants and a median duration of pituitary dysfunction of 7 years. Participants were classified as APD (42.6 %), AVP-D (19.3 %), PanHypo (26.6 %), and clinical controls (11.5 %). The most common etiologies for a pituitary dysfunction were pituitary tumors or cysts (61.6 %) and idiopathic (18.4 %). Patients across all groups showed impaired sleep quality, clinical levels of anxiety, and sub-clinical levels of depression. Fatigue and insomnia levels were uniformly high, with significant variability in insomnia levels across subgroups.
Conclusion
This large, systematic survey demonstrates that sleep disturbances, anxiety, and fatigue are prevalent across all subtypes of pituitary dysfunction. The findings highlight the need for targeted diagnostics and interventions to address these symptoms, which significantly affect the quality of life in patients with pituitary conditions.

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P911

JOINT3685

Evaluation of internalizing symptoms in mothers of girls diagnosed with central precocious puberty: a pre- and post-treatment analysis

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Objective
Precocious puberty can be a significant source of stress not only for affected children but also for their families, particularly their mothers. This study aims to assess the presence of internalizing symptoms—stress, anxiety, and depression—in mothers of girls diagnosed with central precocious puberty (CPP) and to evaluate how these symptoms change following treatment.
Methods
This prospective study included mothers of girls diagnosed with CPP who presented to our pediatric endocrinology clinic. The Depression, Anxiety, and Stress Scale-21 (DASS-21) was administered before and after treatment. Mothers with a history of psychiatric illness, those using psychotropic medications, or those whose children were not diagnosed with CPP were excluded. Data from 38 participants were analyzed using the Jamovi 2.2.5 statistical software.
Results
The mean age of the girls at diagnosis was 7.01 $\pm$ 0.96 years. The mean age of the mothers was 40.1 $\pm$ 5.95 years, while the fathers' mean age was 43 $\pm$ 6.18 years. The median time from initial presentation to diagnosis was 2.5 months (IQR: 1), and the mean duration from treatment initiation to reassessment was 12 $\pm$ 8.05 months. At baseline, the median maternal stress score was 4 (IQR: 5), anxiety score was 4 (IQR: 3.75), depression score was 3 (IQR: 4), and total DASS score was 11 (IQR: 10.3). Clinically significant stress, anxiety, and depression were observed in 21.1%, 52.6%, and 31.6% of mothers, respectively. Following an average of 12 months of treatment, the median stress score decreased to 2 (IQR: 5), anxiety score to 1.5 (IQR: 4), depression score to 0 (IQR: 2.75), and total DASS score to 4 (IQR: 10.5). The prevalence of clinically significant stress, anxiety, and depression dropped to 2.6%, 28.9%, and 15.8%, respectively. Statistical analysis confirmed a significant reduction in all internalizing symptoms post-treatment ($P < 0.01$). No significant correlations were found between DASS scores and child's age, time to diagnosis, maternal age, or paternal age.
Conclusion
These findings suggest that mothers of children with CPP experience significant psychological distress at the time of diagnosis, which improves following treatment. Given the emotional burden associated with early puberty, incorporating psychosocial support into the management of CPP could be beneficial for both patients and their families.

Keywords
anxiety, depression, puberty precocious, psychiatry, stress.
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P912

JOINT3713

A case of aggressive AIP-mutated pituitary acrogigantism treated with pasireotide

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Introduction
Pituitary acrogigantism is a rare disease caused by chronic growth hormone (GH) hypersecretion usually from a pituitary adenoma that occurs during childhood/adolescence and nearly half of cases have a genetic cause. Pathogenic

variants in the *AIP* gene are responsible for about 30% of cases, are associated with aggressive pituitary tumours that can be challenging to treat medically with first-generation somatostatin analogs. There are several reports that treatment with pasireotide long-acting release (PAS-LAR) can lead to tumour regression in *AIP*-related acromegaly.
Objective
To report a new case of aggressive *AIP*-mutated pituitary acrogigantism successfully treated with Pasireotide LAR.
Methods
Clinical presentation, imaging, laboratory data and immunohistochemical staining features were analyzed. Evaluation for the presence of any pathogenic/likely pathogenic variations in pituitary and neuroendocrine tumor related genes were assessed by whole exome sequencing.
Results
A 15-year-old male presented with headache, visual acuity loss, back pain, weakness, loss of appetite, and rapid growth for the last 3 years. His height was 183.5 cm and he weighed 52 kg. ECG: sinus bradycardia. Ophthalmological review revealed optic nerves atrophy. An MRI showed an invasive supra-para-retrosellar macroadenoma (3,8x3,6x3,8 cm) with extension towards the posterior cranial fossa, third ventricle compression and basilar artery involvement. His plasma hormone concentrations were: prolactin 1116.5 ng/ml, GH 690 ng/ml, IGF-1 537 ng/ml, TSH 4.59 mU/l, fT4 1.16 ng/dl, fT3 2.99 pg/ml, DHEA-S 625 mg/ml, cortisol 9.81 mg/dl. Due to his hyperprolactinemia, cabergoline was started and rose to a dose of 0.5-1.0 mg/day. Hormone levels after three weeks were as follows: prolactin 232 ng/ml, GH 1023 ng/ml, IGF-1 501 ng/ml. He therefore underwent a partial endoscopic transnasal tumour resection that resulted in a decrease of GH and prolactin levels (prolactin 9.54 ng/ml, GH 70.0 ng/ml) but IGF-1 was elevated (567,2 ng/ml) and he had permanent hypopituitarism in other axes. Immunohistochemistry showed GH (90%) and prolactin (10%) positive cells in the pituitary adenoma with weak staining (+) for SSTR2 and moderate (++) staining for SSTR5, with a Ki-67 of 5%. A pathogenic heterozygous missense variant in exon 6 of the AIP gene (c.811 C>T; p.Arg271Trp) was detected. Treatment with Signifor LAR 40 mg/28 days and cabergoline 0.25 mg/day were started. A significant decrease in tumour volume, improvement in visual fields and IGF-1 normalization were achieved during 36 weeks of treatment.
Conclusion
Pasireotide long-acting release treatment may be beneficial in *AIP* mutated patients with acrogigantism and positive immunohistochemical staining of tumour cells for SSTR5.

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P913

JOINT2508

Cytokines and chemokines modulate the growth of pituitary adenoma/neuroendocrine tumors: preliminary results of a monocenter prospective pilot study

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Introduction
Cytokine and chemokines have been recognized to be involved in the progression and prognosis of pituitary adenoma/neuroendocrine tumors (PAs/PitNETs), also known as pituitary adenomas. We aim to investigate the expression of cytokine and chemokine in PAs/PitNETs, and their association with PAs/PitNETs clinical and biological behavior.
Patients and methods
A prospective and monocenter study was performed on 16 patients diagnosed for PAs/PitNETs. Cytokine and chemokine were detected on freshly collected PAs/PitNETs samples. Tumor infiltering immune cells were investigated on formally fixed and paraffin-embedded PAs/PitNETs samples. Clinical, biochemical, molecular and morphological data were collected from patients' medical records.
Result
Out of 72 patients with PAs/PitNETs that underwent surgical removal at the Neurosurgery Division of our Institution between January and June 2023, sixteen patients were enrolled in the study. Out of 42 cytokines and chemokines that we investigated, we found that all tumors expressed IL-1b, IL-2, IL-3, IL-8, CCL2, EGF, CXCL1, CXCL1 -a, CCL5, SDF1, CCL17, MDC, VEGF, PDGF88 and the leptin. A positive correlation was detected between the intensity score of EGF and CXCL1 ($P = 0.003$, r:0.7), of EGF and CXCL1-a ($P = 0.01$, r:0.61); of EGF and CCL5 ($P = 0.004$, r:0.68); and of CXCL1 and CCL5 ($P = 0.003$, $r = 0.684$). An inverse correlation was identified between intensity score of CXCL1 and IL-2 ($P = 0.002$, r:-0.7). A positive correlation was detected between the number of tumor-infiltering CD68+ macrophages and the CCL2 intensity score ($P = 0.008$, $r = 0.695$). No correlation was identified between the presence of circulating anti-pituitary antibodies and presence of tumor cytokines and chemokines. EGF was significantly more expressed in tumors with MIB1>3% (IS:1515 IQR:1642), than in tumor with MIB1<3% (IS: 81 SD: 292, $P = 0.014$); the IS of the other cytokines/chemokines did not differ in tumor with MIB1<3% and in those with MIB1>3%. Invasive PAs/PitNETs had a higher expression of EGF (IS:465 IQR:1232, $P = 0.002$), of CXCL1 (IS:1756 IQR:2055, $P = 0.01$), of CCL17 (IS:351 IQR:609, $P = 0.002$) then not invasive PAs/PitNETs (EGF IS:260, IQR:520; GRO:718 IQR:890; CCL17:147, IQR:443). PAs/PitNETs with invasion of the cavernous sinus expressed higher levels of EGF (IS:652 IQR:1457, $P = 0.004$), of CXCL1 (IS:2170 IQR:2308, $P = 0.02$) and lower IL-2 levels (IS:326 IQR:729, $P = 0.02$), then not invasive cavernous sinus PAs/PitNETs (EGF IS:212 IQR:476; CXCL1 IS: 719 IQR:859, IL-2 IS:326 IQR:729).
Conclusion
Our preliminary results support that in PAs/PitNETs, the cytokines and chemokines generate an immune network, that may contribute to regulating the cell proliferation and pattern of growth.

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P914

JOINT311

Aggressive prolactinomas: unveiling mechanisms of dopamine agonist resistance through exomic, tanscriptomic, and metabolic strategies

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Background/Aims
Pituitary tumors are the second most common intracranial neoplasm, of these, prolactinomas are the most frequent functioning subtype. For this type of tumor, dopamine agonists (DA) constitute the treatment of choice. However, a subset of patients (30-50%) exhibits resistance to DA treatment. This resistance may involve different molecular mechanisms, which remain largely unclear and not fully understood. The aim of this project is to characterize the allelic variants and transcriptomic profile of aggressive, treatment-resistant prolactinomas through whole-exome and whole transcriptome analysis.
Methods
We evaluated 12 patients with DA-resistant lactotroph tumors and 6 non-tumoral pituitaries by whole exome sequencing (WES) and whole transcriptomic sequencing (WTS). Nine of the 12 tumors were categorized as totally unresponsive whereas three were considered partially resistant.
Results
WES identified approximately 18,000 variants, of which only two (*TP53* c.C817T p. R273C and one in *SF3B1* c.C1873T p. R625C) were considered pathogenic. These variants are known to play a pathogenic role in other tumors and are associated with tumorigenesis. The most frequent mutational signature was *SBS5* which is associated with normal cellular damage of DNA processes. The tumor mutational burden (TMB) was similar in both the partially and the totally resistant tumors. In the WTS analysis, prolactinomas showed different degrees of transcriptomic heterogeneity between partial and null responses. Interestingly, the null response group exhibited molecular events related to metabolism, which were linked to antifolate resistance, fatty acid degradation, and sphingolipid

metabolism. Furthermore, metabolic characterization revealed high heterogeneity, mainly in pathways associated with lipid metabolism.
Conclusions
We conclude that prolactinomas are genomically stable, which could indicate that mechanisms other than somatic mutations are involved in lactotrophic tumorigenesis and that differences in response to DA treatment may result from transcriptomically heterogeneous clones.

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P915a

JOINT835

"Cortisone-loop" an educational tool that ensures the quality of care for children with adrenal insufficiency in sweden, how does it work in practice? evaluation in nirthern sweden

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Background
Adrenal insufficiency (AI) is a severe condition that requires lifelong substitution with cortisone and/or mineralocorticoid. A good initial education to AI patients/families is the key to understand the severity of disease, for better compliance and management of critical situations throughout life. Pediatric care in Northern Sweden is offered at five county level hospitals and at university hospital level therefore AI care and education may vary due to experiences of the staff and number of patients. In 2019 the worksheet was implemented to ensure high-quality care and information regardless of the clinićs experience or geographic location.
Aim
To evaluate use of the worksheet in pediatric clinics in Northern Sweden regarding the management of patients suffering from AI. To study the patient's and their famiĺys understanding of the disease and management of cortisone substitution under different conditions.
Result
In 2019 the Swedish endocrine nurse group presented a worksheet for patient education in pediatric clinics throughout the country. This contains questions with evidence-based knowledge, and from real-life situations/activities discussed with patients/family during follow-up at pediatrics care. For evaluation, we sent a questionary to six pediatric clinics and to forty patients with AI in Northern Sweden. Questionnaire for medical staff included questions about knowledge of worksheet, use in clinical practice and how to develop this educational material to be used more. Answers from clinicians showed: 100% found educational material useful and were satisfied with the content, but only 85% used it in daily practice. Two clinics (15%,) dońtt use the material due to low amounts of AI patients and medical resources. All clinicians suggested continuous training in the use of the worksheet. Questionary to the patients/families included questions like knowledge about your disease, managing of critical situations and suggestion for improvement of education. Answers from thirty-seven patients showed great satisfaction with education and wishes to continue as we do now. Patients from clinics that didǹt use the worksheet were educated from the university hospital.
Conclusion
Standardization of education by using the worksheet in all children's clinic in Northen Sweden increase the quality of patients' education. Patients receive equal education regardless of the clinic's experience or geographical location. The evaluation in Northern Sweden showed needs for caregivers continuous training in the use of the worksheet.

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P916

JOINT2512

Biological maturity and body composition changes during pubertal growth: a longitudinal study of korean adolescents

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Objective
To conduct a systematic and comprehensive analysis of body composition changes across pubertal growth stages in Korean adolescents, focusing on the age at onset of growth spurt (AOGS) and age at peak height velocity (APHV).
Materials and Methods
This study utilized longitudinal data from 77 boys and 122 girls aged 7-16 years. The Superimposition by Translation and Rotation (SITAR) model was applied to estimate individual growth curves and identify the timing of pubertal growth. Fourteen anthropometric and body composition variables were examined, including height, weight, lean mass, fat mass, and various derived measures. Body composition and its changes were systematically analyzed in alignment with pubertal growth stage.
Results
For girls, the mean AOGS was observed at 8.75 years, with APHV occurring at 10.92 years. For boys, AOGS occurred at 9.68 years and APHV at 11.91 years. Significant increases in height, weight, and lean mass components were observed around both AOGS and APHV for both sexes, with changes more pronounced around APHV, particularly for boys. Height velocity at AOGS was 6.02 cm/year for boys and 5.97 cm/year for girls, increasing to 10.41 cm/year and 8.30 cm/year respectively at APHV. Body fat percentage increased significantly around AOGS in both sexes (boys: +2.16 percentage points, girls: +1.94 percentage points) but showed different patterns around APHV, with girls maintaining relatively stable ratios (-0.24 percentage points) and boys experiencing a significant shift towards decreased adiposity (-3.92 percentage points).
Conclusion
This study provides detailed insights into pubertal growth patterns and body composition changes in Korean adolescents around AOGS and APHV. The SITAR method applied to longitudinal data enabled the examination of individual growth trajectories and within-person changes throughout pubertal development. This comprehensive analysis of body composition parameters enhances our understanding of developmental patterns and sexual dimorphism in pubertal growth processes, contributing to a broader perspective on adolescent development.

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P917

JOINT3487

Differentiating AVP deficiency and primary polydipsia: a clinical and biochemical perspective

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Background
Polyuria and polydipsia require differentiation between arginine vasopressin (AVP) deficiency and primary polydipsia (PP), as both involve excessive water intake and urine output but have distinct pathophysiology. This study aimed to compare biochemical, clinical, and hormonal differences between AVP deficiency and PP to identify distinguishing diagnostic markers.
Methods
A retrospective observational study was conducted on 36 patients who underwent a water deprivation test at Ankara Bilkent City Hospital between February 2019 and December 2024. Patients were categorized as AVP deficiency (complete or partial) and PP based on clinical and biochemical findings. Plasma and urine osmolarity, sodium, chloride, magnesium, and anterior pituitary hormones (LH, GH, ACTH..) were analyzed.
Results
Among 36 patients, 55.6% had AVP deficiency, while 22.2% were diagnosed with PP. Nocturia was significantly more prevalent in AVP deficiency (96.2%) than PP (12.5%, $P < 0.001$). Fluid intake exceeded 10 liters/day in 62.5% of PP patients, whereas AVP deficiency patients typically consumed 5–10 liters/day. Plasma osmolarity was lower in PP, and urine osmolarity was significantly lower in PP than AVP deficiency ($P = 0.011$). Sodium ($P = 0.030$), chloride ($P = 0.040$), and magnesium ($P = 0.010$) were significantly reduced in PP. Hormonal analysis showed elevated LH ($P = 0.011$) and GH ($P = 0.028$) in PP compared to AVP deficiency.
Discussion
Findings suggest that nocturia frequency, fluid intake patterns, and specific biochemical markers (sodium, chloride, magnesium) may assist in differentiating PP from AVP deficiency. The lower urine osmolarity in PP highlights impaired urine concentration despite intact AVP function, while electrolyte disturbances suggest altered water balance regulation. Additionally, although LH and GH levels were statistically higher in PP, this does not necessarily imply clinical significance. These distinctions reinforce the importance of integrating biochemical, clinical, and hormonal assessments for accurate diagnosis.

Table: Key Biochemical and Hormonal Differences Between AVP Deficiency and PP.

Parameter	AVP Deficiency ($n = 26$)	PP ($n = 8$)	*P*-value
Nocturia (%)	96.2	12.5	<0.001
Urine Osmolarity (mOsm/l)	101±48	129±41	0.011
Sodium (mEq/l)	142±3	138±4	0.030
Chloride (mEq/l)	108±3	105±4	0.040
Magnesium (mg/dl)	2.0±0.2	1.8±0.1	0.010
LH (U/l)	5.65±7.77	11.78±11.99	0.011
GH (ng/mL)	0.27±0.54	0.43±0.39	0.028

Conclusion

This study underscores the diagnostic value of urine osmolarity, plasma sodium, chloride, magnesium, and anterior pituitary hormones in differentiating AVP deficiency from PP. Incorporating these markers into routine evaluation may improve diagnostic precision and guide targeted management strategies. Further large-scale studies are recommended to validate these findings and optimize diagnostic criteria.

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P918

JOINT550

Update on the use of robotic surgery and artificial intelligence for pituitary tumors

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Introduction

The use of robots in medical procedures is quickly replacing interventions performed by humans. Robotic surgery has significantly advanced the field of endocrine surgery, offering a range of benefits over traditional techniques. This review presents an update on the use of robotic surgery and artificial intelligence for pituitary tumors.

Methods

A systematic search of literature was conducted using the search terms robotic surgery, artificial intelligence, pituitary tumors, safety, outcome, and cost.

Results

Pituitary tumors are common neoplasms. They represent approximately 15-20% of all intracranial tumors and are benign in the majority of cases (e.g., pituitary adenomas). Pituitary carcinomas are rare neoplasms representing 0.1-0.2% of all pituitary tumors. Most pituitary adenomas are functioning tumors, mainly producing prolactin and/or growth hormone. Pituitary microadenomas (size up to 1 cm), especially prolactinomas, can benefit from pharmaceutical treatment. Transsphenoidal surgery plays an important role in the management of pituitary tumors, especially for the treatment of pituitary macroadenomas. In the context of pituitary gland operations, robotic assistance is particularly beneficial for transsphenoidal procedures where access through tight spaces with delicate surrounding tissues is required. Autonomous surgical robots can be categorized into various levels of autonomy, including partially autonomous systems performing specific tasks under human supervision, collaborative autonomy where robots work alongside human surgeons, and fully autonomous systems capable of completing entire procedures independently. The robotic system's fine motor control and enhanced visualization increase dexterity and facilitate precise tumor removal, crucial for avoiding damage to nearby neurovascular structures. However, significant limitations restrict the applicability of robotic neurosurgery. The next generation of robotic assistance should prioritize size decrease, operating angles flexibility, and drilling with bony removal ability. While fully autonomous robotic surgery remains a long-term goal, the ongoing integration of artificial intelligence (AI) and robotics is rapidly advancing. This integration is set to revolutionize the future of robotic surgery and promise to further enhance the precision, safety, and effectiveness of surgery involving the pituitary gland. However, the current high cost of these new procedures remains a potential limitation.

Conclusion

Robotic surgery has been growing in popularity and feasibility. It offers improved dexterity and precision for the removal of pituitary tumors compared to traditional transsphenoidal surgery. Future collaboration between human surgeons and advanced robotic systems holds significant potential for improving patient care and surgical outcomes. The ongoing integration of AI and robotics can further enhance the precision, safety, and effectiveness of the surgery of pituitary tumors.

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P919

JOINT2823

Defective Nitric oxide pathway signalling - a link between premature birth and altered mini-puberty?

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Mini-puberty is the period of transient hypothalamic-pituitary-gonadal (HPG) axis activity shortly after birth, before the axis is 'switched-off' until puberty. The amplitude of mini-puberty has been shown to be exaggerated in babies born preterm, with potential consequences later in life for neuronal maturation, pubertal disorders, behavioural and metabolic conditions. Nitric oxide (NO) is a key player in regulation of mini-puberty and reproductive development, with Nitric oxide synthase 1 (NOS1) deficiency leading to abnormal mini-puberty in mice and congenital hypogonadotropic hypogonadism in humans. We interrogated 63 patient samples from the Finnish mini-puberty cohort (75% born $<$ 37/40 gestation) part of the 'miniNO' project (grant 847941), for variants in genes associated with NO signalling pathways. Whole genome sequencing was filtered for rare and predicted in-silico to be pathogenic to protein function. We identified two preterm infants with variants of interest. One female patient, born at 24.7 weeks, carried a missense heterozygous variant (c.1855A$>$T, p.M619L) in *NOS1*. The variant is rare in the healthy population (gnomAD European frequency of 0.39%). She displayed a very exaggerated mini-puberty with peak urinary luteinising hormone (LH) of 208 IU/l, with corresponding oestradiol of 16662 pmol/l. At follow-up aged 14.8 years the patient is pre-menarche, suggesting pubertal delay. The affected residue is located in the highly conserved oxygenase domain of NOS1. *in vitro*, the maximal NO output from cells transiently expressing the p.M619L mutant was significantly attenuated compared to wild-type NOS1, suggesting decreased NOS1 activity. In addition, the p.M619L variant was able to dimerise with wildtype NOS1 in co-immunoprecipitation experiments, suggesting an impairment of functional homodimer formation, which may underly pathogenicity of the heterozygous variant. A second female patient, born at 32.1 weeks had a missense heterozygous variant (c.296G$>$A, p.S99N) in the NOS1 associated protein 1 gene (*NOS1AP*). The variant has gnomAD European frequency of 0.57%. The patient demonstrated a flat mini-puberty profile with peak LH of 0.97 IU/l and at the current age of 12.5 years has mild puberty delay (Tanner stage B2). NOS1AP is expressed in GnRH neurons and co-expressed with NOS1. The S99N variant is located within the phosphotyrosine-binding domain of NOS1AP, with a role in neuronal dendritic development and cell proliferation and migration. Functional characterisation is in progress. Here we identify rare exonic variants in genes within the NO synthesis pathway in patients with preterm birth and abnormal mini-puberty, providing potential human evidence for the role of NO signalling in prematurity and HPG axis regulation.

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P920

JOINT1439

A phase 2, open-label, multiple-ascending-dose trial evaluating anti-ACTH antibody lu AG13909 in adults with cushing's disease: balanced trial design

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Introduction

Cushing's disease (CD) is a rare disorder caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma. Autonomous ACTH production induces hypercortisolemia, which is associated with increased morbidity and mortality. There is an unmet need for well-tolerated and effective treatments to treat hypercortisolemia. Lu AG13909 is a novel, high-affinity, anti-ACTH monoclonal antibody that inhibits ACTH-induced signaling. Here, we describe

the BalanCeD trial design (NCT06471829), evaluating the efficacy, safety, tolerability, and pharmacokinetic/pharmacodynamic profile of Lu AG13909 in adults with CD.
Methods
BalanCeD is a phase 2, interventional, multi-site, open-label, multiple-ascending-dose trial with dose titration, which is being conducted in specialist sites across Europe, including Georgia. Eligible participants have ACTH-driven CD (defined by current Pituitary Society consensus guidelines) and 24-hour urinary free cortisol (UFC) >1.5 times the upper limit of normal. Participants may have had pituitary surgery >3 months prior to screening. Participants who had previously received cortisol-lowering medication must have completed a predefined washout period prior to dosing. The trial consists of 3 parts: Part A (22–30 weeks), Part B (32–52 weeks), and an Extension Period (52 weeks, with an additional 16-week Safety Follow-up Period). Part A includes an intravenous titration period to identify the dose that provides the optimal clinical response based on tolerability and pharmacodynamic assessments, a subcutaneous period, and a Safety Follow-up Period. Part B includes a subcutaneous titration period to identify the optimal dose for normalization of mean UFC, a maintenance period, and a Safety Follow-up Period. Part B will be initiated based on a Dosing Conference, evaluating the cumulative safety, tolerability, pharmacokinetics, and efficacy data from ≥ 3 participants in Part A; Part B may be initiated before the finalization of Part A. Only participants enrolled in Part B can opt into the Extension Period, which will evaluate long-term efficacy and safety. The primary efficacy endpoint is the response rate of UFC normalization at the end of the titration periods of Part A and Part B. Secondary endpoints include treatment-emergent adverse events and multiple pharmacokinetic endpoints.
Conclusions
The BalanCeD trial aims to evaluate the efficacy, safety, tolerability, and pharmacokinetics/ pharmacodynamics of Lu AG13909 in adults with CD. Findings from this trial will reinforce the development of Lu AG13909 as a novel anti-ACTH treatment strategy for patients with CD.

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P921

JOINT1538

MRI-based radiomics of the pineal gland in girls does not provide informative data for the diagnosis of central precocious puberty

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Introduction
The diagnostic gold standard for central precocious puberty (CPP) is the gonadotropin-releasing hormone (GnRH) stimulation test. Additionally, magnetic resonance imaging (MRI) of the brain and of the hypothalamus-pituitary region is required to exclude central organic causes. Recent technological advancements have contributed to the development of a new approach in medical imaging called radiomics. Our recent study has shown that radiomics of the pituitary gland is a promising tool for diagnosing CPP. The role of the pineal gland in the onset of puberty is long debated with conflicting Results.
Aim
Herewith, we investigated the features of the pineal gland in relationship with the onset of puberty, using radiomics, with the aim to assess whether there are any specific changes that could assist physicians in the diagnostic workup of CPP.
Methods
Forty-five girls with a confirmed diagnosis of CPP and 47 pre-pubertal, age- and sex-matched subjects (control group) were retrospectively enrolled. Two readers (R1, R2) with different levels of expertise in pediatric neuroradiology blindly segmented the pineal gland on MRI studies for radiomic features (RFs) calculation and performed a manual evaluation of the number and the diameter of pineal cysts. Cross-validated linear discriminant analysis was used to develop both a radiomic model and a reference model for each reader based on the pineal cysts features. Radiomics was evaluated in terms of 1) predictive performances (metrics: ROC-AUC, accuracy, sensitivity, and specificity); and 2) reliability of predictors between readers (metric: intraclass correlation coefficient, ICC). Finally, the correlation between cysts features and basal/peak gonadotropin levels was also investigated.
Results
Two radiomic features were identified as the most predictive of CPP for both readers. However, these features were not the same for R1 and R2 readers, and their values showed poor inter-reader reliability. Unpromising performances in the validation set were obtained for the radiomics of the pineal gland (ROC-AUC of 0.64 for R1 and 0.59 for R2). These results were significantly lower than the findings we had found for the pituitary gland, which achieved ROC-AUC of 0.81 and 0.76 for R1 and R2, respectively. Similarly, the reference model based on pineal cysts features demonstrated poor performance (ROC-AUC $= 0.52$, both readers). No significant correlations ($\alpha=0.05$) between cysts features and basal/peak gonadotropin levels were observed.
Conclusion
Radiomic features of the pineal gland in girls with CPP have shown no supporting evidence of differences compared with prepubertal controls.

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P922

JOINT1891

Hormonal support for very young transgender adolescents aligns body composition with identified gender

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Background
There is lack of data on the physical changes occurring in very young transgender people undergoing puberty suppression (PS) and gender-affirming hormone therapy (GAHT). This study aimed to investigate how body composition changes in terms of fat mass (FM) and lean mass (LM) according to birth-assigned sex and affirmed gender during PS and GAHT.
Methods
This retrospective study included data from 201 adolescents starting PS under 15yr at a national gender service (139 trans boys and 62 trans girls). Data from 127 of them who subsequently received GAHT were available. Height, weight, BMI, total LM and FM were collected using Tanita body composition analyser. Participants were divided into two groups: 'in puberty' (Tanner stage 2-3, or testicular volume <15ml) and 'completing puberty' (Tanner stage 4-5, or testicular volume >15ml) adolescents.
Results
Among 'in puberty' trans boys, total FM increased on PS (2.49 kg, 95% CI 1.66;3.33) similar to LM (2.41 kg, 95% CI 1.85;2.97). In contrast, with 'completing puberty' trans boys the increase of total FM (1.80 kg, 95% CI 1.21;2.39) was higher than total LM (0.97 kg, 95% CI 0.63;1.30). Looking at Z-scores, 'in puberty' trans boys showed increases in FM after 3 years of PS (from 0.70 to 1.2), and mean LM z-scores decreased in both 'in puberty' (from 0.98 to 0.5) and 'completing puberty' (from 1.16 to 0.80). During GAHT, 'in puberty' trans boys showed a greater increase of total LM (6.28 kg, 95% CI 3.54;9.02); body composition after 2 years was FM 27% and LM 73% (vs FM 30% and LM 70% at baseline). Mean FM z-scores at 2yr of GAHT in both groups decreased over baseline but remained higher in comparison with the identified gender. In contrast, 'completing puberty' trans girls showed a greater increase of total FM during PS (4.27 kg, 95% CI 1.50;7.03), whereas body composition only changed slightly during GAHT. However, mean FM z-scores at 2yr of GAHT in trans girls were in normal range (0.1) according to the affirmed gender.
Conclusions
Early hormonal intervention accelerates FM gain in both genders. GAHT masculinises body composition with gains in LM for trans boys, but aligns FM for trans girls with that for typical cisgender girls.

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P923

JOINT1926

Shredded AIP pituitary sequel

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Introduction
Familial Isolated Pituitary Adenomas (FIPA) syndrome is characterized by the presence of Pituitary Neuroendocrine Tumors (PitNET) in at least two family members, without clinical features suggestive of other genetic syndromes. Germline mutations in the Aryl Hydrocarbon Receptor-Interacting Protein gene (*AIP*) are identified in ~10-20% of FIPA cases, with low penetrance (12.5-30%) and an autosomal dominant inheritance pattern. These mutations are often associated with early-onset PitNET, typically secreting growth hormone, prolactin, or both. The AIP structure contains an alpha-helix and three tetratricopeptide repeat (TPR) domains in the C-terminal region, crucial for protein-protein interactions. This study investigates the impact of a novel *AIP* variant in a 17-year-old girl with an invasive macroprolactinoma and a family history of PitNET.
Methods
AIP germline mutations were investigated by direct DNA sequencing of the AIP gene exons 2, 4, 5, and 6 using the Sanger method. The impact of genetic variants on protein structure was assessed using the NextProt platform. The proband's family was investigated for the presence of PitNET and AIP variants.
Results
Genetic analysis identified a novel heterozygous variant in exon 4 of the *AIP* gene (c.479delC) in the proband: a frameshift mutation causing a premature stop codon (Ter170). This nonsense variation leads to the loss of TPR1-3 and the alpha-helix, key functional C-terminal domains. The mother and five maternal relatives of the proband carried the variant: one had a PitNET and the others did not show any clinical manifestations. The proband presented a grade IV KNOSP macroprolactinoma at age 17, responding to cabergoline with tumor shrinkage and prolactin normalization. The other carrier was diagnosed at age 39 with an invasive GH-secreting PitNET and required medical therapy after surgery and Gamma-Knife radiosurgery due to residual disease.
Discussion and Conclusions
The c.479delC *AIP* variant identified in this study is associated with FIPA, with a confirmed incomplete penetrance and invasive, aggressive early-onset GH- and PRL-secreting PitNETs in patients displaying the FIPA phenotype. The variant causes the loss of AIP molecular interaction domains, potentially contributing to tumorigenesis. These findings highlight the importance of genetic screening in families with a history of PitNETs, enabling early diagnosis and personalized treatment strategies.

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P924

JOINT2947

The prevalence of brain abnormalities in children with central precocious puberty or early and fast puberty

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Method
From 2011 to 2022, children who were diagnosed CPP or EFP in our center and had completion of cranial magnetic resonance imaging(MRI) were studied. 1087 children were enrolled, including 908 girls (668 CPP, 240 EFP) and 179 boys (89 CPP, 90 EFP), and divided into 3 groups depending on the detection and the types of intracranial lesions. Group 1: no intracranial lesion, Group 2: confirmed hypothalamic hamartoma and glioma, and Group 3: other intracranial lesions. The age of puberty onset, serum levels of FSH, LH, bone age (BA), and Z score of height for BA (SDSBA) at the diagnosis were analyzed.
Results
In girls, 132 cases be found intracranial lesions (14.5%). In boys, 35 be found intracranial lesions (19.6%), with no difference from girls ($P = 0.089$).33.7% (17 in Group 2) Girls <6 years old be found intracranial lesions, higher than that ≥ 6 years old, the latter was 12.1% (only 2 in Group 2)($P<0.001$). Boys <7 years old also had increased incidence of intracranial lesions than that ≥ 7 years old: 53.8% (5 cases in Group 2) vs 16.9% only 1 in Group 2) ($P = 0.004$). No difference of incidence of brain lesions in girls with CPP and EFP (15.3% vs 12.5%, $P = 0.296$), as well as in boys(22.5%, 16.7%, $P = 0.432$). Group 2 had earliest onset of puberty (average age was 1.9 years for girls, 1.0 years for boys), but no difference of acceleration of bone age and height SDSBA were found at diagnosis when compared with group1 and group3 ($P > 0.05$). puberty No diference was found of the age of onset of puberty, baseline LH and FSH, LH peak after stimulation, aceleration of BA as well as height SDSBA between group1 and group3 ($P > 0.05$).
Conclusion
hypothalamic hamartoma and glioma are more common in children with CPP, especially in girls under the age of 6 or boys under the age of 7. In girls above the age of 6, and boys above 7 years old, suffered from CPP or EFP, incidence of intracranial lesions was lower than expected, and most are Incidental lesions, and have little relevence with the process of puberty.

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P925

JOINT304

Glucocorticoid withdrawal syndrome, a potential marker for prolonged remission after transsphenoidal surgery in cushing's disease: insights from a single center 20-year retrospective cohort

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Background
Cushing's disease (CD) is a rare condition with variable surgical outcomes. This study aimed to assess remission and recurrence rates in CD patients undergoing transsphenoidal surgery (TSS) in a contemporary cohort at a major referral center in Israel, and to identify predictive factors for these outcomes. We anticipated that microadenomas would have higher remission rates than macroadenomas.
Methods
This was a retrospective analysis of 97 CD patients who underwent TSS at Tel Aviv Sourasky Medical Center from 2002 to 2022. Remission was defined by a set of biochemical criteria and clinical improvement. Suspected recurrence was confirmed by pathological dexamethasone suppression and/or an elevated urinary free cortisol. Univariate and multivariate analyses were used to identify predictors of remission, while Kaplan-Meier survival analysis and Cox proportional hazard modeling were employed to determine factors associated with recurrence.
Results
The overall remission rate was 63.9%, 69% for first time surgery, and 30.7% for repeat TSS. Contrary to our hypothesis, remission rates were similar between microadenomas (58.7%) and macroadenomas (73.5%), $P = 0.148$. By multivariate logistic regression, predictors of remission were adenoma presence in pathology specimens (OR = 31.25, $P < 0.001$) and first-time surgery status (OR = 9.42, $P = 0.002$), while a younger age seemed to play a contributory factor (OR = 0.963, $P = 0.05$). The overall relapse rate was 22.6% over a median follow-up of 63 [IQR 35-109.5] months. Of all the variables considered, glucocorticoid withdrawal syndrome (GWS) emerged as a novel, and the only significant apparent protective factor against recurrence ($P = 0.045$).
Conclusions
This study, the largest and most up-to-date analysis of short and long-term TSS outcomes for CD in Israel, is somewhat at odds with some established notions about remission predictors, including the initial hypothesis about microadenomas. Likewise, the identification of GWS as a novel predictor of long-term remission, requires confirmation, but could provide a potential avenue for post-operative monitoring and follow-up care in the local context. Moreover, it highlights the necessity to assess outcomes at the patient, and local healthcare-specific level.

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P926

JOINT1756

"Bioimpedance vector analysis in hyponatremic patients with syndrome of inappropriate antidiuresis: a prospective multicenter study"

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Purpose
The syndrome of inappropriate antidiuresis (SIAD) is the leading cause of hypotonic hyponatremia with preserved extracellular fluid (ECF) volume,

accounting for nearly half of hospital cases, but remains a diagnosis of exclusion. Accurate classification of hyponatremia and timely treatment are essential to prevent complications and serum sodium (s-Na) overcorrection. International guidelines prioritize ECF volume classification over etiology for prompt treatment. Bioelectrical impedance vector analysis (BIVA) uses low-frequency current (50 kHz) to measure body resistance (Rz) and reactance (Xc), accurately estimating ECF. It does not rely on body geometry or tissue models and is independent of body weight, generating the Biavector plotted on a Cartesian RXc graph. This study compares the Biavector of SIAD patients to the Italian reference population to identify a potential "BIVA pattern".
Methods
We prospectively analyzed BIVA and biochemical data from SIAD patients in two different Endocrinology Divisions in Northern Italy from November 2020 to December 2024. Inclusion criteria were a definitive SIAD diagnosis and concurrent BIVA and biochemical data. Exclusions included patients with hyponatremia from other causes, corrected s-Na after appropriate treatment, or unavailable BIVA data. BIVA confidence analysis allowed for the comparison of vector positions and hydration status across populations. Mean Biavector displacements were compared to the latest Italian reference data (Campa *et al*., 2023) using Hotelling's T^2 test.
Results
Fifty-nine patients (56% female, age 73 [63-78.5]) were analyzed, with 63% diagnosed with senile idiopathic SIAD. In the entire cohort, the s-Na corrected for glycemia was 129 [126-131.8] mmol/l, with a p-Osm of 265 [258-273] mOsm/Kg, u-Osm of 441.6 $\pm$ 142 mOsm/Kg, u-Na of 88.5 $\pm$ 42.2 mmol/l, and copeptin levels of 4.9 [2.9-7.2] pmol/l. BIVA confidence analysis revealed a significant Biavector displacement in both female and male patients ($P < 0.0001$). This was characterized by a lower phase angle (PhA), possibly due to the slightly older age compared to the reference population, and a shorter Biavector, confirming a pathological yet subclinical state of overhydration.
Conclusion
Our data highlight the potential utility of BIVA analysis as an inexpensive and time-efficient tool to support the challenging differential diagnosis of patients with preserved ECF hypotonic hyponatremia due to SIAD.

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P927

JOINT1195

Macular ganglion cell complex thickness and the post-illumination pupil response before and after chiasm decompression in pituitary adenoma patients with and without visual field loss

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Objective
Compression of retinal ganglion cell (RGC) axons in the optic chiasm of patients with pituitary adenoma can cause lasting visual impairment. It can also cause retrograde axonal degeneration, leading to significant thinning of the retinal macular ganglion cell complex (mGCC). Retinal thinning due to RGC damage may precede the detection of visual field defects (VFD). The aim of this study was to assess mGCC thickness and the post-illumination pupil response (PIPR) as indicators of structural and functional RGC health in patients with optic chiasm compression with and without VFD, and to determine the effect of transsphenoidal chiasm decompression.
Design
Prospective, observational study with preoperative and postoperative assessments in two predefined groups.
Methods
We studied 16 patients with a pituitary macroadenoma causing chiasm compression: eight with preoperative visual fields defects (VFD+ group) and eight without (VFD-group). Assessments took place preoperatively at baseline, and at 3 and past 12 months postoperatively. Retinal thickness was assessed with spectral domain optical coherence tomography (SD-OCT), and pupillometry was performed to determine the PIPR after blue light.
Results
At this time, we present preliminary data of the preoperative and first postoperative assessment at 3 months. Successful decompressive surgery was achieved in all but one patient. Preoperative mGCC thickness was significantly lower in the VFD+ group vs the VFD-group (nasal mGCC mean difference 40 µm, 95% CI 31–50 µm, $P < 0.001$), and all measurements in VFD+ patients were below the minimum thickness measured in VFD- patients. Postoperative assessment showed stable retinal thickness in both groups, regardless of visual improvement. PIPR results were variable with no significant between-group or pre-postoperative within-group differences, although several patients in both groups showed a PIPR decrease after surgery.
Conclusion
Our preliminary results show that VFD are related to significant mGCC thinning, and that thinning persists 3 months after decompressive surgery, suggesting residual retinal damage. Based on the available evidence, implementation of SD-OCT in the standard diagnostic work-up of patients with optic chiasm compression has the potential to provide valuable information for preoperative counselling and planning of surgical intervention. The role of pupillometry and the PIPR requires further exploration. Comprehensive analysis of follow-up data is pending.

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P928

JOINT2531

Complete remission of headaches in aggressive pitnets treated with pasireotide. correlation with systemic inflammation biomarkers (SIBs)

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Introduction
Aggressive PitNets, defined as rapidly growing and resistant to the standard treatment tumors, often present with severe headaches and require individualized multimodal treatment. Pasireotide exhibits antitumor properties and a unique analgesic effect in PitNets.
Objectives
To correlate headaches and SIBs in aggressive PitNets treated with pasireotide.
Methods
We analyzed data regarding the severity of the headaches (according to NRS scale) from 19 patients — 11 men and 8 women with different PitNets: 10 somatotropinomas (38.5%), four corticotropinomas (23.1%), two silent corticotropinomas (7.6%), two gonadotropinomas (7.6%), and one prolactinoma (3.8%) treated with pasireotide in correlation with SIBs.
Results
The average age on diagnosis was 45 years (min -13; max – 86). The maximum tumor diameter was 89 mm. 18/19 (95%) patients were treated pharmacologically before pasireotide implementation. All patients with acromegaly were previously treated with first-generation somatostatin analogs (SA). The patients treated surgically 14/19 were significantly younger than others (40 vs. 66 years), $p = 0.014$. 15/19 patients complained of headaches. The mean value on the NRS scale at baseline was 6,5 (max-10; min-2), while after the pasireotide was 0,7 (max-4; min-0). 100% of patients reported alleviation or disappearance of headaches (OR – 1.34; 95%CI (0.702-1.950), $p<0.001$). Furthermore, a correlation between baseline NRS and WBC was found (rho=0.478, $p=0.05$) Patients with acromegaly (acro) achieved higher PLT/lYMPH ratio values than others (nonacro) (187,2 vs 119,5), $P = 0.006$. Moreover, we observed a strong correlation between higher PLT/lYMPH ratio and higher GH and IGF-1 values (rho=0.736, $P = 0.01$ and rho=0.709, $P = 0.05$). Furthermore, we observed a strong correlation between baseline NRS and NEU/PLT ratio in nonacro group (rho=0.859, $P = 0.01$). In 15/19(79%) patients, the tumor dimensions stabilized or shrank; in 4 patients, the follow-up MRI has not yet been performed. 79% obtained biochemical control of the disease.
Conclusion
Pasireotide is a second-generation SA used in acromegaly and Cushing's disease. Nevertheless, it effectively achieves biochemical control in other PitNET subtypes and relieves headaches.
Keywords
Pasireotide, Aggressive PitNets, Acromegaly, Cushing syndrome, systemic inflammation biomarkers.

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P929

JOINT975

Hyponatremia in severe hypothyroidism ("the HYPO2 study")

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Background
Current guidelines recommend excluding hypothyroidism as a differential diagnosis for euvolemic hyponatremia[1]. However, there is a growing debate on hypothyroidism-induced hyponatremia, with poor evidence on its clinical significance. Especially data in severe hypothyroidism and myxedema is lacking.
Aim
To assess the prevalence of hyponatremia in patients with severe hypothyroidism and identify potential comorbidities associated with its development.
Design and Methods
Retrospective observational study, conducted at the University Hospital of Basel in Switzerland. Data were collected over a 10-year period (01/2014-11/2024) from in-and outpatients, who presented with free thyroxine (fT4) levels $<$8pmol/l with and without the diagnosis of myxedema, as documented in patients' chart.
Results
A total of 820 cases were analyzed, showing a mean sodium level of 138 ± 5 mmol/l, TSH level of 56 ± 62 mU/l and fT4 level of 5 ± 2 pmol/l. The prevalence of hyponatremia in the cohort was 19% ($n = 155$). No significant association was found between fT4 and sodium levels. Within this cohort, severe hypothyroidism, clinically defined by the treating physician, was identified in 45 cases (76% female, mean age of 63 ± 15 years), including 12 cases of myxedema. The prevalence of hyponatremia in this subgroup was 22%, which was comparable to the overall cohort ($P = 0.7$). Further characterization of the hyponatremic population showed a higher frequency of comorbidities compared to the normonatremic group, including malignancy (30% vs 9%), cardiovascular disease (60% vs 43%), heart failure (20% vs.14%), infectious disease (40% vs. 20%) and kidney disease (30% vs. 43%). Presence of malignancy was a significant predictor of lower sodium levels (-5mmol/l, $P = 0.04$), while no significant correlation was found between fT4 levels and sodium levels ($P = 0.6$) or development of hyponatremia ($P = 0.9$). Also, the mortality rate within index hospitalization was higher in the hyponatremic group compared to the normonatremic group (20% vs 6%).
Conclusion
Our analysis suggests that the prevalence of hyponatremia in severe hypothyroidism is comparable to the general hospitalized population, which is estimated to be around 20%[2]. Hyponatremia in our cohort cannot solely be explained by the presence of severe hypothyroidism. Instead, presence of comorbidities such as malignancy seem to play a major role in the development of hyponatremia in severe hypothyroidism.
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P930

JOINT1038

Effects of dulaglutide on oxytocin plasma levels in healthy men: a secondary analysis of a randomized, double-blind, placebo-controlled crossover study

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Background
In animal studies, systemic and central injections of GLP-1 were found to increase plasma oxytocin concentrations. Additionally, recent rodent research revealed that 70% of GLP-1 receptor-positive neurons in the paraventricular nucleus also expressed oxytocin receptors. When oxytocin and GLP-1 were co-administered systemically, there was a significant increase in action potential firing in oxytocin-receptor-positive neurons in the paraventricular nucleus. Based on these findings, considering the functional and anatomical proximity as well as the synergistic effects, we hypothesized that dulaglutide may modulate and increase oxytocin plasma levels in humans.
Methods
This is a secondary analysis of a randomized, double-blind, placebo-controlled crossover trial of healthy eugonadal men, age 18-50 years with active and satisfactory sex lives that examined the effect of the GLP-1 RA dulaglutide on sexual desire as a primary endpoint. Participants were randomly assigned (1:1) to receive either dulaglutide or placebo for four weeks. Oxytocin plasma levels were measured repetitively in a standardized manner, with three samples taken every 15 minutes at baseline and at the evaluation visit. We used the mean of these three measurements for our analysis. Changes within individuals were then compared after four weeks of treatment with the GLP-1 receptor agonist dulaglutide vs placebo using paired *t*-tests.
Findings
The median [IQR] age of participants at inclusion was 24.5 [21.0, 29.0] years, and the median BMI was 23.85 [22.15, 25.00]. Mean (SD) oxytocin baseline levels were comparable between groups: 50.6 pq/ml (17.0) in the treatment group and 50.5 pq/ml (18.2) in the placebo group. After 4 weeks of treatment with dulaglutide and placebo oxytocin concentrations remained stable and were 53.2 pq/ml (12.7) and 50.5 pq/ml (17.8), respectively. Mean (SD) change from baseline in oxytocin concentrations was + 2.6 pq/ml (21) in the treatment group and 0.0 pq/ml (19.4) in the placebo group. The estimated difference between the two treatment was: 2.58 [95% CI −12.9, 18.4].
Interpretation
Our study found no significant change in oxytocin plasma levels following a four-week treatment with dulaglutide vs placebo. Differences in results compared to animal data may be due to lower dosing, central vs peripheral administration, choice of GLP-1 RA, or acute vs chronic use. In addition, whether the results would be different in women or in people with obesity/diabetes mellitus, where altered GLP-1 metabolism is expected, needs to be investigated in future studies.
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P931

JOINT2074

Disrupted ACTH and cortisol response to osmotic and non-osmotic stress in patients with AVP-deficiency

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Background
Arginine vasopressin is synthesized in the magnocellular neurons of the hypothalamic supraoptic (SON) and paraventricular nuclei (PVN) and stored in the posterior pituitary. It is released into the bloodstream in response to increased osmolality or non-osmotic stimuli such as hypovolemia or stress. During stress, specialized PVN neurons co-release corticotropin-releasing hormone (CRH) and AVP. AVP amplifies CRH-induced adrenocorticotropic hormone (ACTH) secretion. Elevated cortisol or AVP levels exert negative feedback on the hypothalamus and pituitary to regulate CRH and ACTH secretion. However, disruptions in the AVP system can impair this feedback mechanism, resulting in sustained cortisol elevations.
Methods
This is a secondary analysis of a prospective study conducted at seven tertiary medical centers in Europe and Brazil (2018 to 2022), that utilised the hypertonic saline and the arginine infusion for the diagnostic evaluation of patients presenting with polyuria-polydipsia syndrome. ACTH and cortisol were measured at baseline and expected peak for hypertonic saline and arginine stimulation in patients with AVP-Deficiency and primary polydipsia (i.e., clinical controls). The primary objective was to investigate the effect of hypertonic saline and arginine on the HPA axis response between both groups. The ACTH and cortisol differences were compared between groups using a linear mixed effects model and between the stimulation tests using linear regression model.

Findings
This analysis included 20 patients with AVP-Deficiency and 10 clinical controls. Upon arginine (non-osmotic stress), patients with AVP-Deficiency showed a greater increase in plasma ACTH (difference: -9.2 ng/l [95% CI -17 to -1.8]) and plasma cortisol (difference: -141 nmol/l [95% CI -242 to -40]) comparted to clinical controls. Upon hypertonic saline (osmotic stress), the change in plasma ACTH was similar between patients with AVP-Deficiency and clinical controls (difference: -0.31 ng/l [95% CI -11 to 10]), while the increase in plasma cortisol was greater in patients with AVP-Deficiency compared to clinical controls (difference: -78 nmol/l [95% CI -188 to 32]). Independent of the type of stimulation, patients with AVP deficiency exhibited a significantly greater increase in plasma ACTH (-7.0 ng/l [95% CI -13.3 to -0.8], $P = 0.04$) and plasma cortisol (-106 nmol/l [95% CI -188 to -24], $P = 0.02$) compared to clinical controls, with no significant effects between stimulation type and ACTH ($P = 0.36$) or cortisol response ($P = 0.09$).
Interpretation
This study demonstrates an altered sustained ACTH and cortisol response pattern to non-osmotic and osmotic stress in patients with AVP-Deficiency, indicating impaired regulation of the HPA axis.

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P932

JOINT2285

Long-term outcomes of gonadotropin-releasing hormone analogue-treated obese girls with central precocious puberty

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Background
Both central precocious puberty (CPP) and obesity cause advanced bone maturation and accelerated growth. Gonadotropin-releasing hormone analogue (GnRHa) is the standard treatment for preserving final height (FH) potential in girls with CPP. It is unclear whether GnRHa-treated obese girls with CPP achieve less favorable FH outcomes as compared with non-obese girls.
Objective
To study long-term outcomes of obese girls with idiopathic CPP (iCPP) who were treated with GnRHa in comparison with those with normal weight.
Methods
Medical records of 233 obese and 334 normal-weight girls with iCPP who had been treated with either monthly or 3-monthly leuprolide or triptorelin acetate, and attained FH at Ramathibodi Hospital, Thailand, between 2007 and 2024 were reviewed. Long-term outcomes of GnRHa treatment, focusing on FH, height gain (FH – pre-treatment predicted adult height), time to menarche after GnRHa discontinuation and body mass index (BMI) were collected and compared between obese and normal-weight iCPP girls.
Results
Medians (IQRs) age at diagnosis of obese and normal-weight iCPP girls were 7.5 (7.0, 7.8) and 7.5 (7.1, 7.8) years, respectively ($p=0.304$). Mid-parental height (MPH) was not different between both groups. At diagnosis, obese girls with iCPP were taller (height SDS: 1.53 (0.70, 2.20) vs. 0.85 (0.18, 1.43), $p<0.001$) and had more bone age (BA) advancement (2.5 (1.8, 3.2) vs. 1.9 (1.1, 2.6) years, $p<0.001$). GnRHa treatment was started and discontinued at 8.3 (7.8, 8.7) and 11.5 (10.7, 12.1), and 8.2 (7.8, 8.8) and 11.7 (11.0, 12.5) years of age in obese and normal-weight girls, respectively. BA at treatment discontinuation was not different between groups. Compared with normal-weight girls, obese girls had greater height gain (8.6 (5.9, 11.8) vs. 7.4 (4.7, 10.4) cm, $p=0.012$), and FH SDS (0.42 (-0.24, 0.99) vs. 0.15 (-0.40, 0.69), $p=0.002$). Duration from GnRHa discontinuation to menarche of obese girls was less than that of normal-weight girls (12.0 (8.4, 18.0) vs. 14.4 (9.6, 20.4) months, $p=0.012$). BMI SDSs at FH were significantly lower than those at diagnosis in both groups (obese: 1.17 (0.53, 2.07) vs. 1.77 (1.31, 2.59), $p<0.001$, normal-weight: -0.32 (-0.96, 0.30) vs. 0.21 (-0.38, 0.61), $p<0.001$).
Conclusions
Despite having greater BA advancement at diagnosis, obese girls achieved greater height gain and FH than normal-weight girls who had comparable MPH, suggesting greater height at diagnosis might compensate for FH attainment. Menstruation began earlier in obese girls following GnRHa discontinuation. BMI SDSs decreased from diagnosis to FH in both groups.

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P933

JOINT675

Early prolactin normalization and tumor shrinkage predict the first-year response to cabergoline treatment in invasive macro-giant prolactinomas

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Introduction
Invasive macroprolactinomas respond less favorably to dopamine agonist (DA) therapy compared to non-invasive macroadenomas and microadenomas. Understanding the frequency of a good response (GR) —defined as prolactin (PRL) normalization and $\geq$50% tumor volume reduction—and its predictors may aid timely clinical decision-making. Therefore, the current study focused on assessing GR frequency at the first-year follow-up and determining predictive factors of this response in patients with invasive macro-giant prolactinomas.
Methods
This retrospective cohort study included 38 patients (32 males, 6 females; mean age 41.9$\pm$12.8 years) with invasive macro-giant prolactinomas (baseline median PRL: 2530 (1726–5451) ng/mL, mean longest tumor diameter: 36.4$\pm$12.8 mm) who were followed for at least one year under cabergoline therapy. PRL levels and tumor volume changes were analyzed at early and late follow-ups. Patients were classified as good responders (GRs) or poor responders (PRs) based on their first-year outcomes.
Results
At the first-year visit, 17 patients (44.7%) achieved a GR. Baseline parameters such as presenting symptoms and signs, hormonal studies, tumor invasion characteristics, and KNOSP scores were comparable between groups, but GRs had significantly higher normoprolactinemia rates (70.6% vs. 23.8%,$P = 0.004$) and greater tumor shrinkage (57.3$\pm$15.6% vs. 41.9$\pm$21.9%,$P = 0.02$) at 3–6 months evaluations. In the multivariate logistic regression analysis, the best-reduced model to predict GR in the first year included tumor shrinkage percentages (aOR:1.06 (95% CI: 1.01-1.12), $P = 0.023$) and nadir PRL levels (aOR:0.97 (95% CI: 0.94-0.99), $P = 0.019$) at 3-6 months. ROC analyses revealed that an early tumor shrinkage cut-off rate of 44.9% (88% sensitivity, 62% specificity) and an early PRL cut-off level of 30 ng/mL (75% sensitivity, 77% specificity) were identified as effective follow-up parameters to predict GR in the first-year. The median available follow-up duration for the patients was 23.5 (17.0-48.0) months. All GRs maintained PRL normalization and $\geq$50% tumor volume reduction, while 33.3% and 42.9% of PRs failed to meet these goals, respectively, at the last visit ($P = 0.009$, $P = 0.002$). Three of the PRs required surgery during follow-up.
Conclusion
Approximately half of invasive macroprolactinoma patients achieved the composite goal within one year of cabergoline therapy. Early follow-up studies, rather than baseline characteristics, are strong predictors of treatment success. In the early assessments at 3-6 months of these symptomatic invasive tumors under cabergoline treatment, cases with PRL levels of 30 ng/mL or lower, or tumor shrinkage of 45% or more, are highly unlikely to require surgery in the first year or subsequent visits.

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P934

JOINT556

Early life exposure to antibiotics and precocious puberty in children: a nationwide population-based cohort study

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Background
Antibiotics exposure in early life may have association with central precocious puberty (CPP), but evidence is limited. This study explored the association of

antibiotics exposure with CPP using nationwide population-based cohort in South Korea.
Methods
Children who had regular health check-up at 4–6 months and 66–71 months of age were included and followed up until 10 years in boys and 9 years in girls. The diagnosis of CPP was based on the ICD-10 code and the prescription of gonadotropin-releasing hormone agonists. Multivariable Cox proportional hazards model was used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (Cis) for CPP according to age at first prescription of antibiotics and the number of antibiotic classes, respectively.
Results
Among 322,731 children (135,232 boys and 187,499 girls), 291,703 (90.4%) were prescribed antibiotics before 1 year of age. Compared with those prescribed antibiotics after first year of life, girls who received antibiotics before 3 months of age had an increased risk of CPP (aHR 1.231 [95% CI 1.119–1.355], $P < 0.001$), followed by those prescribed antibiotics at 6–9 months (aHR 1.205 [95% CI 1.098–1.322], $P < 0.001$), 3–6 months (aHR 1.169 [95% CI 1064–1.284], $P = 0.001$), and 9–12 months (aHR 1.146 [95% CI 1.042–1.261], $P = 0.005$) after adjusting for covariates. Furthermore, girls who used 5 or more classes or antibiotics had a higher risk of CPP compared to those who used 2 or less classes. However, in boys, no significant association was observed between age at first prescription or the number of antibiotic classes and CPP.
Conclusions
Exposure to antibiotics in early life and many numbers of antibiotics may be associated with a higher risk of CPP in girls. The effects of long-term antibiotics exposure on pubertal development and underlying should be further investigated.
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P935

JOINT1131

Exosomal miRNA expression profiles and pathway enrichment analysis in girls with central precocious puberty and premature thelarche

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Context
Central precocious puberty (CPP) is rapidly increasing in prevalence among girls, with most cases being idiopathic. Exaggerated thelarche (ET) and premature thelarche (PT) are variants of early puberty that can be difficult to distinguish from CPP in initial clinical evaluations. Exosomal microRNAs are stable biomarkers capable of crossing the blood-brain barrier. However, human studies on miRNAs in CPP and related conditions remain limited.
Objective
To identify distinct exosomal miRNA profiles in girls with CPP, ET, and PT, and explore the target genes and pathways involved in pubertal development.
Methods
This cross-sectional study included 27 girls aged 6-8 years, categorized into CPP, ET, PT, and control groups. Serum exosomal miRNAs were sequenced, differentially expressed miRNAs (DEmiRNAs) were analyzed, target genes were predicted, and pathway enrichment analysis was performed.
Results
Distinct exosomal miRNA patterns were observed among CPP, ET, and control groups, identifying 307 DEmiRNAs. The PT group showed a distinct miRNA expression from the control group but not show clear separation from the CPP or ET groups. Enriched pathways included AGE-RAGE, MAPK, and mTOR signaling, with group-specific enrichment observed in Hippo and neurotrophin signaling pathways.
Conclusions
This study identifies distinct serum exosomal miRNA patterns in CPP, ET, and PT groups. The enrichment of the AGE-RAGE pathway suggests a potential link to dietary habits. Serum exosomal miRNAs may serve as biomarkers or therapeutic targets, providing insights into environmental factors influencing early puberty.
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P936

JOINT3062

Optimizing laboratory defined macroprolactin algorithm for follow-up patients

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Introduction
Macroprolactinaemia is a well-known analytical problem in the diagnostics of hyperprolactinaemia, usually detected with the polyethylene glycol (PEG) precipitation method. Due to the lack of harmonization in macroprolactin detection and reporting results, this study proposes and evaluates the usefulness of an in-house-developed algorithm. This study aimed to assess whether repeating the PEG precipitation resulted in any difference in recovery and explore the potential for rationalizing the precipitation procedure.
Materials and Method
This is a retrospective study based on extracted data for 547 follow-up patients, of which 453 (83%) were women and 94 (17%) were men. All patients with prolactin concentration above the upper reference limit defined by the manufacturer (women: 23.3 µg/l; men: 15.2 µg/l) were included in the study according to the in-house algorithm. Prolactin concentrations were measured before and after PEG precipitation on the Roche cobas e801 analyser (Roche Diagnostics GmbH, Mannheim, Germany) using the Elecsys Prolactin II sandwich electrochemiluminescence immunoassay. Macroprolactinaemia was defined based on the percentage recovery of prolactin (%Recovery), calculated using the total prolactin (PRL) and the post-PEG prolactin concentration (%Recovery = 100 x PRL/post-PEG prolactin). The normality of data distribution was tested with the D'Agostino-Pearson test. The Wilcoxon rank-sum test was employed to determine the difference between the recoveries of repeated measurements. %Recovery data and the interval between repeated measurements were expressed as median and interquartile range.
Results
%Recovery for the total prolactin concentration was 84 (75-87) %, which was nearly identical to the repeated measurement at 84 (75-88) %. Analysis of the %Recovery data from repeated measurements in follow-up patients ($n = 547$) showed no significant difference ($P = 0.247$). The median interval between repeated measurements was 2.1 (1.2-3.1) years.
Conclusion
Our results demonstrated no statistically significant difference in recovery values between repeated measurements, indicating that the PEG precipitation protocol could be simplified by prolonging the follow-up period. Although the exact pathogenesis of macroprolactinaemia remains unknown, it is regarded as a benign and long-lasting condition consistent with this study's findings.
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P937

JOINT2940

Discrepancy between central and peripheral ACTH response to desmopressin stimulation: two cases

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Introduction
Desmopressin stimulation testing (DST) is increasingly used in the differential diagnosis between central and ectopic ACTH-dependent hypercortisolism since CRH became unavailable. Herein, we report two patients with Cushing's disease (CD) and negative DST (10 µg IV) (defined as <50% and <20% increase of ACTH and cortisol levels, respectively) but with positive petrosal sinus ACTH response to desmopressin administration.
Case Presentation
Case 1: A 47-year-old Greek woman, with 1-year history of dyslipidaemia and hypertension, was investigated for Cushingoid phenotype (central obesity, moon face, facial plethora, hirsutism, buffalo hump and supraclavicular fat pads). Hormonal work-up revealed ACTH-dependent hypercortisolism [late night serum cortisol 308 nmol/l (NR <208), 1-mg overnight dexamethasone suppression 286 nmol/l (NR <50), 24h urine free cortisol 724 nmol (NR 11.8-485.6), ACTH 51

pg/ml]. DST led to 45% and 14% rise in peripheral ACTH and cortisol levels, respectively. Pituitary MRI revealed a 3 mm lesion. Due to its size, inferior petrosal sinus sampling (IPSS) was performed. Central-to-peripheral ACTH gradient, before and after IV desmopressin, was indicative of CD. Desmopressin administration led to 593% increase of petrosal sinus ACTH levels compared to 27.4% increase of peripheral ACTH levels. Transsphenoidal adenomectomy resulted in Cushing's remission. Case 2: A 22-year-old Greek woman was investigated for hypercortisolism due to 1-year history of fatigue, muscle weakness, substantial weight gain, hirsutism, easy bruising, round face and abdominal striae. Hormonal evaluation was indicative of ACTH-dependent hypercortisolism [1-mg overnight dexamethasone suppression 13.1 μg/dl (NR < 1.8), 24h urine free cortisol 317 μg (NR 20.9-292.3), ACTH 47 pg/ml]. DST was negative (8.97% and 16.90% increase in peripheral ACTH and cortisol levels, respectively). Pituitary MRI revealed a 4 mm central microadenoma. IPSS with IV desmopressin identified pituitary origin of ACTH excess. Desmopressin administration led to 400% and 46% increase of petrosal sinus and peripheral ACTH levels, respectively. The patient is currently awaiting transsphenoidal surgery.

Discussion

To our knowledge, only four other patients unresponsive to DST but with positive central ACTH response in IPSS after desmopressin administration, as in our cases, have been described. The discrepancy between central and peripheral ACTH levels after desmopressin administration may be attributed to different sampling intervals between DST and IPSS or cyclic hypercortisolism. Short and transient increase in ACTH secretion after desmopressin, detected in the petrosal sinus but not significantly affecting ACTH peripheral levels may also contribute. Our cases highlight that desmopressin administration during IPSS is useful even in patients with negative desmopressin stimulation testing.

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P938

JOINT3399

Medium-term effects of surgical therapy vs. medical treatment in patients with remission of cushing's disease

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Cushing's disease (CD) is associated with high morbidity and mortality if not adequately treated. The first-line therapy is transsphenoidal surgery (TSS), where indicated, followed by medical therapy and/or radiotherapy and/or bilateral adrenalectomy based on clinical context. The aim of this study was to evaluate any differences in anthropometric, clinical, hormonal, and metabolic parameters, including CD-related comorbidities, between patients who achieve remission after surgical therapy (group S) and those who achieve it through medical therapy (group P), also stratifying them by sex.

Methods

We retrospectively assessed 47 patients with CD (37 women), all treated with TSS except for 2, followed at the Endocrinology Unit of the AOU of Messina from 2014 to 2024; of these, 33 achieved remission after surgery (27 women) and 14 after medical therapy (10 women). Parameters were evaluated before surgery and/or medical therapy (T0) and one year after disease remission achieved through surgery or medical therapy (T1).

Results

At T1, patients in group S compared to T0 showed a significant reduction in waist circumference (WC), transaminase levels, glycated hemoglobin, serum cortisol, urinary free cortisol (UFC), ACTH, DHEAS, an improvement in cardiovascular comorbidities, and a higher incidence of central hypothyroidism. In contrast, patients in group P, compared to T0, showed significant reductions in ACTH, serum cortisol, and DHEAS without significant differences in terms of comorbidities. When comparing the two groups at T1, patients in group S had significantly lower values of WC, triglycerides, and serum cortisol and a significantly reduced prevalence of striae rubrae, easy bruising, hypertension, and cardiomyopathy, compared to patients in group P. After stratification by sex, at T1: males (M) in group S showed lower total and LDL cholesterol values and a higher incidence of hypogonadism and GHD compared to females (F); in group P, males had a higher incidence of cardiomyopathy, hypogonadism, and diabetes compared to females.

Conclusion

One year after remission of CD, patients in surgical remission showed a significant improvement in some typical disease signs and cardiometabolic profile compared to the pharmacological remission group. Additionally, after stratification by sex, in the pharmacological remission group, M showed a poorer cardiometabolic profile than F.

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P939

JOINT2646

Effect of bone age at GnRH agonist treatment cessation on near adult height in korean girls with central precocious puberty

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Introduction

In treatment of central precocious puberty (CPP) girls, existing literatures suggest that stopping treatment around a bone age (BA) of 12 years may result in the most favorable adult height, but there are few real-world studies that compare the effects of BA at the time of treatment cessation on final adult height. Therefore, we investigated whether the differences of BA at treatment cessation significantly influence near adult height (NAH).

Methods

A retrospective study was conducted on 117 CPP girls treated with GnRH agonists. Patients were followed up until their BA was 13 years or older after treatment cessation. Predicted adult height (PAH) at treatment initiation and NAH at the last visit were calculated using the Bayley-Pinneau method. This study compared growth outcomes across three groups classified by BA at treatment cessation ('11.5 year', '12 year', '≥12.5 year') and assessed correlations between several clinical factors and NAH outcomes.

Results

Mean chronological age (CA) at treatment initiation was 8.4 years, and mean BA at treatment initiation was 10.1 years. Differences between BA and CA (BA-CA) at treatment initiation were 1.37 year in the 11.5 year group, 1.78 year in the 12 year group, and 2.05 year in the ≥12.5 year group ($p<0.001$). Predicted adult height (PAH) at treatment initiation were 159.16 cm, 160.03 cm, and 156.82 cm, respectively ($p<0.05$). NAH of each group were 163.89 cm, 164.64 cm, and 163.28 cm, respectively ($p=0.423$), and differences between PAH at treatment initiation and NAH (NAH-PAH) were 4.73 cm, 4.61 cm, and 6.46 cm, respectively ($p<0.05$). Multivariate regression analysis showed significant positive associations of NAH with MPH, height SDS at treatment initiation and cessation, and negative association with the difference between BA and CA at treatment cessation.

Conclusion

Our findings suggest that even patients with markedly advanced BA at the start of treatment could achieve comparable NAH if the treatment duration is sufficiently prolonged. So individualized treatment plans considering BA advancement and height at the end of treatment are essential for the best growth outcomes in CPP patients.

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P940

JOINT2541

Neurofibromatosis type 1 in the eyes of an endocrinologist - a disease requiring a coordinated care

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We performed the retrospective analysis of 66 pediatric patients with NF1 hospitalized at the University Clinical Hospital in Wrocław in 2018-2024. The aim of the study was to assess the scale of endocrine problems in the analyzed group of patients. 22 patients (33.33%) were hospitalized in the Department of Pediatrics, Endocrinology, Diabetology and Metabolic Diseases. These children were referred to the Clinic due to: short stature (8/22 patients - 36.36%), premature puberty (5/22 patients - 22.72%), rapid progression of puberty, primary amenorrhea and body weight deficiency, hyponatremia, hypernatremia, hypothyroidism, hypertension, obesity, as well as due to routine endocrinological assessment due to the underlying disease (2 patients - 9.09%). Hormonal disorders requiring treatment were found in 6/22 children (27.27%). GnRH-

dependent precocious puberty was diagnosed in 5 of them, whereas multi-hormonal hypopituitarism and diabetes insipidus in one patient. In all patients with GnRH-dependent precocious puberty, CNS magnetic resonance imaging revealed pathological NF1 changes, including those affecting the optic pathway and the hypothalamic and pituitary region. Patients were included in the triptorelin treatment program at the average age of 7 years and constituted 4.5% of all patients remaining in the program in the studied years. Two boys came to the Clinic for the first time with advanced puberty (Tanner scale: 3/4 and 4 degrees), considered too progressed to achieve optimal efficacy of triptorelin therapy. Both of them presented clinical symptoms of NF1 from early childhood that allowed for the earlier diagnosis of NF1. Unfortunately, early signs of puberty were missed in both boys, leading to short stature as a consequence of delayed treatment.

Conclusion

1. The analysis confirms the multidisciplinary nature of neurofibromatosis type 1, which requires vigilance and care from many specialists.
2. The most common endocrine disorder in children with NF1 is GnRH-dependent precocious puberty caused by nodular lesions affecting the optic pathway and the hypothalamus. Therefore, a group of patients with CNS lesions in these areas should also remain under constant care of an endocrinologist.
3. The basic, underestimated and often overlooked tools for monitoring the proper development of each patient (including a patient with NF1) are: the Tanner scale (for assessing the puberty status) and percentile charts (for observing the growth pattern).

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P941

JOINT455

Galactorrhea and headache in an 18-year-old transfeminine youth: a case report

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An 18-year-old transfeminine youth presented with galactorrhea for two months, accompanied by intermittent headaches but no other neurological symptoms.

Medical History

The patient was diagnosed with HIV at 15 years of age and has been on antiretroviral therapy (atazanavir, ritonavir, abacavir/lamivudine). Laboratory results revealed a CD4 count of 654 cells/μL, CD4 percentage of 27%, and undetectable HIV viral load. She has a history of PTSD due to sexual assault and MDD, managed with escitalopram (10 mg/day) and trazodone (50 mg/day as needed).

Gender-Affirming Hormone History

At age 11, the patient began self-prescribing oral contraceptives (ethinyl estradiol 0.035 mg and cyproterone acetate 2 mg) based on a friend's suggestion, using them inconsistently due to breast pain and financial limitations. Later, she purchased 17β-estradiol and cyproterone acetate online, following advice from a senior acquaintance, and intermittently used intramuscular hormones advertised online, including estradiol benzoate (3 mg) and progesterone (50 mg). She also performed regular self-breast massages for augmentation.

Clinical Findings

Physical examination showed bilateral breast engorgement and galactorrhea, with normal neurological findings. Laboratory results indicated elevated prolactin (261.5 ng/mL), estradiol (167.8 pg/mL), and low testosterone (0.429 nmol/l), with normal thyroid function. MRI revealed a pituitary microadenoma (3.5 × 2.7 × 2.6 mm) with a small cystic component.

Clinical Course

The patient was advised to discontinue injectable hormones, reduce estrogen doses, and stop breast massage. Despite this, she attended follow-ups irregularly and continued self-prescribed gender-affirming hormone therapy and breast massage against medical advice. Over time, her galactorrhea improved, with prolactin levels decreasing to 83.8 ng/mL at six months and normalizing after two years. Her headaches also resolved.

Conclusion

This case highlights the risks of self-prescribed hormone use in transfeminine youth, emphasizing the need for medical supervision to prevent endocrine complications. Accessible care and regular follow-up are crucial for safer outcomes.

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P942

JOINT1971

Temperament, character, and quality of life in patients with acromegaly: factors affecting psychosocial processes

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Objective

This study aimed to evaluate the character and temperament dimensions in acromegaly patients, and to examine the effects of the disease and the treatments on depression, anxiety, and quality of life (QOL).

Methods

77 acromegaly patients (41 women, 36 men) who were followed up in pituitary center and came for a check-up between 2023-2024 were included in the study. The patients filled out the Acroqol, Temperament and character inventory-revised (TCI-R), Hospital Anxiety and Depression scale. The patients' age, gender, IGF-1 values, comorbidities and treatments were recorded.

Results

There was a positive correlation between age and anxiety scores ($r = +0.228$, $P = 0.046$), and in addition, higher anxiety levels were shown in female patients compared to male patients (7.8 ± 4.3 vs. 5.4 ± 3.6, $P = 0.01$) and in patients who underwent surgery compared to those who did not (7.1 ± 4.2 vs. 3.8 ± 3.1, $P = 0.023$). Depression scores were higher in patients who underwent pituitary surgery compared to those who did not (7.3 ± 4.3 vs. 3.7 ± 3.4, $P = 0.017$). We also showed that QOL was negatively affected in female patients (53.3 ± 22.3 vs. 66.4 ± 22.8, $P = 0.013$), and in those underwent transsphenoidal surgery (56.2 ± 22.5 vs. 81.4 ± 17.9, $P = 0.002$), or radiotherapy (32.9 [30.1–63.1] vs. 65.9 [42.1–80.6], $P = 0.021$). Furthermore, QoL was also decreased with increasing disease duration ($r = -0.248$, $P = 0.030$). Personality dimensions based on TCI scores showed differences according the size of pituitary adenoma at initial presentation and presence of hypopituitarism. Patients with macroadenoma ($n = 50$) had higher novelty seeking (NS) (112 [103.5–120.2] vs. 104.5 [96–112.2], $P = 0.049$) and perseverance (PS) (118 [105.7–126.2] vs. 107 [97.2–118.2], $P = 0.031$). Patients with hypopituitarism of any type ($n = 16$) had lower PS scores (114 [103–123] vs. 116 [98–123.5], $P = 0.013$) compared to those who had not.

Conclusions

The results revealed gender and pituitary-directed therapies might influence general psychological health and QoL of patients with acromegaly. It was also found that disease-related features such as adenoma size and hypopituitarism migh affect personality profile.

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P943

JOINT1545

Septo-optic dysplasia: clinical phenotype and impact on the child and family

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Objectives

To describe the clinical phenotype and impacts on child quality of life (QOL) and family function in children with septo-optic dysplasia (SOD).

Methods

Children with SOD, aged 0-17 years, who attended a single tertiary centre and their parents/carers, participated. A combination of parental surveys describing antenatal history, child medical history, health system utilisation, and validated questionnaires to assess impact on the child and family—KIDSCREEN-27, McMaster family assessment device (FAD), Fatigue Severity Score (FSS) and PedsEyeQ—were completed, with child responses to the KIDSCREEN-27 and PedsEyeQ where appropriate. Comparison for maternal findings was with data from the Western Australian (WA) Midwives Notification System (MNS), and for validated questionnaires with other studies.

Comparisons of cohort maternal features to the general population.

	SOD	Comparison	*P*-value	Reference
Mean BMI	23.2 ± 3.9 (n = 26)	26.3 ± 5.7 (n = 392,306)	0.005	MNS
Low or normal BMI	20/26 (76.9%)	191,568/392,306 (48.8%)	0.004	MNS
Inadequate pregnancy weight gain	14/27 (51.8%)	141/664 (21.2%)	<0.001	Queensland 2011

MNS data from 2006-2023.

Results

Consent was received for 47 children, and 45 surveys (16 females, mean age 10.3 years) were available for analysis. Approximately half (24/45) had pituitary dysfunction or developmental delay (22/45) and 14/45 had neither. Speech and language, social/emotional delay, learning delay and intellectual disability were seen more frequently in those with hypopituitarism than those without ($P < 0.05$). Feeding difficulties were reported in 8/25 term neonates, 5 requiring nasogastric feeding. Mean maternal BMI was lower than the WA population (23.2 vs 26.3, $P = 0.005$). 51.8% of mothers had less antenatal weight gain than recommended, more than double the general population (21.2%, $P < 0.001$). Children saw a mean of 3.4 medical specialties and 2.0 allied health disciplines, with 31/37 travelling at least 20km to attend. KIDSCREEN-27, McMasters FAD and FSS scores were similar to comparison groups in other studies while PedsEyeQ functional vision quality of life scores were lower.

Conclusion

SOD is a heterogenous condition, and mothers may have suboptimal antenatal weight gain and lower maternal BMI compared to the general population. Neonatal feeding difficulties were common, with nasogastric feeding often required. As expected, vision related QOL was reduced in individuals with SOD. Despite the complexity of symptoms, this study did not discern a difference in health-related quality of life scores using KIDSCREEN compared with general population norms. Additional studies assessing maternal weight status, neonatal feeding challenges and quality of life are required to further delineate their involvement in SOD.

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P944

JOINT1274

Impact of gender-affirming hormone therapy on cardiovascular function: a cross-sectional study

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Background

Cardiac parameters and cardiovascular risk (CVR) differ between sexes. Numerous studies have reported an increased CVR among adult transgender individuals, attributed to the metabolic changes associated with gender-affirming hormone therapy (GAHT) and lifestyle factors. However, the impact of GAHT on CV function remains poorly understood, especially if started during adolescence.

Methods

Echocardiographic evaluation was performed in 47 trans men (TM) and 6 trans women (TW), undergoing GAHT since 5-10 years. Assessments included diastolic and systolic cardiac function, cardiac and aortic diameters, and aortic stiffness index (SI). Additionally, CVR factors (such as glucose and lipid profiles, obesity, smoking and drinking habits, and hypertension) were analysed.

Results

Mean GAHT duration was 6.5 (±1.6SD) years in TM and 7.6 (±1.7SD) years in TW, median age was 23.4 (IQR 2.2) and 25.3 (IQR 2.7) years, respectively. Gonadal hormone suppression was obtained with progestins (TM) and cyproterone acetate (TW) in all but one individual per group (who received gonadotropin-releasing hormone agonist). Diastolic dysfunction grade 2 was diagnosed in one TM, while systolic function was normal in all individuals. A mildly dilated left ventricle (LV), after correction for body surface area (BSA), was observed in 6 TM when categorized by the experienced gender (EG), but only in 3 when categorized by the sex registered at birth (SRAB). LV mass/BSA mildly increased in 7 TM when categorized by SRAB, in none when categorized by EG. No correlation between LV mass/BSA and GAHT duration was found. Aortic diameters Z-scores where aligned more with EG than with SRAB in both groups. SI was 5.2 ± 2.3 SD in TM and 5.9 ± 1.9 SD in TW, (reference values 2.65 ± 0.55). Multiple regression analysis was conducted in TM, but not in TW due the small sample size, and showed a positive association only between SI and BMI (P-value = 0.02).

Conclusions

GAHT for more than 5 years induces a shift in cardiac parameters towards the EG. SI is significantly increased in both TM and TW undergoing GAHT, representing an independent risk factor for CV disease and highlighting the need for careful long-term follow-up.

Key-words

GAHT, cardiovascular, aortic stiffness, echocardiography.

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P945

JOINT1738

CAm^{2}029 octreotide subcutaneous depot provides stable control of IGF-I and improves key symptoms throughout a 4-week post-dose interval: analysis from the ACROINNOVA 1 trial

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Background

Standard-of-care medical therapies (injectable somatostatin receptor ligands) aim to control the excess insulin-like growth factor-I (IGF-I) levels characteristic of acromegaly. Symptom control is also key. However, increased symptoms towards the end of dosing intervals are reported by some patients, possibly indicating waning biochemical control. Designed for self-administration by injection, CAm^{2}029 is a novel subcutaneous octreotide depot with a prolonged-release, long-acting formula developed using FluidCrystal® technology. The efficacy of CAm^{2}029 was evaluated in ACROINNOVA 1, a 24-week, Phase 3 trial (NCT04076462). Superior IGF-I control (IGF-I ≤upper limit of normal [ULN]) vs placebo (72.2% vs 37.5%; $P = 0.0018$) and symptom control were demonstrated in patients previously controlled. We report further analyses in patients receiving CAm^{2}029, evaluating IGF-I and symptom control over a 4-week interval from administration of the final CAm^{2}029 dose.

Table Patients with symptoms of acromegaly.

Symptom	W20*	W22	W24/EOT
		n/N$_{all}$ † (%)	
Fatigue	30/42 (71.4)	28/41 (68.3)	28/42 (66.7)
Headache	19/42 (45.2)	16/41 (39.0)	13/42 (31.0)
JOINT pain	30/42 (71.4)	27/41 (65.9)	34/42 (81.0)
Paraesthesia	14/42 (33.3)	12/41 (29.3)	13/42 (31.0)
Soft tissue swelling	16/42 (38.1)	13/41 (31.7)	13/42 (31.0)
Sweating	19/42 (45.2)	21/41 (51.2)	21/42 (50.0)

*Prior to final CAM2029 administration; †Patients completing treatment with CAM2029 and attending assessment.

Methods
Over a 24-week treatment phase, patients randomised to CAm^{2}029 received 20 mg every 4 weeks ($\pm$1 week); the final dose was administered at week (W) 20. Assessments of IGF-I levels and symptom severity (via the Acromegaly Index of Severity [AIS]; JOINT clinician and patient evaluation of key symptoms) took place at least every 4 weeks throughout the treatment phase, including at W20 prior to CAm^{2}029 administration, W22 and W24/end of trial (EOT).
Results
Forty-eight patients were randomised to CAM2029 and 42 (87.5%) completed treatment. Mean IGF-I/ULN values remained stable over W20, W22 and W24/EOT (0.82, 0.81 and 0.79, respectively). A slight reduction (improvement) in mean AIS overall scores was observed from W20 (4.5) to W22 (4.3) and W24/EOT (4.2). The proportions of patients affected by symptoms of acromegaly across the dose-to-assessment interval are shown in the Table.
Conclusions
Patients established on CAM2029 maintained stable control of IGF-I at all timepoints across the 4 weeks, post-dose. Symptoms were also well controlled throughout the dosing interval, with patients experiencing improvements in some key symptoms such as headache and fatigue. These data indicate that CAm^{2}029 continuously and consistently reduces the burden of disease for patients across the 4-week dosing interval.

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P947

JOINT1643

BMI trajectories during childhood in girls with precocious puberty: a national register-based study

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Background
Childhood obesity is increasing globally and has been linked to early puberty in several epidemiological studies. Low birth weight and subsequent rapid weight gain during infancy and early childhood have been suggested to play a role in this association.
Objectives
We aimed to identify distinct body mass index (BMI) trajectories from birth until 10 years among girls diagnosed with precocious puberty, hypothesizing that specific BMI patterns throughout childhood correlate with pubertal timing.
Methods
We included girls diagnosed with precocious puberty (ICD-10 diagnosis: DE30.1) or central precocious puberty (DE22.8A) as recorded in the Danish National Patient Registry. Data on height and weight for BMI were retrieved from birth and until 10 years, utilizing the Danish Medical Birth Registry and the Children's Database. Only girls diagnosed between ages 4-9 years and with a minimum of three BMI measurements at ages 0-0.5 years, 0.5-3 years and 3-8 years were included (n = 1874). Data-driven latent class trajectory (LCT) modeling was employed to define distinct BMI trajectories for girls experiencing early puberty.
Results
We identified four distinct BMI trajectories. Class 1 (24.1%) or the "very early accelerating" class experienced a marked infancy peak within normal BMI ranges but an early adiposity rebound from 2.5 years. Class 2 (37.4%) had a BMI trajectory within the normal range. Class 3 (30.4%), or the "early accelerating" class, had an initial BMI trajectory within normal limits but then an early adiposity rebound from four years. Class 4 (8.2%) or the "early peak" class had a low BMI at birth but a steep increase during the first year of life (high infancy peak) and remained overweight according to the World Health Organization's classification until 10 years of age. Three out of four classes (62.7%) were at risk of overweight from 7 years of age.
Conclusions
The majority of girls with precocious puberty followed a trajectory characterized by early adiposity rebound and overweight from 7 years of age. This study may facilitate the identification of children at risk of precocious puberty.

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P948

JOINT3036

The intra-individual periodicity of serum GH patterns in acromegaly is very high and independent of disease control: analysis of 650 GH time series from 106 patients

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Background
Growth hormone (GH) is secreted in a pulsatile manner from the anterior pituitary in healthy individuals. In acromegaly, most commonly caused by a GH-secreting pituitary adenoma, the ensuing GH patterns are traditionally described as erratic and irregular due to a substantial shift toward non-pulsatile release. Given the clinical reliance on serum GH and insulin-like growth factor I (IGF-I) as diagnostic and therapeutic biomarkers, it is crucial to establish evidence-based data on GH secretion dynamics in acromegaly. Further investigation into the temporal patterns of GH release may refine diagnostic criteria and improve treatment monitoring in affected individuals.
Aim
The aim of the study is to investigate the day-to-day reproducibility and variability of GH secretion.
Methods
We analyzed medical records of acromegaly patients who received standard treatment and care between 2012 – 2021, including those with a minimum of 3 three GH profiles in conjunction with an oral glucose tolerance test (OGTT) composed of 11 measurements over 3 hours following an overnight fast. To quantify variability in GH secretion patterns, cross correlation analysis and dynamic time warping (DTW), a non-linear alignment algorithm, were applied. DTW distances were computed to assess intra-individual stability across repeated measurements and inter-individual variability among each patient.
Results
We obtained and analyzed 650 GH profiles from 106 patients, of whom the diagnostic GH profile was available in 21 patients. 33 patients were controlled by surgery alone and 72 patients were treated medically with a somatostatin analogue (SA) alone (n = 54) or in combination with a GH antagonist (n = 18). The inter-individual DTW distance was 0.136 with 95%Cl (0.135; 0.138) whereas the intra-individual DTW distance was 0.050 (95%Cl 0.046; 0.055), yielding a ratio of the intra-/inter-individual DTW distance of 0.367 (95%Cl 0.335; 0.403), p $<$0.0001. The intra-/inter-individual DTW distance was independent of treatment modality. Also, the intra-individual cross-correlation coefficients were significantly higher (0.166 (95%Cl 0.137; 0.195)) than inter-individual correlations (0.003 (95%Cl -0.001; 0.007)), P $<$ 0.0001, indicating greater consistency in GH secretion patterns within individuals over time.
Conclusions
1. The unique and highly conserved GH pattern in serum from individual patients challenges the dogma of disorderly GH secretion in acromegaly.
2. This periodicity is independent of disease control and treatment modality suggesting an intrinsic clock within the pituitary somatotrope that is preserved after tumorous transformation.
3. It remains to be studied if our findings depend on the oral glucose load.

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P949

JOINT1118

Cardiovascular morbidity in acromegaly

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Background
Previous research on acromegaly has demonstrated increased morbidity and mortality that are mainly attributable to early cardiovascular diseases (CVD). The aim of our study was to define more comprehensively the risk of CVDs in acromegaly.
Methods
This nation-wide registry study included all Finnish acromegaly patients diagnosed in 1980–2015 at the age of over 16 years. Ten controls matched for age, sex and the area of residence were assigned to each patient. National registries were used to obtain cardiovascular diagnoses given to patients and controls in specialised medical care. CVD-related follow-up started at the acromegaly diagnosis and ended on the date of the CVD of interest, death, or emigration, or the common closing date 31.12.2019. In addition, CVD-related morbidity was analysed for a 10-year period before the acromegaly diagnosis. Clinical data of the acromegaly patients were collected from the Finnish University Hospitals. Morbidity due to different CVDs in patients vs controls was assessed with Kaplan-Meier and Cox regression analyses.
Results
We identified 571 acromegaly patients, of which 565 had sufficient data to be included in the analyses. The incidence of acromegaly was 4.0 [IQR 2.9–4.7] cases/million /year. Mean age at diagnosis was 48.9 (SD 13.3) years. 75% of the tumours were macroadenomas (diameter$\geq$ 10 mm). The median follow-up time was 17.2 [IQR 8.7–26.5] years for the patients and 17.5 [9.4–27.5] years for the controls. Morbidity due to any CVD was found to increase up to 10 years before the acromegaly diagnosis and remained elevated for the whole study period, compared to the controls [HR 2.26 (95% CI 2.04–2.51]. The greatest increase was noted for valvular heart diseases and cardiomyopathies [HR 2.88 (2.24–3.70)], followed by diseases of pulmonary arteries [HR 2.88 (1.96–4.22)] and hypertension [HR 2.30 (2.01–2.64)]. Morbidity was also increased due to arrhythmias [HR 1.77 (1.49–2.11)], heart failure [HR 1.72 (1.35–2.19)], cerebrovascular disease [HR 1.46 (1.16–1.85)], coronary artery disease [HR 1.41(1.16–1.71)] and other diseases of arteries and veins [HR 1.89 (1.60–1.71)].
Conclusion
Acromegaly patients suffered from increased morbidity across all subgroups of CVDs. Morbidity due to any CVD increased years before the acromegaly diagnosis, probably reflecting a long diagnostic delay. We are currently analysing the cardiovascular risk factors and the effect of biochemical control of acromegaly on the cardiovascular prognosis of the patients, to be presented at the meeting.

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P950

JOINT860

Soluble alpha Klotho concentrations in patients with pituitary adenomas

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Background
Alpha klotho is mainly expressed in the kidney but also in other organs, such as the pituitary gland. Soluble alpha klotho (sαKL) is a circulating protein that has been linked to endocrine functions. We previously showed high sαKL concentrations in active acromegaly. However, little is known about sαKL in pituitary adenomas beyond acromegaly.
Objective
To evaluate sαKL concentrations in patients with different types of pituitary adenomas.
Methods
We used an ELISA (IBL, Hamburg, Germany) to measure sαKL in patients prior to surgery for Cushinǵs disease (n = 21, 6 males), prolactinoma (n = 44, 13 males), or non-functioning pituitary adenomas (NFPA, n = 9, 3 males), and compared concentrations to those seen in patients with active acromegaly (n = 29, 9 males). We also compared concentrations (mean [interquartile]) of sαKL to the classical biomarkers in acromegaly (IGF-I and IGFBP3).
Results
SαKL concentrations (pg/ml) were significantly higher in patients with acromegaly (Acro.: 5109 [2859-10232]) compared to all other groups (Cushing (Cush.: 728 [593-982], Prolactinoma (Prol.: 922 [786-1298], NFPA (922 [782-1111]; (Acro. vs. Cush. and Prol., $P < 0.0001$ for both comparisons and Acro. vs. NFPA, $P = 0.0003$). As expected, IGF-I and IGFBP3 were significantly higher in patients with acromegaly (753.9 [485.3-938.3], 6388 [5506-7354]) compared to patients with other pituitary adenomas (Cush.: 175.3 [110.4-228.8), 3212 [2501-3835], Prol.: 163.0 [134.0-201.5], 3896 [3433-4279], NFPA: 120.0 [104.5-174.0]), 3426 (3013-3759), Acro. vs. Cush., Prol. and NFPA, $P < 0.0001$ for all comparisons). Concentrations of sαKL, IGF-I and IGFBP3 did not differ significantly between patients with Cushing's disease, prolactinoma and NFPA ($P > 0.05$ for all comparisons). SαKL significantly correlated with IGF-I and IGFBP3 concentrations in patients with acromegaly ($r_s = 0.66$, $P = 0.0001$ and $r_s = 0.43$, $P = 0.02$, respectively), while there was no correlation with IGF-I or IGFBP3 in patients with other pituitary adenomas ($P > 0.05$ for all).
Discussion
Our study shows that in contrast to patients with acromegaly, sαKL is not grossly elevated in other pituitary adenomas. This supports the idea that sαKL concentrations are associated with high GH and/or IGF-I concentrations whereas influences of other hormone active or inactive pituitary adenomas itself might have, if any, a minor influence on sαKL concentrations.

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P951

JOINT2925

Endocrine challenges in hypothalamic-pituitary region tumors in pediatric population: a greek children's hospital perspective

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Background
Intracranial tumors affecting the hypothalamic-pituitary (HP) region, including adjacent structures such as the optic pathway, often disrupt the hypothalamic-pituitary axis due to local tissue damage, neurosurgical intervention, tumor progression, or cranial radiation therapy. Tumors located in the suprasellar and intrasellar regions account for approximately 10% of all central nervous system (CNS) tumors in children, with endocrine abnormalities frequently present at diagnosis.
Aim
Of this monocentric study is to evaluate the endocrine profile of children with HP region tumors who have been managed in our hospital and referred to our Endocrine Department, emphasizing pre- treatment and post- treatment complications and outcomes.
Methods
A retrospective analysis was conducted on pediatric HP tumor cases managed between 2013 and 2023. Endocrine data, including pre- and post-treatment deficiencies, BMI changes, and rGH therapy requirements, were extracted from patient records.

Results
• **Demographics**: Among 41 children (56% girls, 44% boys), the mean age at diagnosis was 8.95 years (SD = 4.8).
• **Tumor Diagnosis**: Craniopharyngiomas were most common (36.6%), followed by pituitary adenomas (20%) and prolactinomas (12%). Other tumor types included germinoma/dysgerminoma, glioma, ependymoma, astrocytoma, hamartoma, Rathke cyst.
• **Pre-treatment Endocrine Status**: Hormonal deficiencies included GH (12.8%), TSH (15.38%), ACTH (7.69%), LH/FSH (5.26%), and ADH (12.5%).
• **Post-treatment Endocrine Complications**: Increased endocrine deficiencies were observed post-treatment, including GH (34.88%), LH/FSH (25.58%), ACTH (51.16%), TSH (67.64%), and ADH (41.86%).
• **Body Mass Index (BMI)**: The mean BMI z-score increased significantly from 1.2 (± 1.54) at diagnosis to 1.7 (± 1.17) at 1-year post-treatment ($P < 0.05$). This significant difference persisted at 2 years, but by 5 years, although a difference was noted, it almost missed statistical significance at the 95% CI.
• **Recombinant Growth Hormone (rGH) Therapy**: rGH therapy was initiated in 32% of patients during follow-up.

Conclusion
Early identification and management of endocrine disorders are essential to improve the quality of life and long-term outcomes in pediatric survivors of hypothalamic-pituitary region tumors. Regular monitoring and a multidisciplinary approach are strongly recommended to address the complex health challenges these patients face. However, the results of this study are limited in their generalizability, as the sample was derived specifically from patients referred to the Endocrine Unit. To obtain more comprehensive insights, further studies are needed that include a broader population of patients with all types of brain tumors, regardless of referral pathways or clinical settings.

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P952

JOINT2415

A case of severe ACTH-dependent cushing syndrome

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Background
ACTH-dependent Cushing Syndrome is associated with increased morbidity and mortality. Diagnostic evaluation may be challenging, especially in the acute setting. We present a case of severe ACTH-dependent Cushing Syndrome attributed to a corticotroph pituitary adenoma (Cushing's Disease, CD) coexisting with an unspecified syndromic cause of GH deficiency and potential hypopituitarism.

Case Presentation
A 39-year-old woman with decompensated heart failure with reduced ejection fraction was admitted to hospital with severe hypertension, hypokalaemia, and hyperglycaemia. The patient reported generalised weakness, oedema and appearance of wide purple striae, starting two months before her admission. On physical examination, she presented with short stature (1.35m), clinodactyly, low-set ears and micrognathia. Upon questioning, she reported primary amenorrhea and short-term treatment with rGH at the time of adolescence, but no medical records could be retrieved. Of note, she had normal breast development. During her hospitalisation she was admitted to the ICU twice due to acute respiratory failure in the presence of ARDS and later due to acute hemorrhagic pancreatitis. Upon imaging, multiple prevalent spinal fractures were noted. Due to the high clinical suspicion of CS, she was referred for endocrine consultation. After full recovery from acute illness, ACTH-dependent Cushing's Syndrome was confirmed, and pituitary MRI revealed a macroadenoma (max diameter 2 cm) with cavernous sinus invasion. She was started on the novel steroidogenesis inhibitor osilodrostat and teriparatide for osteoporosis, while awaiting neurosurgery. After 4 months of treatment, she had clinical and biochemical remission of hypercortisolism with significant improvement of the related comorbidities. Evaluation of hypothalamus-pituitary axes revealed low gonadotropin, GH and IGF-1 levels. Further testing for the presence of concurrent genetic syndrome was performed. Pelvic ultrasound revealed hypoplastic uterus and ovaries; standard karyotype analysis and array comparative genomic hybridization excluded the diagnosis of Turner Syndrome. Subsequent whole exome sequencing analysis revealed a mutation of VUS in the CDH23 gene (c.1339A>G CDH23 gene), which is implicated in both familiar and sporadic pituitary tumours occurrence. Additionally, further trio-exome sequencing analysis detected a likely pathogenic variant in PAX6 (c.728_731delAAAA) and VUS in SOX2 (c.382C>T), genes encoding transcription factors implicated in pituitary development.

Conclusion
Pituitary insufficiency co-existing with a corticotroph macroadenoma is a rare finding. Whether there is an association between the two entities remains an unresolved issue. Despite recent advances, a genetic cause remains unidentified in many cases of hypopituitarism. Future research to discover additional implicated genes will provide better understanding on the molecular pathways implicated in pituitary development.

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P953

JOINT362

Diagnostic delay in children with intracranial germ cell tumour and high burden of endocrinopathies among survivors

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Objective
Compared to the Western population, incidence of intracranial germ cell tumour (IC-GCT) is significantly higher among Chinese children. These children often present with neurological symptoms or endocrine dysfunction. Endocrine deficits may present with insidious symptoms that precede neurological findings for years, often leading to delay in diagnosis especially among primary care or general pediatricians. This study reviewed clinical features of a cohort of Chinese children with IC-GCT, focusing on initial endocrine manifestations, time lag in diagnosis and long-term disease burden.

Methods
This is a retrospective, cohort study. We identified children with IC-GCT diagnosed ≤ 18 years managed at the Hong Kong Children's Hospital from 2008-2023. Demographics, presentation and tumour-related outcomes were analyzed.

Results
74 children (73% males) diagnosed with IC-GCT at median age of 12.6 years (IQR 10.5-16.5) with median follow-up of 4.4 years (IQR 2.2-11.1) were included. The majority (63.5%) had germinoma and 17.6% were metastatic at diagnosis. IC-GCTs were suprasellar (40.5%), pineal (18.9%), bifocal (17.6%), or at the basal ganglia/thalamus (16.2%). Endocrine deficits were already present in 68.9% of children at diagnosis (diabetes insipidus 59.5%, adrenal insufficiency 55.4%, central hypothyroidism 52.7%, growth hormone deficiency 43.2%, hypogonadotropic hypogonadism 29.7%, precocious puberty 10.8%), and all children with suprasellar tumour exhibited at least one endocrinopathy. Interval between onset of endocrine symptoms and definitive diagnosis of IC-GCT ranged between 0.9 to 71.8 months (median 11.9 months) with more than half (70.3%) being symptomatic for over 6 months. Those with unfavourable oncological outcomes (distant metastasis/relapse/death) had longer symptom interval, though the difference was not statistically significant. At last follow-up, 68.9% required at least one medication for endocrine sequelae. Additionally, there was significant rise in BMI from 17.8 kg/m^2 at diagnosis to 21.6 kg/m^2 at last follow-up, with more of those with endocrinopathies showing ≥ 10% increase in BMI. Low bone mineral density was also common, with 63.2 % having either TBLH/lS z score ≤ -2 on DXA measurements.

Conclusion
Substantial proportion of children with IC-GCT experienced delay in time to diagnosis, which was associated with worse disease outcome. This highlighted the importance of raising both patient and clinician awareness, as well as the need for early neuroimaging in children displaying pituitary hormone deficiencies. For survivors, attention has to be drawn to weight status and bone health in order to optimize long-term well-being.

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P954

JOINT843

DISCERN: delta copeptin in the investigation of SIAD and CSW: evaluating the role of a novel biomarker

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Background
The current diagnostic methods for syndrome of inappropriate antidiuresis (SIAD) and cerebral salt wasting (CSW), relying on clinical and biochemical indicators are imprecise. As existing gold standard techniques using radioisotope methodologies are confined to research settings due to high costs and limited accessibility, there is an urgent need for novel biomarkers to enhance diagnostic accuracy.
Objective
To evaluate the change in serum copeptin levels, as an early diagnostic tool in children to differentiate SIAD and CSW.
Methods
A prospective observational study was conducted on hyponatremic children (serum sodium $\leq$ 130 meq/l). Subjects with endocrine disorders, chronic systemic diseases, diarrhea, hypovolemic shock, or those using diuretics were excluded. At baseline, copeptin, NT-proBNP, and fractional excretion of uric acid (FEUA) levels were measured. Subsequently, each subject received 0.9% NS according to their maintenance requirements for six hours. During this period, fluid deficits and polyuria, if present, were managed with fluid replacement. Symptomatic hyponatremia was treated with 3% NS. After six hours, samples were again collected for copeptin and NT-proBNP. The subjects were followed until serum sodium levels normalized to differentiate CSW from SIAD based on FEUA levels.
Results
We studied 15 subjects (73.3% male), of whom 11 were diagnosed with SIAD and four with CSW. The cohort predominantly consisted of patients with tuberculous meningitis (66.67%). Baseline copeptin levels showed no correlation with the degree of hyponatremia ($r = 0.126$). However, delta copeptin was significantly different between the two cohorts and showed a decrease in the SIAD group [-16.43 (-39.07, -4.57) vs 7.94 (-2.30, 29.80) pmol/l, $P = 0.024$]. A cutoff value for delta copeptin of -9.62 pmol/l, yielded a sensitivity of 100% and a specificity of 63.6% for CSW (AUC [95% CI], 0.864 [0.665–1.00]). Chronic hyponatremia developed in 2 SIAD subjects (18.18%), and these subjects had lower weight-for-age z-score [-4.48 (0.33) vs. -2.03 (1.34), $P = 0.037$], lower baseline sodium levels [122 (0.00) vs. 128.31 (2.06), $P = 0.001$] and higher FEUA [32.78(3.19) vs 14.66(5.11), $P = 0.000$]. The utility of other biomarkers (delta NT pro-BNP, copeptin/urine sodium and serum uric acid) in this diagnostic algorithm could not be established.
Conclusion
Our study demonstrates the role of delta copeptin as a potential diagnostic biomarker in the evaluation of SIAD vs CSW, although its validity needs to be ascertained in larger studies.

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P955

JOINT2769

CAM2029, a self-administered subcutaneous octreotide depot, improved pros and symptoms in patients with ACROMEGALY in the acroinnova 2 phase 3 trial: final analysis of the core phase results

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Background
Patients with acromegaly have an unmet need for therapies with a lower treatment burden that do not require healthcare-professional administration. CAm^{2}029 utilises FluidCrystal® technology and provides a long-acting octreotide subcutaneous depot, self-administered via an autoinjector pen. ACROINNOVA 1 (NCT04076462) was a Phase 3, 24-week, randomised, double-blind trial of CAm^{2}029 in patients who are biochemically controlled (insulin-like growth factor-I [IGF-I] $\leq$ upper limit of normal [ULN] on standard-of-care [SoC] somatostatin receptor ligands at baseline [octreotide long-acting repeatable/lanreotide Autogel]). The primary endpoint was met, demonstrating superior biochemical control with CAm^{2}029 vs placebo. Long-term safety, efficacy and patient-reported outcomes (PROs) with CAm^{2}029 were further evaluated in ACROINNOVA 2 (NCT04125836), a 52-week, open-label Phase 3 trial.
Methods
Patients enrolled into ACROINNOVA 2 directly or after completing ACROINNOVA 1. Directly enrolled patients had IGF-I $\leq 2\times$ULN on SoC. Patients received CAm^{2}029 20 mg every 4 weeks (± 1 week) for 52 weeks (ACROINNOVA 1 prior-placebo: 28 weeks). The primary endpoint characterised safety. PROs included Acromegaly Quality of Life Questionnaire (AcroQoL), Treatment Satisfaction Questionnaire for Medication (TSQM) and severity of signs and symptoms over time (assessed using Acromegaly Index of Severity [AIS]). Data are shown for the overall population for the core 52 weeks.
Results
Of 135 patients enrolled (directly enrolled, $n = 81$; prior-placebo; $n = 18$, prior-CAm^{2}029, $n = 36$), 127 completed treatment. PROs and symptom burden continuously improved from baseline to week 52; results also indicated improvement from week 24 to 52 (Table). CAm^{2}029 was well tolerated, with no new safety signals identified.
Conclusions
Long-term treatment with CAm^{2}029 reduced the symptom burden of patients over 52 weeks, providing continuous improvements in QoL and treatment satisfaction scores vs SoC baseline. ACROINNOVA 2 demonstrates the combined patient benefits of convenient administration, improved QoL, treatment satisfaction and symptom control provided by CAm^{2}029.

PROs/symptom burden.

AcroQoL and TSQM (Higher scores indicate improvement)				
		Change from baseline		
		Week 24		**Week 52**
	n	**Mean (95% CI)**	**n**	**Mean (95% CI)**
AcroQoL(range 0–100)				
Total score	128	1.8 (-0.1, 3.8)	123	3.0 (1.0, 5.0)
TSQM domain scores (range 0–100)				
Convenience	115	12.0 (8.6, 15.4)	112	15.4 (12.0, 18.8)
Effectiveness	116	0.9 (-3.2, 5.0)	113	5.4 (2.1, 8.8)
Global satisfaction	116	0.5 (-3.2, 4.2)	113	4.0 (0.8, 7.2)
AIS(Lower scores indicate improvement)				
	n	**Baseline, Mean (standard deviation)**	**n**	**Change from baseline to week 52, Mean (95% CI)**
AIS Overall score (range 0–18)	135	4.3 (3.4)	124	-1.2 (-1.7, -0.6)

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P956

JOINT3912

Metformin administration improves treatment response in non-diabetic patients with acromegaly

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background
Acromegaly, a condition caused by excess growth hormone (GH) secretion, often requires lifelong pharmacological treatment. Current therapies, including somatostatin receptor ligands (SRLs) and GH receptor antagonists (pegvisomant), are associated with high costs and accessibility challenges. Metformin, a widely used antidiabetic drug, was suggested to have potential benefits in endocrine disorders.

Objective
To evaluate metformin as an adjunctive therapy in non-diabetic patients with acromegaly.
Methods
we analyzed a case series of four male patients with acromegaly treated with SRL ($n = 4$) and/or pegvisomant ($n = 2$). Metformin (500mg-850mg) was added to their existing treatment regimens, and we monitored biochemical response (insulin-like growth factor I; IGF-I), glycemic control (HbA1C), and treatment costs for 3-6 months. Additionally, we assessed *in vitro* the action of metformin on pituitary GH, using a rat Gh promoter reporter vector and determining GH secretion from human GH-secreting pituitary tumors in primary cell culture ($n = 11$).
Results
All four patients were previously treated with SRLs (octreotide LAR or lanreotide) and two received in addition pegvisomant. Addition of metformin reduced IGF-I in all patients, and enabled dose adjustments of SRLs and pegvisomant that resulted in cost savings (EUR/month 482.80 ± 289.88), while maintaining biochemical control. Glycemic control was maintained in all patients. One patient experienced improved gastrointestinal symptoms and weight loss (5kg). *in vitro*, metformin significantly reduced rGh promoter activity, and suppressed GH secretion beyond 20% in 6/11 primary cultures (% suppression 23 ± 2.45). Addition of metformin to octreotide suppressed GH secretion in all cases (% GH suppression 36 ± 6.49). In the *in vitro*-octreotide responder tumors, addition of metformin potentiated octreotide's antisecretory action (% suppression 37 ± 5.18 vs. 25 ± 4.26).
Conclusion
This small case series study suggests that metformin addition to the currently standard SRL/pegvisomant treatment may be useful at improving biochemical control and reducing treatment costs in patients with acromegaly. Our *in vitro* data indicate a direct pituitary action for metformin on GH synthesis. Further large-scale studies are needed to evaluate the efficacy and safety of metformin as adjuvant treatment in non-diabetic patients with acromegaly.

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P957

JOINT2971

Medical treatment in acromegaly: imunohistochemical features of responder patients

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Introduction
Identifying acromegaly patients most likely to benefit from long-acting somatostatin receptor ligands (SRLs) and/or growth hormone receptor antagonist is important, as these are the primary medical therapies for active disease.
Material and Methods
The retrospective analysis included 38 naive acromegaly patients (without preoperative medical treatment), with active disease following transsphenoidal (TS) surgery, treated with octreotide / lanreotide ($n = 38$) or pasireotide ($n = 9$) and/or pegvisomant ($n = 8$) if uncontrolled under first generation SRLs (fgSRLs). Key immunohistochemical (IHC) markers, including hormone expression, proliferation index (Ki-67), tumor granulation pattern (sparsely/densely, based on cytokeratin granulation), and somatostatin receptor 2 and 5 (SSTR2, SSTR5) status were evaluated.
Results
Mean age at diagnosis was 45 years (±11). Eight patients (21%) also underwent postoperative radiotherapy. All tumors were acidophilic, had positive IHC expression for growth hormone (GH) and pituitary specific transcription factor 1 (PIT-1), with a Ki-67 proliferation index of <3%. Knosp grade >1 was observed in 84.2% of cases, with a maximum tumor diameter at diagnosis of 22.2 mm (± 10.47). The granulation pattern (densely) correlated with the response to fgSRLs ($P < 0.01$). SSTR2 expression did not correlate with the fgSRLs responder status, although densely granulated tumors had higher SSTR2 expression. Also, the patients resistant to fgSRLs expressed higher SSTR5 levels ($P = 0.003$). The response to pasireotide correlated with the sparsely granulated pattern ($P = 0.002$) and SSTR5 expression ($P < 0.0001$). Sparsely granulated tumors expressed greater levels of SSTR5 ($P = 0.002$). No IHC markers were found to correlate with pegvisomant response (sample size limitation may have played a role).
Conclusion
Pituitary neuroendocrine tumor granularity represents a good predictor for the response to first and second generation SRLs in active acromegaly. Besides this, SSTR5 expression is predictive for the response to pasireotide. There are distinct IHC profiles that may help predict response to targeted medical therapy in acromegaly, and treatment should be initiated and individualized based on postoperative IHC features.

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P958

JOINT1932

Defining the clinical value of MYD88, a component of the inflammasome machinery, as a diagnosis, prognosis and therapeutic tool in brain endocrine cancers

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Glioblastoma (GBM) stands as the most prevalent and lethal primary brain endocrine cancer (ECR) due to the late-stage diagnosis and the resistance to gold standard therapy, which results in a low survival rate after diagnosis (8-9 months) and poor prognosis of patients. Consequently, the identification of novel diagnosis/prognosis biomarkers and therapeutic targets becomes critical to improve the clinical management of this devastating endocrine-related cancer. Here, we focus on the study of the inflammasome, a molecular machinery activated by cellular stress and damage which triggers the maturation and release of proinflammatory cytokines, being closely associated to the modulation of immune responses and cell death, as well as with tumor microenvironment (TME), a well-known hallmark of cancer. Specifically, we initially characterized the expression levels of the inflammasome components in a well-characterized cohort of GBM patients ($n = 63$) and compared with non-tumor brain (NTB; $n = 19$) samples by using a validated qPCR array based on microfluidic technology. Our results revealed a profound dysregulation of the expression pattern of the inflammasome machinery in our cohort of GBM samples, which was later validated in different external cohorts using RNA-seq and microarray data. Remarkably, the expression of key inflammasome components, especially *MYD88*, was associated to several clinical parameters of aggressiveness/poor-prognosis (e.g. survival rate, recurrence, EGFR amplification and MGMT methylation status). Of note, MYD88 expression was also found to be associated with diverse pathways of relevance in GBM pathophysiology (e.g. epithelial to mesenchymal transition, hypoxia, angiogenesis or NFkB-signaling). Moreover, the modulation of the expression of *MYD88 (*through transitory silencing by siRNA or pharmacological inhibition) significantly reduced several key tumor functional parameters in GBM cell models *in vitro*, including cell-proliferation, tumorspheres or colonies formation and migration rate. Taken together, this study demonstrates the critical role of inflammasome machinery in GBM pathophysiology, highlighting the importance of *MYD88* alteration as a potential driver of GBM aggressiveness. Consequently, *MYD88* could serve as a novel diagnostic and/or prognostic biomarker, and potential therapeutic target that might be useful to improve the quality of life of GBM patients.

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P959

JOINT1544

Menstrual health: schoolgirls' knowledge and hygiene practices

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In order to fight against menstrual ignorance, as highlighted by the WHO over the last few years, we carried out a cross-sectional, descriptive and quantitative observational study using anonymous questionnaire. We surveyed schoolgirls' knowledge of puberty and menstrual management. Our study was conducted in

public and private educational institutions (schools and colleges) in the governorate of Ben Arous (**Tunisia**) and included 720 schoolgirls aged 8 to 14 years old. Results figured that 393 girls had already experienced their **first period** with a median age at menarche for these girls of **12.63 years** (minimum age 8 years; maximum age 14 years). Our serie assessed girls' knowledge of the characteristics of menstruation during normal puberty. Schoolgirls' main source of information about menstrual health was family for 443 girls (61.6%), but also Internet in 23.3% ans schoolmates in 15.1%. Outcomes showed that only 474 girls (65%) knew that menstruation occurs following a monthly **cycle**. We also noticed that 252 participants (35%) knew that menstrual cycle becomes mostly **regular** after 2 years of menarche. Similarly, our research uncovered that 246 of our schoolgirls (34%) knew the normal **duration** of menstruation whereas 452 (63%) knew the normal **length** of menstrual cycle. Moreover, In terms of identifying abnormalities, the data revealed that only 343 of the girls surveyed (48%) recognised that the absence of menstruation after 04 years from the onset of puberty should be considered as pathological. Wheareas, only 337 girls (46.8%) recognised secondary amenorrhoea as requiring medical care. As far as menstrual hygiene is concerned, only 169 of all girls included in our study (less than 25%), admitted that the menstrual period required **extra hygiene precautions**. According to our study, 343 of he girls assessed (47.6%) adhere to **changing** their menstrual pads four to six times a day during period in order to maintain adequate hygiene. On the other hand, almost all of the girls we questionned (696 or 96.7%) claimed that their schools **lack the sanitary facilities** they need (or could need) in order to manage their menstrual period. This study revealed deficiencies in the menstrual hygiene knowledge and practices of schoolgirls in Ben Arous. These results highlight the need to integrate appropriate menstrual education and to improve sanitary facilities in schools.

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P960

JOINT1095

From CRH to the desmopressin era: a comparative study of stimulation tests in cushing's disease

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Purpose
CRH-based dynamic tests can be used in the differential diagnosis of ACTH-dependent Cushing's syndrome(CS) and the differentiation of CS from non-neoplastic hypercortisolism. However, after the worldwide cessation of CRH production as of December 2022, desmopressin-mediated dynamic tests are recommended as an alternative. In this study, we aimed to compare the responses of ACTH-secreting pituitary adenomas to desmopressin and CRH stimuli.
Methods
Patients who underwent a CRH or desmopressin-stimulation test for CS between December 2019 and September 2024 and who were histopathologically diagnosed with CD postoperatively were included in the study. Patients' age, sex, screening test results for CS, baseline ACTH and cortisol levels, peak ACTH and cortisol levels during the tests, the test minute at which peak values were reached, and the rates of peak increase in ACTH(%ΔACTH) and cortisol(%ΔCort) after stimulation were recorded.
Results
A total of 30 CD patients were included in the study. Of these, 18 had a CRH-stimulation test, and 12 had a desmopressin-stimulation test. 27 patients were female(90%), and three were male(10%). The mean age was 44.70±14.44 years. The results of the patients' baseline and screening tests for CS are shown in Table 1. The basal and peak ACTH and cortisol levels of the patients during the stimulation tests and the comparison between groups are shown in Table 2. No statistically significant difference was found when comparing the distributions of peak ACTH minutes and peak cortisol minutes of the tests($P = 0.580$ and $P = 0.518$, respectively).
Conclusion
CRH and desmopressin stimulate ACTH and subsequent cortisol secretion to different degrees. Diagnostic criteria for CRH stimulation are well established, whereas this experience is not yet available for desmopressin. However, using similar diagnostic criteria for these two tests seems doubtful regarding diagnostic adequacy. To use the desmopressin stimulation test more effectively, prospective studies with large patient groups should be performed.

Table 1: The results of the patients' baseline and screening tests for Cushing's Syndrome.

Test	n	Value
ACTH(pg/mL)	30	38.42±30.63
Cortisol(μg/dl)	30	20.60(12.50-28.20)
Serum Cortisol after 1 mg DST(μg/dl)	29	14.45±9.67
Serum Cortisol after 2 mg DST(μg/dl)	29	12.14±7.93
24-hours-urinary free cortisol(μg/day)	30	61.20(6.42-939.00)
Late-night salivary cortisol(μg/dl)	23	0.60±0.36
Late-night serum cortisol(μg/dl)	28	16.01±5.12

Table 2: Basal and peak ACTH and cortisol levels of both stimulation tests and comparison between groups.

Parameter	CRH-stimulation	Desmopressin-stimulation	p
Basal ACTH pg/mL(n)	36.13±22.22(18)	42.15±41.99(11)	0.617
Basal Cortisol μg/dl(n)	18.80(12.50-128.20)(18)	21.10(13.10-24.70)(12)	0.692
Peak ACTH pg/mL(n)	159.51±167.73(18)	103.06±115.20(11)	0.336
Peak Cortisol μg/dl(n)	35.05(21.50-43.10)(18)	30.70(19.90-46.50)(12)	0.095
%ΔACTH(n)	340.63±271.44(18)	159.85±175.28(11)	**0.038**
%ΔCort(n)	77.93±50.29(18)	43.03±26.12(12)	**0.021**

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P961

JOINT3584

The effect of GNRHA therapy initiation age on final height in girls with central precocious puberty

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Introduction
Precocious puberty is defined as puberty onset before 8 years in girls and 9 years in boys. Elevated estradiol accelerates growth but leads to premature epiphyseal closure, potentially resulting in short final height. In central precocious puberty (CPP), gonadotropin-releasing hormone agonists (GnRHa) mitigate psychosocial effects—such as early menarche—and improve final height. However, the effect of hormone initiation time on final height is controversial in the literature.
Aim
This study aims to determine the effect of GnRHa treatment initiation age on final height. We are analyzing CPP patients treated in our clinic from 2000 to 2024. Of the targeted 300 patients, 150 girls have been evaluated. This interim report presents our findings.
Methods
Patients were categorized into four groups based on treatment initiation age (Group 1: ≤7.99 years, $n = 30$; Group 2: 8–8.99 years, $n = 55$; Group 3: 9–9.99 years, $n = 52$; Group 4: ≥10 years, $n = 13$). Parameters were compared using one-way ANOVA and Bonferroni post-hoc tests.
Results

Table Baseline Characteristics and Final Heights of the Four Groups.

	Group 1 ($n = 30$)	Group 2 ($n = 55$)	Group 3 ($n = 52$)	Group 4 ($n = 13$)	All ($n = 150$)	*P* values
Age (years)	7.07±0.63	8.42±0.29	9.43±0.29	10.37±0.38	8.67±1.07	<0.001
HSDS	1.13±1.02	0.92±1.05	0.95±0.90	0.18±1.17	0.91±1.02	0.043
BMI SDS	0.89±1.03	0.86±0.86	0.79±0.79	0.53±1.04	0.81±0.89	0.644
MPH SDS	-0.81±0.95	-0.70±0.96	-0.67±0.84	-0.90±0.91	-0.73±0.91	0.810
BA (years)	8.58±1.23	10.01±0.87	11.05±0.79	11.52±0.62	10.21±1.33	<0.001
PFH SDS	-1.08±1.03	-1.34±0.82	-1.02±0.98	-1.31±1.13	-1.17±0.95	0.321
FH (cm)	162.08± 6.44	160.18± 5.84	159.61± 4.83	156.42± 5.15	160.04± 5.71	0.023Φ
FH SDS	-0.18±1.10	-0.50±1.00	-0.59±0.82	-1.14±0.88	-0.52±0.97	0.024Ψ
FH SDS – MPH SDS*	0.63±0.86	0.20±0.81	0.07±0.77	-0.23±0.51	0.20±0.82	0.003♣

Values are presented as mean ± standard deviation. HSDS: height standard deviation score, BMI: body mass index, SDS: standard deviation score, MPH: mid-parental height, BA: bone age, PFH: predicted final height, FH: final height *This parameter indicates the difference between the FH SDS and the MPH SDS. Φ **Group 1 vs. Group 4** showed a significant difference in final height. Ψ **Group 1 vs. Group 4** showed a significant difference in final height. ♣ Significant differences were found for **Group 1 vs. Group 3** and **Group 1 vs. Group 4**.

Conclusion
Earlier treatment led to significantly greater final height and superior FH SDS and FH SDS–MPH SDS values. These findings emphasize the importance of early diagnosis and intervention. Once finalized, our study will contribute valuable data to the literature.

Keywords
GnRH analogue, Precocious puberty, Final height.
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P962

JOINT3481

A rare cause of isolated hypogonadotrophic hypogonadism: spry4 gene mutation

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Introduction
Congenital hypogonadotrophic hypogonadism (CHH) is a rare condition with heterogeneous clinical findings resulting from inadequate secretion of normal pulsatile gonadotropin-releasing hormone (GnRH). More than 50 genes have been reported to cause delayed puberty or infertility. Isolated HH/Kallman syndrome cases reported with SPRY4 gene mutation are quite rare in the literature. Here, a case of short stature complaint and heterozygous variant detected in SPRY4 gene is presented.
Case Presentation
A 14.3-year-old male patient applied to the pediatric endocrinology clinic with a complaint of short stature. The patient, who was born at term with a birth weight of 3400 grams, had hypospadias surgery at the age of 7. The patient's neuromotor developmental stages were normal and there was a history of distant consanguinity between the parents. In his physical examination, body weight: 54 kg (-0.42 SDS), height: 150 cm (-2.23 SDS), bone age: 12.7-year-old; testicular volumes 2ml/2ml, penis length: 3.5 cm ($<$10p), coronal hypospadias, pubis stage 2, no axillary hair. The patient, whose basal FSH and LH values were low, underwent LHRH stimulation test and was observed to have pih FSH: 2.51 mIU/mL, peak LH: 0.58 mIU/mL T. testosterone: $<$0.025 ng/mL. The patient's other anterior pituitary hormone levels were within normal range, Inhibin B: 87.1 pg/mL (169-216), IGF1: 121 ng/mL (177-507), IGFBP3: 3.30 mg/l (3.5-10). The patient had no findings of synkinesis and anosmia, and bilateral sensorineural hearing loss was detected in the hearing test. Renal ultrasonography showed double collecting systems in both kidneys, and pituitary MRI showed partially empty sella. Lumbar BMD Z score (corrected for height): -1.95. Karyotype: 46, XY, and WES analysis revealed c.203G$>$A heterozygous variant in the SPRY4 gene. It was found to be compatible with hypogonadotropic hypogonadism with/without anosmia 17 (OMIM: 615266). The patient was started on physiological induction hormone replacement therapy with hCG + FSH protocol.
Conclusion
SPRY4 gene, which encodes a member of SPRY family, is located in 5q31.3 location region. In addition to being in the FGF8 synexpression group, it is also an inhibitor of the RAS-MAPK pathway. Hypogonadotrophic hypogonadism (with/without anosmia), craniofacial defects, dental anomalies, hearing disorders, bone mineral disorders have been reported in this rare SPRY4 gene mutations.

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P963

JOINT1176

A scoping review to explore eating behaviour and psychological mechanisms associated with obesity in patients with craniopharyngioma

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Introduction
Craniopharyngiomas are low-grade suprasellar intracranial tumours commonly associated with obesity. This scoping review explored the potential impact of hyperphagic eating behaviour on the development of obesity in craniopharyngioma patients and to help identify areas for future intervention.
Methods
PRISMA-ScR and JBI methodology was followed. Five databases and two trial registries were searched. All published studies with all study designs were included for both adult onset and childhood craniopharyngioma, including those with or without obesity. The following categories were also included if they demonstrated their impact on eating behaviours: neuroimaging, endocrine response, energy expenditure, sleep, and neuropsychology.
Results
Evidence surrounding eating behaviours in craniopharyngioma patients was sparse with only 18 of the 54 included papers using validated eating behaviour assessments. Eating behaviour was included as a primary outcome (n = 7), secondary outcome (n = 12), or commented on without formal measurement (n = 35). Few studies included patients with adult-onset craniopharyngioma (n = 8), or compared patients with craniopharyngioma with and without obesity (n = 2), and no papers were identified assessing eating behaviours as an intervention for craniopharyngioma-related obesity. Six papers identified more pathological eating behaviour in the craniopharyngioma population whilst two papers found evidence to the contrary. Twelve papers commented on the impact of GLP1 analogues on eating behaviour, demonstrating limited impact on eating behaviours but long-term data on this is lacking. Four case-control studies examined endocrine response and eating behaviours, demonstrating a possible connection between salvia oxytocin levels, fasting ghrelin and adverse eating behaviours in those with craniopharyngioma associated obesity, albeit not consistently. Four studies identified a decrease in resting energy expenditure or basal metabolic rate in those with craniopharyngioma, whilst two further papers reported no difference. Structural imaging studies have correlated increased adverse eating behaviours with extensive intracranial lesions. A variable neural response was noted in craniopharyngioma such as an increase in the activation of the insula and cerebellum when viewing high calorific food. No studies commented on sleep.
Discussion
The quality of evidence on eating behaviours in those with craniopharyngioma and their impact on obesity is poor with mixed findings. Further understanding of eating behaviour following craniopharyngioma is needed, through longer-term research using validated measures. Clinical practice may benefit from exploration of eating behaviour to enhance patient-centred care by informing treatments tailored to patient needs.

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P964

JOINT1464

An assesment of data completeness in GloBE-Reg, an international registry for studying saftey & effectiveness of novel therapies

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Introduction
The completeness of data within a registry can be directly linked to the quality and reliability of data within a registry and this can directly impact the accuracy of research findings generated from data within that registry. The project focus is to evaluate the completeness of the dataset within the GloBE-Reg registry (https://globe-reg.net/).
Methods
Core data variables were categorised into 'mandatory' (n = 15), and 'non-mandatory' fields (n = 12). Completeness was assessed as a median score of completeness per patient and an overall median percentage completeness for that category. To accurately identify whether or not a variable had been completed, any field left blank or 'unknown' was taken as incomplete.
Results
The analysis examined 2,435 cases that were enrolled in GloBE-Reg registry between October 2022 and December 2024. These cases were from 28 centres in 18 countries with a median number of cases per centre of 28 (10th and 90th centile, 5, 145). All core data fields that were mandatory had a median completeness of 100% (100,100). When the completeness rate for non-mandatory data were categorised, of the 12 non-mandatory fields, 7 (58%) had a completion rate of $>$ 75% with a median completeness of 100% (0,100) and the remaining 5 (42%) had a completion rate of $<$25% with a median completeness of 0% (0,100). The fields which fell into the highest quartile were, Patient follow-up status, Country of birth, Country of usual residence, Data shared for research purposes, Participation in other registries, Name of other registries and registry ID(s). The fields which fell into the lowest quartile were, Can be contacted for patient reported outcomes (PRO), Consent for newsletters, Biobank sample availability, Biobank details,

Biobank patient ID. Of the 28 centres, 26 (92%) achieved a median completeness of 100% (0,100) for the non-mandatory data. The median number of cases at these 26 centres was 28 (5, 147). The remaining 2 centres had a median completeness of 50% (0,100), with 34 and 20 cases in these two centres. There was no association between the number of cases and percentage completeness at the centre.
Conclusions
Despite some variability there is generally a high level of completeness of mandatory and non-mandatory fields within GloBE-Reg core data. Future analysis will extend to all variables in the minimum data set within the registry, to provide a comprehensive assessment of registry completeness.
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P965

JOINT3410

Case series and review of the literature on the surgical management of hypophysitis: the endocrine outcome seems to be worsened by surgery

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Aims
Hypophysitis is an inflammation of the pituitary gland or stalk, lacking standardized diagnostic and treatment guidelines. This study aims to explore the role of surgery in the diagnosis and treatment of hypophysitis.
Patient and Methods
We conducted a monocentric retrospective observational study in a university tertiary hospital. Patients over 15 years of age diagnosed with hypophysitis thanks to histological documentation between January, 1st, 1994 and October, 31st, 2023 were included. A literature review was also performed on cases involving surgical and medical management, collecting data on characteristics, endocrine function, surgery, and complications.
Results
Nine patients were included in our cohort, with surgery primarily performed due to visual disturbances (75%). Almost half were initially suspected of having an pituitary adenoma. All patients recovered their visual function after surgery. The literature review regarding surgical management covered 289 operated patients from 21 articles, among which 204 had partial or complete surgical resection.

	Observation $n = 263$		Glucocorticoids $n = 137$		Resection $n = 219$		p
New deficiency AVP-D	0/159	0%	0/94	0%	16/108	14.8%	**<0.0001[BC]**
Corticotroph deficiency	10/100	10%	0/94	0%	14/141	9.9%	**0.0065[AB]**
Thyrotroph deficiency	4/100	4%	0/94	0%	12/108	11.1%	**0.0016[B]**
Panhypopiutarism	0/100	0%	0/94	0%	9/86	10.4%	**<0.0001[BC]**
≥ 1 deficiency	21/151	13.9%	2/94	2.1%	52/211	24.6%	**<0.0001[ABC]**
Recovery of deficiency Gonadotroph deficiency	9/152	5.9%	17/90	18.9%	10/152	6.6%	**0.0012[AB]**
≥ 1 deficiency	38/204	18.6%	37/116	31.9%	29/219	13.2%	**0.0002[AB]**

[A]$P < 0.05$ between observation and glucocorticoids [B]$P < 0.05$ between glucocorticoids and resection [C]$P < 0.05$ between observation and resection.

Endocrine impairment was observed in 66.5% patients. Forty percent underwent surgery due to a misdiagnosis of adenoma, and 40% for visual impairment. After surgery, 20% developed new endocrine deficiency, while 13% showed hormonal improvement. Surgery resulted in visual improvement in about 80% cases. Non-endocrine complications remains rare but could be severe (5%). Neuropathology was contributive in 98.3% cases. The literature review of all management covered 661 patients. Glucocorticoids prevent the occurrence of new deficiency (2.1%) compared with surgery (25%) or observation alone (14%) ($P < 0.001$). Glucocorticoids improve endocrine function and leading to the recovery of at least one deficiency in 32% cases, better than surgery (13.2%) or observation alone (19%) ($P = 0.002$).
Conclusion
Surgical management in hypophysitis has clear diagnostic value and is part of the therapeutic armamentarium. It should be discussed as a first-line treatment for visual impairment. The risk of worsening endocrine function should be balance with the value of surgery when indicated.
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P966

JOINT489

"Long-term hormonal and clinical outcomes in empty sella syndrome: a retrospective cohort analysis"

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Introduction
In most cases, empty sella is an incidental neuroradiological finding associated with varying degrees of pituitary gland flattening, often without clinical significance. However, empty sella syndrome (ESS) involves pituitary hormonal dysfunction, typically hypopituitarism, presenting with heterogeneous clinical manifestations and hormonal alterations that can occasionally be severe. Significant variability in data and underestimation of findings have left much of this condition underexplored. This study evaluates pituitary function in patients with ESS over an extended follow-up period, providing insights into its pathogenesis and management.
Design
A single-centre, retrospective cohort study conducted from 2003 to 2024, including patients from our endocrinology outpatient clinic with neuroradiologically confirmed ES and comprehensive hormonal assessments.
Methods
Hormonal (including basal and dynamic stimulation tests), biochemical, clinical, and neuroradiological data were analyzed at diagnosis and follow-up (minimum of three months).
Results
A total of 101 patients (77% female, mean age 54.5 $\pm$ 15 years) were included. ESS was categorized functionally as partial (63.4%), total (6.9%), or without pituitary deficiency (29.7%). Hypopituitarism was observed in 66.3%, with hypogonadism (5.9%), secondary adrenal insufficiency (30.7%), growth hormone deficiency (3.9%), hypothyroidism (3%), diabetes insipidus (4%), hyperprolactinemia (12.9%), and multiple deficiencies (5.9%). Post hoc pairwise analysis revealed that partial ES was associated with a higher likelihood of pituitary insufficiency compared to total ES in both females ($P = 0.0030$) and males ($P = 0.0226$). Among females, total ES showed a significant association with pituitary deficiency absence compared to partial ES ($P = 0.0344$). Multinomial regression indicated men had a lower but marginally non-significant odds of secondary adrenal insufficiency ($P = 0.052$), while women exhibited a greater likelihood of hypoadrenalism compared to hypogonadism, diabetes insipidus, or hyperprolactinemia. MRI findings were marginally significant for hypogonadism ($P = 0.042$) but not for other hormonal alterations. A significant association was observed between MRI findings and PES type ($P = 0.047$).
Conclusions
This cohort study identifies novel epidemiological features of ES, revealing that nearly two-thirds develop hypopituitarism and over 30% experience secondary adrenal insufficiency. These findings emphasize the necessity for further research into its pathogenesis, tailored management approaches, and vigilant monitoring for early identification and treatment of hormonal deficiencies.
Keywords
empty sella, hypopituitarism, hypogonadism, hypoadrenalism, hyperprolactinemia, neuroendocrinology, hormonal assessment.
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P967

JOINT1898

Clinical manifestations and health care utilisation in septo-optic dysplasia, with particular focus on overweight and obesity

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Purpose
To describe the clinical phenotype, and burden of health care utilisation in children with septo-optic dysplasia (SOD).
Methods
A single-centre retrospective chart review of patients with SOD seen at a single tertiary centre between 2003 and 2023 was performed. Data were obtained from the clinical record, electronic patient administration system and medical imaging reports, with comparison to local paediatric population data reported by the Australian Bureau of Statistics. An elevated BMI was defined as >1 SDS, and obesity as >1.65. Health care utilisation was assessed by reporting the number of medical and allied health specialties involved, and annual frequency of inpatient, outpatient and emergency department presentations.
Results
Eighty-one children were enrolled (median age 11.6 years, 32 females), 62/81 with bilateral optic nerve hypoplasia. Of 71 children with pituitary and anthropometric data, 41 had hypopituitarism and 31 had an elevated BMI. 37/51 children with pituitary structural defects had hypopituitarism compared to 3/20 without ($P < 0.001$). Children with SOD had higher rates of elevated BMI than the general population (42.5% vs 26.2%, $P = 0.001$) and obesity was more prevalent in those with (33%) and without (24.1%) hormonal deficiencies than the general population (6%, $P < 0.001$). Children with BMI elevation had greater median height SDS scores than those with a normal BMI (0.45 vs -0.78, $P = 0.001$). This was seen in those with and without hypopituitarism, but not demonstrated in those with GH deficiency ($P = 0.103$). Children with hypopituitarism who had an elevated BMI, developed this at a younger age than those without hypopituitarism (median 2.4 years [interquartile range 2.0-5.0] vs 5.9 years [4.1-10.5], $P = 0.038$). 12/31 with elevated BMI and 6/19 with obesity met criteria for these at 2 years of age. Approximately two thirds (55/81) were diagnosed in infancy. The median age at diagnosis of first endocrinopathy was 0.6 years (0.2-3.8). The median number of medical and allied health specialties seen was 9, with 70/81 seeing 5 or more specialties. Children with hypopituitarism had more frequent emergency department presentation, inpatient admission, and outpatient appointments than those without pituitary dysfunction.
Main Conclusions
SOD is a complex multisystem disorder. Regarding BMI elevation, although those with hormonal deficiencies have greater prevalence and develop BMI elevation earlier, prevalence is higher in children with SOD irrespective of pituitary function. The high rates of healthcare attendance in multiple specialties support the importance of treatment in a multidisciplinary clinic to ensure comprehensive care and minimise burden on families.

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P968

JOINT1615

Clinicopathological characteristics associated with the prognosis of recurrent gonadotroph tumors

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Background
Although gonadotroph tumor regrowth is frequent after pituitary surgery, the systematic use of adjuvant radiotherapy is limited by its long-term complications. In this context, it is important to predict which tumors are most likely to regrow after surgery, and especially, which tumors are most likely to regrow rapidly, and thus which patients might benefit the most from adjuvant radiotherapy vs active surveillance. Clinicopathological characteristics associated with the prognosis of radiotherapy-naïve, recurrent pituitary tumors are currently unknown.
Methods
Here, we performed a longitudinal, observational, retrospective, monocentric cohort study, with the aim of analyzing the clinicopathological characteristics associated with the prognosis of recurrent, radiotherapy-naïve gonadotroph tumors, specifically with the progression-free survival after a second pituitary surgery.
Results
Forty-four patients with recurrent gonadotroph tumors met the inclusion criteria. Ten of these patients had received adjuvant radiotherapy after the second surgery and were excluded from the study cohort. Of note, none of these 10 patients with adjuvant radiotherapy after the second surgery has progressed during the available follow-up ($P = 0.009$). In addition, we found that the Ki67 index of radiotherapy-naïve, recurrent gonadotroph tumors was the only parameter statistically associated with the progression-free survival after the second surgery, $P = 0.02$. Specifically, radiotherapy-naïve gonadotroph tumors with a positive Ki67 index had lower progression-free survival after the second surgery (median 31 months) compared to radiotherapy-naïve gonadotroph tumors with a negative Ki67 index (median 75 months).
Conclusion
Our study confirms the good efficacy of adjuvant radiotherapy for gonadotroph tumors. In addition, our study pinpoints that the Ki67 index could be used to guide the management strategy for recurrent gonadotroph tumors that are still radiotherapy-naïve by the time of the second pituitary surgery. Specifically, a positive Ki67 index should tilt the balance towards adjuvant radiotherapy instead of active surveillance.

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P969

JOINT326

Glucagon stimulation test and insulin tolerance test provide equally strong stimulus for growth hormone and cortisol secretion: a cross-over study

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Background
Insulin Tolerance Test (ITT) and Glucagon Stimulation Test (GST) constitute two most commonly used tests in assessment of anterior pituitary function in terms of both growth hormone (GH) and cortisol secretion. We compared concentrations of glucose, cortisol and GH during ITT and GST in 19 subjects (five males), mean age 33.8 years (range 19-60), mean BMI 27.8 kg/m^2 (range 16.5-47.6). Patients were investigated for amenorrhoea ($n = 8$), had history of pituitary macro- ($n = 2$), or microadenomas ($n = 5$), isolated diabetes insipidus ($n = 1$), iatrogenic glucocorticoid-induced adrenal suppression ($n = 1$), hypopituitarism after congenital CMV infection ($n = 1$), or history of cranial irradiation (astrocytoma), $n = 1$. Both Insulin Tolerance Test and standard fixed-dose GST (0, 30, 60, 90, 120, 150 and 180 minutes) were performed in all subjects.
Results
As expected, minimal glucose concentrations were lower during ITT (29.7 ± 7.67 mg/dl, at 30 minutes of ITT) than during GST (73.6 ± 9.67 mg/dl, at 180 minutes of GST, $P < 0.001$) though glucose fluctuations (ΔGlucose) were higher during GST (77.8 ± 22.6 mg/dl vs 56.7 ± 10.9 mg/dl, $P = 0.002$, for GST and ITT, respectively). There was, however, no difference in either cortisol (ΔCortisol 9.28 ± 3.79 µg/dl vs 8.49 ± 3.46 µg/dl, $P = 0.4$), or growth hormone fluctuations during both tests (ΔGH 10.23 ± 10.36 ng/ml vs 10.52 ± 9.67 ng/ml, $P = 1.0$, for GST and ITT, respectively).
Conclusion
Despite the absence of frank hypoglycaemia during GST, in contrast to ITT, both tests lead to similar increments in cortisol and growth hormone in adult individuals. Hence, Glucagon Stimulation Test should not be considered as an "inferior" option in comparison to Insulin Tolerance Test for assessment of an anterior pituitary function.

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P970

JOINT1751

Sellar and parasellar lesions in the childhood, adolescence and transition age

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Background

Recognizing sellar and parasellar lesions (S&PL) during childhood, adolescence, and transition age can be challenging and is often delayed due to the rarity of these diseases.

Objective

To investigate the clinical characteristics and types of pediatric S&PL:pituitary adenomas (PAs), and nonpituitary lesions (neoplastic, inflammatory).

Methods

A total of 195 patients (11.7%) with PAs diagnosed before the age of 25 were identified from the Department of Neuroendocrinologýs PA database ($n = 1668$) spanning the past 20 years and compared with 47 pediatric patients with nonpituitary S&PL. We analysed gender, age at diagnosis, size and type of S&PL.

Results

A total of 242 patients S&PL were included in the study (189 females,78.1%), with a mean age of 19.6±0.3years (range,3-25). Among these,195 patients had PA, with a mean age of 20.5±0.2years (range,10-25;161 females,82.6%). Of the PA patients,56 (28.7%) were younger than 18 years at the time of diagnosis. Functional PAs were significantly more common ($n = 151$;77.4%) compared to non-functioning PAs ($n = 44$;22.6%). Prolactinomas were the most prevalent type of functional PAs ($n = 133$;68.2%), with 89 microadenomas (86 in females). Thirteen patients (6.2%) had somatotropinomas, most of which were macroadenomas ($n = 12$), with male predominance ($n = 9$). Five patients (2.6%) had corticotropinomas, including three microadenomas (2 in males). Non-functioning PAs accounted for 44 cases (22.6%), with 18 microadenomas (17 in females). Patients with corticotropinomas were younger than those with prolactinomas or non-functioning PAs (17.4±1.4 vs. 20.6± 3.2 and 20.4±3.3years, respectively; $P < 0.05$). Microadenomas ($n = 111$;56.9%) were significantly more prevalent than macroadenomas ($n = 63$;32.3%;$P < 0.05$;tumor size unknown in 21). In conrast,47 patients with nonpituitary S&PL were significantly younger than the PA group (mean age:16.1±0.9 vs. 20.5± 0.2years,$P < 0.001$) and exhibited a male predominance ($n = 28$,59.6%). Craniopharyngiomas were the most common type of nonpituitary lesion ($n = 22$,46.8%), followed by germinomas ($n = 10$,21.3%). Other neoplastic lesions included three xanthogranulomas, one chordoma, one glioma and one granulosa cell tumor ($n = 6$,12.8%). Additionally, histiocytosis X was identified in five patients (10.6%) and hypophysitis was diagnosed in four (8.5%). Among patients with nonpituitary lesions, almost all ($n = 42$,89.4%) underwent surgery, and 22 patients (46.8%) received radiation therapy. Hypopituitarism was common in this group, with 39 patients (83%) diagnosed with multiple pituitary hormone deficiencies (PHD), five (10.6%) with isolated PHD, and 15 (31.9%) with ADH deficiency. Only three patients maintained normal pituitary function (6.4%).

Conclusion

Sellar and parasellar lesions in pediatric patients are rare. Among PAs, functioning tumors, particularly microprolactinomas, are the most common phenotype, with a notable female predominance. Microadenomas are uncommon in adolescent males. Somatotropinomas are predominantly macroadenomas with a male predominance, contrary to corticotropinomas (microadenoma, no sex difference). Patients with nonpituitary S&PL tends to be younger, predominantly male, and more frequently present with hypopituitarism and ADH deficiency compared to those with PAs. Managing these pediatric patients is particularly challenging due to the risk of late-onset complications (endocrine, metabolic, bone, and cardiovascular disorders).

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P971

JOINT1485

A Novel autosomal recessive multiple pituitary hormone deficiency and obesity syndrome associated with the SH2B1 gene

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Introduction

The SH2B1 gene encodes an important adaptor protein that is involved in the leptin-melanocortin pathway. Heterozygous variants of SH2B1 have been linked to various conditions, but homozygous variants have not been documented. This report presents a case of a homozygous SH2B1 variant associated with syndromic obesity and multiple pituitary hormone deficiencies. **Case:**A fifteen-year 7-month-old female, presented with the absence of menstrual bleeding despite having started oral contraceptive therapy for primary amenorrhea. She had delayed neuromotor development. Parents were second degree cousins and were both obese. Mother's and father's body mass index (BMI) were 35.9 kg/m^2, 31.5 kg/m^2, respectively. Her target height was 152.5 cm (-1.8 SDS). On physical examination; weight was 63.65 kg (1.1 SDS), height was 147 cm (-2.57 SDS), and BMI was 29.46 kg/m^2 (2.45 SDS). Pubic hair stage was 4 and breast development was Tanner stage 1. The patient had acanthosis nigricans and central obesity, along with a low hairline, short neck, and micrognathia. Cataract, strabismus, amblyopia, myopia, astigmatism, and mild hearing loss were also detected. The WISC-R test indicated mild intellectual disability. Laborotory findings were as follows; TSH: 1.6 mU/l (0.51-4.17), fT4: 0.94 ng/dl (0.98-1.63), FSH: 8.6 mIU/mL (3.5-12.5), LH: 4.59 mIU/mL (2.4-12.6), estradiol (E2): <25 pg/mL (30.9-90.4), AMH: 0.26 ng/mL (1.9-8.3), ACTH: 28.1 ng/l (7.2-63.3), cortisol: 15.8 mg/dl (4.82-19.5), IGF-1: 147 mg/l (151-485), prolactin (PRL): 2.75 mg/l (4.79-23.3). In the LHRH test performed due to delayed puberty, peak FSH was 29.6 mIU/mL, LH 82.1 mIU/mL, with E2 <25 pg/mL. Puberty was delayed, and hormone levels indicated central hypothyroidism, hypoprolactinemia, and hypothalamic hypogonadotropic hypogonadism. Abdominal and pelvic ultrasound revealed grade 2 hepatosteatosis and a hypoplastic uterus with right ovary 1.8 cc, and left ovary 2.99 cc. Pituitary MRI was normal. Clinical exome panel for syndromic obesity revealed a homozygous c.2083G>A (p.Val695Met) pathogenic variant in *SH2B1* gene. Both parents were heterozygous for the same variant.

Conclusion

The homozygous *SH2B1* variant identified in this patient is associated with a novel syndrome characterized by obesity, short stature, intellectual disability, hearing loss, cataracts, and multiple pituitary hormone deficiencies. These findings have not been reported in heterozygous SH2B1 variants and provide new insights into the gene's role. The SH2B1 gene may be important for defining an autosomal recessive syndrome with these features.

Keywords

Syndromic obesity, hypopituitarism, hypogonadism, SH2B1.

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P972

JOINT2090

Delayed puberty as the initial presentation of combined oxidative phosphorylation deficiency 55

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Background

Combined Oxidative Phosphorylation Deficiency 55 (COXPD55) is a rare mitochondrial disorder caused by mutations in the POLRMT gene, which encodes the mitochondrial RNA polymerase critical for mitochondrial gene expression and genome replication.

Case Presentation

A 17.3-year-old female presented with primary amenorrhea and a reportedly absent uterus. Anthropometric assessment indicated a height SDS of -5.31, weight SDS of -4.67, BMI SDS of -0.93, occipitofrontal circumference of 48 cm (-6.86 SD), and sitting height of 65.9 cm (-5.64 SD). She also exhibited delayed bone age (10.99 years, SDS -6.5) and minimal pubertal development (Tanner stage B2). Notable phenotypic features included microcephaly, alacrima, corneal scarring, learning difficulties, scant scalp hair, low posterior hairline, hypotelorism, hyperconvex nails, and a high-arched palate with a narrow jaw.

Endocrine Evaluation

The patient exhibited hypogonadotropic hypogonadism with low FSH (0.4 mIU/mL; Ref: 0.9-9.1) and LH (<0.3 mIU/mL; Ref: 0.4 - 25) and profoundly reduced estradiol (<18 pmol/l; Ref: 22.3 - 205.2). Thyroid function tests and cortisol levels were within normal limits. IGF-1 and IGFBP-3 were within

reference ranges, at 303.0 ng/mL (Ref: 156 - 479) and 4,207 ng/mL (Ref: 3,705 - 8,065), respectively. DHEA-Sulfate was 7.79 umol/l (Ref: 1.77 - 9.99). Anti-Müllerian hormone was diminished at 0.45 ng/mL. Magnetic resonance imaging initially suggested an absent uterus, but ultrasound confirmed an infantile uterus.
Genetic Analysis
Whole exome sequencing identified a pathogenic POLRMT mutation (c.910C > T, p.Gln304Ter, NM_005035.4). The patient was heterozygous, with maternal heterozygosity and negative paternal testing. Inheritance involved both autosomal recessive and dominant patterns, with the mutation classified as likely pathogenic.
Discussion
Prior COXPD55 cases highlight developmental delay, renal dysfunction, and neuromuscular abnormalities. Bowden *et al*. (2013) described renal Fanconi syndrome with developmental delay and hypotonia, while Olahova *et al*. (2021) reported heterogeneous presentations among 8 patients, including short stature, developmental delay, and eye abnormalities, suggesting the phenotypic variability of COXPD55. However, delayed puberty as the primary clinical manifestation has not been previously reported.
Conclusion
This case is the first to document COXPD55 presenting primarily with delayed puberty and hypogonadotropic hypogonadism, expanding the clinical spectrum of the disorder. The diverse clinical manifestations underscore the importance of early genetic evaluation to facilitate accurate diagnosis and individualized therapeutic interventions.

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P973

JOINT3567

Long-term safety and efficacy of once-daily oral paltusotine in the treatment of patients with acromegaly: ACROBAT advance year 4 analysis

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Background
Paltusotine is a non-peptide, highly selective SST2 receptor agonist in development as a once-daily, oral treatment for acromegaly and carcinoid syndrome. This long-term analysis of safety and efficacy of paltusotine includes patients with acromegaly who have been followed for up to approximately 4 years.
Methods
ACROBAT Advance is an ongoing, single-arm, open-label extension study of paltusotine in patients with acromegaly. Enrolled patients had completed either ACROBAT Edge or Evolve phase 2 parent studies. In Edge, at enrollment all patients were candidates for combination drug therapy: either sub-optimally controlled on an injected SRL (octreotide or lanreotide) alone or in combination with cabergoline, or required combination therapy or pasireotide to achieve normal IGF-I levels. In Evolve, enrolled patients had normal IGF-I levels on injected SRL monotherapy. When the Advance study was initiated, paltusotine was formulated as a capsule (dose range, 10-40 mg); all patients were switched to the tablet formulation (dose range, 20-60 mg) during year 3 of the study. Adjunctive treatment with cabergoline or pegvisomant was allowed in patients who did not attain normal IGF-I levels on the maximum dose of paltusotine.
Results
Forty-three patients were enrolled in Advance (Edge, $n = 32$; Evolve, $n = 11$; 88% of eligible patients): at baseline, mean ± SD age 53.0 ± 11.6 years, 56% female, 86% previous pituitary surgery, and no prior radiotherapy. IGF-I control in Edge and Evolve subsets remained stable at parent study baseline values. For all patients pooled, median (IQR) IGF-I levels were 1.15× ULN (0.84-1.46; $n = 43$) at parent study baseline; in Advance, 1.14× ULN (0.89-1.29; $n = 40$), 1.07× ULN (0.91-1.30; $n = 37$), 1.02× ULN (0.83-1.21; $n = 33$), and 1.01× ULN (0.83-1.13; $n = 20$) at months 12, 24, 36, and 48, respectively. Acromegaly symptoms, as measured using Acromegaly Symptom Diary (score range, 0-70; higher values indicate greater symptom burden), were stably controlled: median (IQR) score of 8.6 (3.6-20.1; $n = 21$) at parent study baseline; in Advance, 10.5 (5.0-18.5; $n = 40$), 10.0 (5.0-23.5; $n = 36$), 11.0 (4.0-26.0; $n = 33$), and 10.0 (4.0-18.0; $n = 20$) at months 12, 24, 36, and 48, respectively. Two serious drug-related AEs (cholelithiasis) were reported. Of the 8 patients who discontinued study, 2 were due to AEs (mild or moderate).
Conclusion
Long-term results (up to ~4 years) show that once-daily oral paltusotine treatment was well tolerated, with stable biochemical and symptom control relative to that observed with injected SRLs.

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P974

JOINT3603

Natural history of non-functioning pituitary microadenomas: A systematic review and individual participant data meta-analysis

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Background
Increased neuroimaging for different indications and thus prevalence of non-functioning pituitary adenomas (NFPAs) is set to impose a significant burden on patients, practitioners, and amplify costs due to the need for complex and extensive follow-up.
Objective
To determine the risk of surgical intervention and the risk of developing a new endocrinopathy during follow-up in patients with conservatively treated micro-NFPAs.
Methods
We conducted a bibliographical search on PubMed and EMBASE identifying relevant studies. Authors of eligible studies were invited to share individual participant data (IPD). Eligible studies were cohort studies including patients with conservatively treated micro-NFPAs with at least one follow-up MRI. Fourteen studies met the inclusion criteria. Six authors provided IPD ($n = 588$). Data were reanalyzed for verification. In case of discrepancies the original authors were contacted for authentication. Data was extracted using a pre-piloted form.
Results
Risk estimates were reported as number of events per 100 person-years (PYs). Estimates were pooled using the two-step approach. Overall risk of surgery was 0.2/100PYs (95%CI: 0.0 to 0.5; $I^2 = 31\%$). Risk of surgery due to visual impairment was 0.1/100PYs (95%CI: -0.1 to 0.2; $I^2 = 0\%$). Risk of developing a new endocrinopathy was 1.3/100PYs (95%CI: 0.3 to 2.2; $I^2 = 47\%$). We found no difference in risk relative to baseline tumor size (≥6 mm or <6 mm), sex, or age (all P-values > 0.25). Data for classical meta-analysis were available for 7 studies ($n = 1079$) and supported the IPD Results.
Conclusions
Events relevant to patients such as surgery or development of new endocrinopathies rarely occurs in patients with micro-NFPAs and routine follow-up can safely be reduced in the majority of these patients. Current guidelines may need to be revisited regarding this issue.

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P975

JOINT1060

Giant cell tumour of the bone mimicking pituitary macroadenoma: a case report

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Introduction
Giant cell tumour of the bone (GCTB) is a rare tumour that is usually benign but can be locally aggressive. GCTB accounts for about 15–20% of all benign bone tumours and typically arises from the epiphysis of long bones. Surgical removal of GCTBs remains the gold-standard treatment. However, there have been a few reported cases where the tumour originated from the sphenoid bone, and in these instances, total surgical removal is often not feasible due to the proximity of critical anatomical structures. More than a decade ago, denosumab was approved as an alternative treatment for this condition.
Case Report
In May 2018, a 16-year-old female patient presented with severe headache, dizziness, vomiting, double vision and right-sided retrobulbar pain. A pituitary MRI demonstrated a large sellar mass that occupied the pituitary gland and invaded the right cavernous sinus. In June 2018, she underwent a paraseptal, transsphenoidal adenomectomy. However, the histological evaluation revealed only physiological pituitary hyperplasia. In August 2018, she returned with alarming symptoms. Following a thorough endocrine examination, she was diagnosed with severe panhypopituitarism and appropriate hormone replacement therapy was initiated. In September 2018, a follow-up MRI showed significant tumour progression, prompting a second surgical intervention. At that time, the tumour measured 33 x 28 x 51 mm, invaded the right cavernous sinus and elevated the optic chiasm. No visual disturbances were detected during the ophthalmological examination. The histopathological results from this surgery confirmed the presence of GCTB. Subsequently, she began treatment with denosumab. Five months later, a new MRI indicated a 40% regression in tumour size. Denosumab therapy was continued until December 2021, during which stable disease was observed both clinically and radiologically, leading to the discontinuation of the drug. However, in July 2022, a follow-up MRI revealed significant tumour progression and denosumab therapy was reinstated. To date, the patient receives 120 mg of denosumab every four weeks, and there has been no further progression of the tumour.
Conclusion
To our knowledge, this case report presents the longest use of denosumab therapy with efficacy and safety for GCTB in the sellar region. We have not observed any side effects from denosumab throughout the six-year treatment period. However, further research is necessary to determine this thyrapy's optimal long-term dosage and duration and to identify other treatment targets that could provide similar tumour control.

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P976

JOINT2521

The systemic effects of hormone replacement therapy for central hypoadrenalism in patients affected by hypothalamic-pituitary diseases: a retrospective and longitudinal study

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Glucocorticoid replacement therapy in secondary adrenal insufficiency is lifesaving, but the currently available literature reveals that overtreatment can result in long-term effects on bone, cardiovascular and metabolic systems. We conducted a retrospective, observational, longitudinal study at our hypothalamic-pituitary pathology unit on 140 patients who had undergone neurosurgery in the hypothalamic-pituitary region before 2020 for PIT-NETs, craniopharyngiomas, Rathke cleft cyst, chordomas and meningiomas, to verify the effects of glucocorticoid replacement therapy. Exclusion criteria encompassed the utilization of corticosteroids for unrelated indications and prior bariatric surgery. The patients were divided into two groups: group A, consisting of 70 patients with pituitary disease and hypoadrenalism who had been treated with glucocorticoid replacement therapy for at least 3 years, and group B, consisting of 70 patients with pituitary disease but without hypoadrenalism. Lipid metabolism, carbohydrate metabolism, body weight and blood pressure were analyzed at baseline (at diagnosis or immediately before neurosurgery) and after 3 years of therapy. Comparing the two groups, there was no difference in age, carbohydrate metabolism, dyslipidemia and hypertension at baseline. At follow-up, a worsening of glucose metabolism was observed in 45/140 patients, and univariate analysis showed a higher incidence in patients receiving glucocorticoid replacement therapy (64.4%) compared to untreated patients (35.6%) ($P = 0.019$). This result was confirmed by multivariate analysis, which showed an association with glucocorticoid replacement therapy ($P = 0.014$) and with the presence of impaired glucose tolerance ($P = 0.016$) and impaired fasting glucose ($P = 0.04$) at diagnosis. Regarding lipid metabolism, 92/140 patients worsened, of whom 56.5% were on treatment ($P = 0.033$) and 43.5% were not. However, upon multivariate analysis, the only significant data were treatment for dyslipidemia at baseline ($P = 0.001$) and central hypothyroidism ($P = 0.001$). The data on arterial hypertension demonstrated deterioration in 54/140 patients: 30 were undergoing glucocorticoid replacement therapy, while the remaining 24 were not ($P = 0.298$). Multivariate analysis showed a statistically significant association with older age at diagnosis ($P = 0.007$) and with hypertension at baseline ($P = 0.001$). In conclusion, a glucocorticoid replacement therapy that includes a holistic management of the patient, in association with the replacement of other possibly deficient axes, does not have an impact on the risk of developing hypertension and dyslipidemia. Instead, glucocorticoid replacement therapy resulted associated to worsening of glucose metabolism, particularly in patients already predisposed.

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P977

JOINT2562

Circulating vitamin D levels predict the occurrence of vertebral fractures in patients with cushing's disease

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Context
Skeletal fragility is a clinically relevant complication of Cushing's disease, occurring in 15%-78% of patients. Limited studies are available on predictors of vertebral fractures. Here, we investigated the correlations between occurrence of incidental VFs (i-VFs) and serum V25OH-D concentrations, before and during cholecalciferol supplementation.
Patients and methods
A longitudinal and retrospective study was performed on patients affected by Cushing's disease, treated and untreated with D3 supplementation. The primary objective of the study was to investigate the correlations between the occurrence of VFs and serum V25OH-D concentrations.
Results
Out of 159 patients diagnosed for Cushing's disease at our center, 26 patients were included. At baseline, the median serum V25OH-D level was 21.1 ng/mL (IQR: 17) in the whole study population. Six patients were affected by osteopenia/osteoporosis (23.1%), and 4 patients carried prevalent VFs (15.4%). The median serum V25OH-D concentration was 20.3 (IQR: 27) ng/mL in patients without osteopenia/osteoporosis and was 24.9 (IQR: 15.7) ng/mL in patients with osteopenia/osteoporosis ($P = 0.648$). The median serum V25OH-D concentration was 22.1 (IQR: 16) ng/mL in patients without prevalent VFs and was 11.3 (IQR: 34) ng/mL in patients with prevalent VFs ($P = 0.166$). Eleven patients were treated with D3 supplementation (42.3%). Serum V25OH-D levels at baseline were slightly but not significantly lower in D3 treated vs untreated patients (20.3 IQR: 27.3 vs. 22 IQR: 18 ng/mL; $P = 0.61$). The median D3 weekly dosage was 12500 IU (IQR: 14500), median duration of D3 supplementation was 37 months (IQR: 26). No adverse events related to D3 supplementation were reported by patients or identified from medical records. At last follow-up, seven patients developed incidental VFs (26.9%): three patients were on D3-supplementation (42.9%), and four were not on D3-supplementation (57.1%; $P = 0.665$). Final serum V25OH-D level was lower in patients with i-VFs (28.6 ng/mL, IQR:4.1) as compared to patients without i-VFs (34.2 ng/mL, IQR:9.6; $P = 0.007$). Patients with i-VFs had lower V25OH-D levels before starting D3 supplementation (11.6 ng/mL IQR:10), then patients without i-VFs

(24.9 ng/mL IQR:25.3, $P = 0.003$). I-VFs occurred more frequently in males (57.1%) then in females (42.9%, $P = 0.047$). The logistic regression confirmed the protective role of V25OH-D levels >12 ng/mL before D3-supplementation (OR: 0.07 95%IC:0.01-0.58 $P = 0.05$), of V25OH-D levels >35 ng/mL during follow-up; and the not-protective role of the male gender (OR: 1.5 95%IC:1.1-2.4 $P = 0.008$).
In Conclusion
Our study proved that D3-supplementation should be consider in patients affected by Cushing's disease to reach circulating V25OH-D levels protective for the occurrence of i-VFs.

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P978

JOINT2884

Assessing multiple variables following arginine test enhances the diagnosis of vasopressin deficiency

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Context
A recent head-to-head multicenter trial established the superiority of hypertonic saline-stimulated copeptin in the diagnosis of vasopressin deficiency (AVP-D), with the arginine test presenting suboptimal performance. Nevertheless, the latter is less costly, better tolerated and easier to perform. We tried to enhance its performance by including other parameters on top of copeptin levels.
Methods
We conducted a retrospective analysis of arginine tests performed at our Unit for suspected AVP-D. Clinical, biochemical and radiological findings were collected. Final diagnosis was defined based on a revision of clinical picture, performed tests and follow-up data.
Results
We considered 19 patients, 8 of them presenting a final diagnosis of AVP-D from different causes (42%). Copeptin response to arginine was flattened in AVP-D patients (AUC 4.48 vs 6.97, $P = 0.11$) but, irrespectively of the indexes and thresholds used, it could not provide good discrimination from primary polydipsia (PP). The best performing index was copeptin level at 90 minutes (cut-off 3.45 pmol/l, sensitivity 87.5%, specificity 63.6%, diagnostic accuracy 73.7%, ROC-AUC 0.773). AVP-D patients at the end of the arginine test presented lower urinary osmolarity (UOsm) and higher plasma osmolarity and sodium (Na) levels. The latter was the best predictor of AVP-D (cut-off 141.5 mmol/l, sensitivity 87.5%, specificity 100%, diagnostic accuracy 94.7%, ROC-AUC 0.989). When combining multiple parameters, we were able to obtain perfect discrimination between AVP-D and PP in our cohort. In a multistep approach, a final Na above 142 or below 140 mmol/l identified alone AVP-D and PP respectively, while in case of intermediate values a copeptin peak <4.1 pmol/l or a final UOsm <428 mOsm/kg correctly diagnosed AVP-D (overall diagnostic accuracy 100%). We also obtained via logistic regression formulas to derive a corrected sodium value providing a diagnostic accuracy of 100% (cut-offs: 138.8 mmol/l based on final Na and peak copeptin; 138 mmol/l based on final Na and UOsm).
Discussion
In our cohort, the use of multiple parameters following arginine stimulation could enhance the test performance up to a complete discrimination between AVP-D and PP. Interestingly, this result could be obtained also without copeptin measurement. Our study has nevertheless various limitations, the most important ones being the small sample analysed and the non-use of hypertonic saline-stimulated copeptin. Larger studies with the use of current gold standard test for comparison are needed to evaluate the replicability of our findings.

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P979

JOINT3359

Cure from acromegaly after long-term medical treatment: may somatostatin receptor ligands drive complete disease disappearance in patients never treated with surgery and/or radiotherapy?

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Context
Although pituitary surgery is the first therapeutic option for acromegaly, several patients are not eligible for or refuse it. Somatostatin receptor ligands (SRLs) are the treatment of choice in these patients.
Aim
To investigate prevalence and determinants of acromegaly cure in patients treated only with SRLs medical therapy.
Methods
Monocentric retrospective study evaluating 43 acromegaly patients (22 women, 21 men, mean age 66.5±10.8 years) treated with SRLs as first line treatment (mean duration 14.1±7.1 years), never undergone to pituitary surgery or radiotherapy.
Results
Overall, 16 patients (37.2%) experienced tumour disappearance at MRI, of which 6 (37.5%) achieved also biochemical remission (IGF-I level <1xULN), with a successfully withdrawn of SRLs therapy without relapse (cure) after long-term (mean 19 years) SRLs therapy. Patients with tumour disappearance at MRI were older ($P = 0.01$), mainly women ($P = 0.002$), with smaller tumours at diagnosis ($P = 0.04$) as compared to those with tumour persistence. After 1 year-SRLs treatment GH levels were significantly lower ($P = 0.04$) and prevalence of IGF-I normalization (IGF≤1xULN, 77% *vs* 44%, $P = 0.07$) slightly higher in the former as compared to the latter. Considering cured patients, they were all women ($P = 0.07$), with significantly lower levels of random GH ($P = 0.02$) and nadir GH after OGTT ($P = 0.03$) harbouring smaller pituitary tumours ($P = 0.09$) at diagnosis as compared to patients with biochemical persistence of acromegaly. At ROC analysis, at diagnosis random GH < 6.1μg/l had 82.3% sensitivity and 80% specificity (AUC=0.802, $P = 0.03$) to predict acromegaly cure after long-term SRLs. Similarly, at diagnosis nadir GH < 1.93μg/l had 100% sensitivity and 66.7% specificity (AUC=0.888, $P = 0.03$) to predict cure after long-term SRLs. According to the median SRLs duration (13 years), patients administered with SRLs for more than 13 years had a significantly higher prevalence of tumour disappearance at MRI (47.8% *vs* 22.7%, $P = 0.04$) and a slightly higher prevalence of disease cure (21.7% *vs* 4.5%, $P = 0.07$) as compared to those with a shorter therapy length. According to the median age at the evaluation (65 years), patients >65 years had a significantly higher prevalence of tumour disappearance at MRI (47.8% *vs* 22.7%, $P = 0.04$) and a slightly higher prevalence of cure (21.7% *vs* 4.5%, $P = 0.07$) as compared to younger patients.
Conclusions
First line medical therapy is a valid option for several acromegaly patients. Among them, women and older patients with small pituitary tumours and lower levels GH at diagnosis could benefit more of this choice, being able to obtain the tumour disappearance at MRI and even the d cure.

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P980

JOINT1376

Clinical profile of patients with hypopituitarism in a tertiary endocrine center in nepal

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Hypopituitarism is an uncommon condition with limited data from Nepal. We retrospectively reviewed data of 36 patients who attended our endocrine center from April 2013 to March 2024. The mean age was 35.88 ± 7.17 years (range 3-69 years). 6 patients were ≤18 years. There were 18 (50%) males and 18 (50%) females. The mean BMI was 25.52 ± 4.76 kg/m^2 (range 14.9 - 33.3). The most common symptom was nausea/vomiting in 14 patients (38.8%) followed by fatigue in 13 patients (36.1%). Visual abnormalities were detected in 12(33.3%) and headache in 12(33.3%) patients. Out of 18 female patients, 15(83.3%) had menstrual disturbances. Secondary amenorrhea was present in 13 patients (72.2%), infertility in 4 patients and loss of libido was present in 3 patients. 2(5.5%) patients presented with pituitary apoplexy. Surgery was the most common cause for hypopituitarism {14(38.8%) patients}, idiopathic in 13 patients (36.1%), surgery + post radiation in 6 (16.6%) patients, Sheehan's syndrome in 2(5.55%) patients, post radiation in 1 patient (2.77%). Co-morbidities like diabetes were seen in 7 (19.4%) and hypertension in 5(13.8%)

patients. One patient had four components of hypopituitarism (hypogonadism + hypothyroidism +hypocortisolism +AVP-D) while most patients 18(50%) had only 2 components (hypocortisolism + hypothyroidism). Hypothyroidism was present in 34 (94.4%) patients. Pituitary adenoma was detected in MRI in 12 patients (33.3%). Among them, 2 had macroprolactinoma, 2 ACTH dependent Cushing disease, 1 had Thyrotropinoma and rest had Nonfunctioning pituitary adenoma (NFPA). Craniopharyngioma was seen in 6 patients (16.6%), Empty sella in 8(22.2%), Meningioma in 2(5.5%) and Rathke cleft cyst 1(2.7%) patient. 7 (19.4%) patients had normal MRI findings. Management was with steroids + thyroxine + Hormone Replacement Therapy (HRT) +desmopressin in 3 patients, steroids + desmopressin in 1 patient, steroids + thyroxine HRT in 9 patients, steroids + HRT + desmopressin in 1 patient, steroids + thyroxine + desmopressin in 2 patients, steroids + thyroxine in 15 patients, thyroxine + HRT in 4 patients and HRT alone in 1 patient (although he was also GH deficient). Steroids used were prednisolone in 25 patients and hydrocortisone in 6 patients. HRT used was OCP in 7 patients, testosterone in 8 patients, HCG and FSH/HMG in 2 patients, both of them (one male, other female) had successful pregnancies. Desmopressin was nasal in 5 patients and oral in 2 patients.

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P981

JOINT2609

Pituitary apoplexy: a retrospective study of 48 patients from a tertiary endocrine center

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Pituitary apoplexy is a rare, potentially life-threatening condition caused by hemorrhage or infarction of the pituitary gland, often involving a pre-existing pituitary adenoma. Prompt diagnosis and intervention are essential to optimize patient outcomes. We conducted a retrospective review of 48 pituitary apoplexy cases diagnosed and managed at our tertiary endocrine center. The cohort was predominantly female (62.5%), with a mean age at diagnosis of 50.9 $\pm$ 17.2 years. Headache was the most frequent presenting symptom (52%), followed by amenorrhea (29%; 93% related to Sheehan syndrome). Other symptoms included visual disturbances (23%), cranial nerve palsies (21%), agalactorrhea (19%; all related to Sheehan syndrome), nausea/vomiting (15%), impaired mental status (11%), and fever (2%). A clear precipitating factor was identified in 15 patients (31%), including 14 due to postpartum hemorrhage (Sheehan syndrome) and 1 to somatostatin analog treatment. Potential associations were noted with intense emotional stress (2 patients) and warfarin therapy (1 patient). Endocrine evaluation at diagnosis revealed multiple pituitary deficits: secondary adrenal insufficiency (83%), secondary hypothyroidism (81%), hypogonadotropic hypogonadism (73%), GH/IGF-1 deficiency (44%), prolactin deficiency (35%), and diabetes insipidus (8%). Patients exhibited an average of 3.1 $\pm$ 1.5 hormonal deficiencies, with only 3 (6%) presenting unremarkable blood test Results Imaging showed macroadenomas in 52% of cases (60% with hemorrhage) with a mean tumor diameter of 21 mm; empty/partially empty sella turcica in 27%; microadenomas with hemorrhage in 4%; and Rathke's cleft cyst with hemorrhage in 2%. Surgery was required in 12 patients (25%), mostly for macroadenomas with significant neurological/visual impairment. Pathology revealed 4 gonadotropinomas, 3 somatotropinomas, 2 corticotropinomas, 2 non-functioning adenomas, and 1 sample without identifiable pituitary tissue. Additionally, 5 patients (10%) underwent radiotherapy. Most patients (92%) required hormone replacement therapy, with 77% on levothyroxine, 77% on corticosteroids (hydrocortisone/prednisone), and 21% on testosterone. Less frequent replacements included estrogen/progesterone (10%), GH (2%), and desmopressin (2%). While pituitary apoplexy is acknowledged as a rare disease, our center has documented a significant number of cases, providing valuable insights into its clinical presentation and management. This highlights the need for increased awareness and prompt diagnosis, essential for improving outcomes in this challenging condition.

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P982

JOINT2487

Effectiveness of serial prolactin measurement in the subsequent detection of pituitary lesions

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Introduction

Hyperprolactinemia is a common reason of referral to endocrinology outpatient clinics. This condition may be due to physiological, pharmacological or pathological causes. After ruling out some of them, many studies suggest performing a serial prolactin measurement to eliminate stress hyperprolactinemia, and then continuing to study those who truly present altered prolactin values. Objective: to evaluate the subsequent effectiveness of serial prolactin measurement in the detection of pituitary lesions.

Materials and Methods

Descriptive study of 53 patients who underwent serial prolactin measurements between the years 2023-24 in follow-up in our clinics. Demographic (sex, age), analytical (basal prolactin, at 20 and 40 minutes) and radiological (magnetic resonance imaging (MRI) of the sella turcica and the presence of a lesion there) variables were collected. Regarding the measurement, a peripheral intravenous line was inserted and a baseline, at 20 and at 40 minutes value was taken. It was established that prolactin was elevated above 20 (men) or 25 (women). The statistical analysis was performed with the IBM SPSS v.25 programme (Statistical significance $P < 0.05$).

Results

53 patients were analysed, 83% of whom were women with a mean age of 29.9 $\pm$ 12.6 years. 73.6% and 77.4% of patients showed normal prolactin levels at 20 and 40 minutes, respectively. Basal and 20-minute prolactin, basal and 40-minute prolactin and basal and 20 and 40-minute prolactin means difference were 4.1 $\pm$ 6.3, 6.4 $\pm$ 10.1, and 2.2 $\pm$ 5.7, all of which were statistically significant. All patients with elevated prolactin levels at 40 minutes underwent sella turcica MRI, and lesions were observed in 58.3% of them.

Conclusion

In most cases, normalisation of prolactin levels is observed when serial measurements are performed at 20 and 40 minutes. In addition, a statistically significant difference is identified between the basal prolactin values and those obtained in subsequent measurements. Also, in most patients with an altered prolactin value at 40 minutes, the presence of a pituitary MRI lesion is observed. This supports the usefulness of serial prolactin measurement, not only to rule out stress hyperprolactinemia, but also to focus the diagnostic procedure on those patients with true hyperprolactinemia.

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P983

JOINT3216

Hyperprolactinemia in children and adolescents: clinical characteristics and etiological spectrum

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Objective

This study aims to evaluate the etiological, clinical, and biochemical characteristics of pediatric patients diagnosed with hyperprolactinemia.

Methods

We analyzed 160 pediatric patients diagnosed with hyperprolactinemia between January 2018 and December 2024. Hyperprolactinemia was defined as prolactin levels exceeding 25 ng/mL in girls and 20 ng/mL in boys on at least two separate occasions, with blood samples taken between 8:00 AM and 9:00 AM. Patients were categorized into two groups based on the underlying etiology: Group-1: Pituitary and Hypothalamic Disorders ($n = 38$), including prolactinomas ($n = 18$), non-functioning pituitary adenomas ($n = 8$), craniopharyngiomas ($n = 7$), and empty sella ($n = 5$). Group-2: Non-Pituitary and Hypothalamic Disorders (n

= 122), including polycystic ovary syndrome (PCOS) (n = 40), drug-induced hyperprolactinemia (n = 33), macroprolactinemia (n = 20), and idiopathic hyperprolactinemia (n = 29). Clinical presentations, biochemical findings, imaging results, and treatment responses were assessed.
Results
The median age at diagnosis was 15.2 years, (range: 2–17.9 years) with a female predominance of 73.1%. The median prolactin level was 45.8 ng/mL (range: 38.3–14,350). The median prolactin level in Group-1 was 213 ng/mL, which was significantly higher than the median level of 44 ng/mL observed in Group-2 ($P <$ 0.05). However, there were no significant differences between the two groups in terms of age, weight, height, and BMI SDS. The most common presenting symptoms were menstrual irregularities, galactorrhea, headache, and pubertal delay. Overweight/obesity were evident in 47.5% of the overall study cohort. Patients with PCOS exhibited the highest prevalence of overweight/obesity, with a rate of 70%. Cabergoline treatment achieved a 100% success rate in patients with prolactinomas. Additionally, at the end of the first year of cabergoline treatment, a significant decrease in BMI SDS was observed in the patients with prolactinomas ($P < 0.05$), with a mean BMI SDS of 0.8 $\pm$ 1.6 at baseline and 0.3 $\pm$ 1.1 after one year of treatment. Risperidone was the responsible agent in 82% of patients with drug-induced hyperprolactinemia, and prolactin levels normalized after drug discontinuation or switching to an alternative medication.
Conclusion
Pediatric hyperprolactinemia exhibits a diverse etiological spectrum, with PCOS and drug-induced cases being more common than previously reported. Prolactin levels can help differentiate pituitary adenomas from other causes, guiding management. Given that mild prolactin elevations were frequently observed in PCOS, it may be considered part of the PCOS phenotype rather than a distinct pathology, potentially reducing unnecessary endocrinological or radiological evaluations. Cabergoline was highly effective in prolactinoma patients, also contributing to BMI reduction, while drug-induced hyperprolactinemia, primarily linked to risperidone, resolved with medication adjustment.

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P984

JOINT2542

Improving tumour localisation in cushing's disease: synergistic use of 11c-methionine pet/ct and osilodrostat

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Background
Optimal long-term outcomes in Cushing's disease (CD) rely on precise localisation and complete resection of the ACTH-secreting adenoma while preserving normal pituitary function. However, adenomas can sometimes evade detection on conventional MRI. 11C-methionine PET/CT (11C-MET PET/CT) has emerged as an alternative imaging modality that may improve visualisation of these elusive tumours. We hypothesised that preoperative cortisol-lowering therapy would lead to increased ACTH levels, heightened tumour metabolic activity, and enhanced 11C-MET PET signal intensity. Osilodrostat, a potent 11-β-hydroxylase inhibitor, has demonstrated superior efficacy and tolerability compared to traditional steroidogenesis inhibitors such as metyrapone and ketoconazole.
Case
A 28-year-old man with a history of juvenile arthritis, total hip replacement, and postoperative pulmonary embolism presented with uncontrolled hypertension, centripetal obesity, purple striae, and significant weight gain, consistent with Cushing's syndrome (CS). Laboratory investigations confirmed ACTH-dependent hypercortisolism, with markedly elevated post-1 mg dexamethasone cortisol of 807 nmol/l (<50 nmol/l), ACTH of 56.7 ng/l (10–30 ng/l), and 24-hour urinary free cortisol (UFC) of 774 nmol/24h (0–164 nmol/24h). Salivary cortisol and cortisone levels were 13.5 nmol/l (<2.6 nmol/l) and 42.7 nmol/l (<18 nmol/l), respectively. Inferior petrosal sinus sampling (IPSS) ruled out an ectopic source of ACTH secretion, however, MRI failed to identify a discrete pituitary adenoma. Functional imaging with 11C-MET PET/CT demonstrated equivocal tracer uptake near the left cavernous sinus, but did not provide definitive adenoma localisation. Given persistent hypercortisolism, the patient was initially treated with metyrapone but intolerance, leading to a switch to osilodrostat (2 mg twice daily, titrated to achieve eucortisolaemia). With cortisol normalisation, ACTH levels tripled, suggesting increased tumour metabolic activity. After three months of sustained eucortisolaemia, repeat 11C-MET PET/CT revealed a markedly increased focal tracer avidity near the left cavernous sinus, providing a precise target for transsphenoidal surgery.
Conclusion
This case highlights a novel preoperative strategy for enhancing adenoma detection in CD. Cortisol-lowering therapy may improve the sensitivity of functional imaging, enabling more accurate tumour localisation and optimising surgical outcomes. If validated in larger cohorts, this approach could significantly enhance surgical cure rates while preserving normal pituitary function.

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Reproductive and Developmental Endocrinology

P26

JOINT437

Reproductive hormones in infertile men with Y chromosome microdeletions

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Background
Microdeletions in the AZF regions of the Y chromosome are well-recognized as a recurrent genetic cause of male infertility. The reproductive system is tightly regulated by hormones of the hypothalamic–pituitary–gonadal axis but large-scale studies investigating the endocrine effects of Y microdeletions are lacking.
Objective
The objective of this study is to investigate the level of reproductive hormones in infertile men with and without Y microdeletions.
Materials and methods
Results from a PCR based Y microdeletion analysis and hormone analyses (testosterone (n=7429), free testosterone (n=7416), LH (n=7509), SHBG (n=7506), FSH (n=7488), inhibin B (n=7535), and INSL3 (n=924)) were obtained from 7615 infertile men (age 20–60) evaluated from 1997 until 2024 at the Department of Growth and Reproduction, Rigshospitalet, prior to fertility treatment.
Results
Out of 7615 analysed patients, 564 (7.4%) had a Y microdeletion and 7051 had no Y microdeletion detected. Patients were grouped based on the specific type of microdeletions: gr/gr (n=263), b1/b3 (n=3), b2/b3 (n=166), b2/b4 (n=45), AZFabc (n=16), AZFbc (n=21) and complex deletions (n=50). Inhibin B and the inhibin B/FSH ratio were significantly lower in patients with b2/b4, AZFabc, AZFbc, and complex deletions ($P < 0.05$) mirrored by significantly higher FSH levels in the same patients ($P < 0.05$). Testosterone and free testosterone concentrations were significantly lower in patients with a AZFabc deletion ($P <$ 0.001), whereas LH was significantly higher in patients with b2/b4, AZFabc and AZFbc ($P < 0.05$). Reproductive hormones in patients carrying gr/gr and b2/b3 deletions did not differ significantly from patients without Y microdeletions. We did not have enough patients in the b1/b3 group or data on INSL3 to allow subdivision into specific types of microdeletions, however across all patients with Y microdeletions INSL3 did not differ significantly (P=0.71) when compared to patients without Y microdeletions.
Discussion and conclusions
Infertile men with larger and complex Y microdeletions have significantly lower inhibin B and inhibin B/FSH ratio along with significantly higher gonadotropins compared to infertile men without Y microdeletions. Only men with complete AZFabc deletions have significantly lower testosterone and free testosterone concentrations. We cannot deduce whether these differences are a direct or indirect effect of the microdeletions.

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P27

JOINT1806

Apoptosis markers and hormonal changes in male infertility

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Introduction
In mammalian testes, hormones regulate germ cell survival, with Sertoli cells playing a key role in spermatogenesis. Hormonal imbalances can trigger apoptosis, regulated by BCL-2 family proteins, which either inhibit (BCL-2) or promote (BAD, BAK, BAX) cell death. The study aimed to explore the correlation between hormones and these four markers.
Methods
The study included 58 semen and blood samples from 37 infertile men and 21 control patients. The infertile patients were classified into three subgroups: azoospermia (AZO; $n=7$; median age $=35.17$ years), oligoasthenospermia/severe oligoasthenospermia (OAS/OASS; $n=5$; median age $=31.40$ years), and oligoasthenoteratospermia/severe oligoasthenoteratospermia (OATS/OATSS; $n=25$; median age $=33.84$ years). RNA isolation, cDNA synthesis, and qRT-PCR were performed to assess gene expression. Hormone levels (Cortisol, Dehidroepiandrosteron-sulfat, Estradiol, Testosterone, Free Testosterone, Sex Hormone Binding Globuline (SHBG), Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), Prolactin and Inhibin B) were measured in serum samples using the electrochemiluminescence and ELISA detection method according to the manufacturer's recommendations. Statistical analysis was performed using GraphPad Prism 10.4.1.
Results
The analysis revealed significant correlations between hormone levels and apoptosis markers in male infertility. In the AZO group, E2, FSH, and LH negatively correlated with BCL2 ($r=-0.74$, $r=-0.67$, $r=-0.62$), BAX ($r=-0.78$, $r=-0.69$, $r=-0.82$), and BAK1 ($r=-0.73$, $r=-0.68$, $r=-0.86$), suggesting a role in suppressing both pro-apoptotic and anti-apoptotic pathways. Notably, SHBG showed a strong negative correlation with BAK1 ($r=-0.92$), while inhibin B positively correlated with BCL2 ($r=0.61$), indicating its involvement in promoting apoptosis-related pathways while supporting cell survival mechanisms. In the OAS/OASS group, testosterone, free testosterone, and SHBG demonstrated strong positive correlations with BCL2 ($r=0.87$, $r=0.66$, $r=0.94$), BAK1 ($r=1.00$, $r=0.84$, $r=0.99$), and BAX ($r=0.94$, $r=0.96$, $r=0.91$), emphasizing the role of androgenic regulation in apoptosis. The OATS/OATSS and control group, showed only one negative correlation between cortisol and BAK1 ($r=-0.50$), respectively DHEA-S and BAK1 ($r=-0.53$).
Conclusion
The findings indicate that hormonal regulation significantly influences apoptosis in male infertility, with AZO and OAS/OASS groups displaying distinct patterns compared to the control and OATS/OATSS groups. These differences indicate disrupted apoptosis regulation, potentially contributing to infertility and further research is needed to uncover underlying mechanisms and develop targeted therapies.

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P985

JOINT1489

Immune protein profiling of polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is a common endocrine disorder among females characterized by hyperandrogenism, polycystic ovarian morphology, menstrual irregularities, and metabolic dysfunctions such as hyperinsulinemia and an increased risk of type 2 diabetes. Immune involvement in PCOS is indicated by a higher incidence of asthma, higher prevalence of autoimmune thyroid disease and respiratory infections. Although PCOS presents with chronic inflammation in peripheral blood, it remains poorly understood how metabolic and reproductive abnormalities impacts the inflammatory and immune profile in PCOS. To fill this knowledge gap, we profiled 92 immune and inflammatory serum proteins in 106 PCOS patients and 58 controls using the Olink Target Inflammation panel. In addition, general patient information (e.g., age) and levels of markers related to metabolic (e.g., BMI, insulin resistance) and reproductive function (e.g., sex hormone-binding globulin, testosterone) were measured and accounted for in our analysis. After adjusting for age and batch effects, our statistical model shows that several proteins are differentially expressed between PCOS and controls. We observe higher concentrations of pro-inflammatory (IL18R1, IL18, and IL1A) and immune exhaustion (PDL1) proteins, which confirm with the chronic inflammation state in PCOS. Women with PCOS have a clear different metabolic and reproductive profiles compared to controls, including higher level of HOMA-IR, triglycerides, and circulating androgens. Principal component (PC) analysis reveals metabolic-driven PC1 and reproductive-driven PC2, indicating that the metabolic profile and reproductive profile contribute differently to inter-individual differences. We computed metabolic and reproductive scores based the sum of z-score transformed clinical variable values for each individual. Interestingly, metabolic and reproductive scores are positively correlated in controls while the correlation disappeared in PCOS, which suggests that reproductive and metabolic relation is disrupted in PCOS. Overall, the levels of differentially expressed immune proteins in PCOS positively correlate with metabolic measurements, while only a few proteins were found to correlate with reproductive measurements. Interestingly, although PCOS patients have a skewed inflammatory profile and higher testosterone concentrations, we identified that IL6, S100A12, and IL20 negatively correlate with testosterone levels in PCOS. Finally, k-means clustering of the PCOS immune proteome revealed two immune subgroups of PCOS, with subgroup A showing a more pro-inflammatory immune profile and a more severe metabolic profile compared to subgroup B. Our study uncovers novel immune proteome alterations in PCOS and the metabolic and reproductive regulation of such proteins. This has important implications for understanding PCOS pathogenesis and identifying pathways for immunomodulatory intervention.

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P986

JOINT1597

The effect of testosterone on gene expression in muscle in klinefelter syndrome – a single nucleus RNA sequencing study

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Introduction
Klinefelter Syndrome (KS) is a genetic condition characterized by an extra X chromosome in males, resulting in a 47,XXY karyotype. This leads to health issues, including hypogonadism, increased risk of metabolic disorders and altered body composition - characterized by higher fat mass and lower muscle mass compared to 46,XY males. KS males routinely receive testosterone replacement therapy (TRT) to lessen these complications, with documented benefits for metabolism and body composition. However, the cellular-level effects of TRT on skeletal muscle in KS remain unclear.
Methods
This study utilized single-nucleus RNA sequencing (snRNAseq) to investigate muscle tissue changes associated with TRT in KS. Skeletal muscle biopsies were obtained from untreated KS males ($n=4$) before initiating TRT, and after one year of treatment. Age-matched 46,XY males ($n=4$) was served as controls. Muscle samples were processed to isolate nuclei, followed by fluorescence-activated nuclei sorting (FANS), and subsequently subjected to snRNAseq using the 10X Genomics platform. The obtained snRNAseq data was integrated and clustered using the Seurat (v5) workflow. Comparative analyses of untreated KS, TRT-treated KS, and 46,XY control muscle samples were performed, enabling detailed insights into cell-specific

transcriptional changes – including differential expression analysis (MAST) and cell-cell communication patterns (MultiNicheNet).
Results
TRT increased testosterone levels to normal ranges in KS males while reducing FSH/lH levels, though not to normal levels. A total of 81,768 nuclei were sequenced, revealing 11 major cell populations: type I, type IIa, and type IIx myonuclei, neuromuscular junctions, fibro-adipogenic progenitors, endothelial cells, muscle stem cells, T-cells, and macrophages. Differential gene expression (DEG) analysis revealed DEGs across all cell types, with 630 DEGs associated with TRT and 287 DEGs associated with KS. Key processes affected included differentiation, proliferation, growth, vascular remodeling, and steroid/androgen signaling pathways. To contextualize these transcriptional changes, cell-to-cell communication analysis was conducted to assess how these changes affected communication pathways. TRT was found to enhance vascular and extracellular matrix remodeling and muscle stem cell activation, while untreated KS muscle relied on maintenance and repair pathways, potentially favoring fibrosis over active regeneration.
Conclusion
This study provides insights into the cellular effects of TRT on skeletal muscle in KS. The findings suggest that TRT promotes a more regenerative and angiogenic muscle state, enhancing structural adaption and tissue remodeling. By identifying key transcriptional and intercellular signaling changes, these results contribute to understanding TRT's therapeutic impact and may aid in optimizing treatment strategies for KS individuals.

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P987

JOINT2

Exploring the relationship between sex hormones and abdominal muscle composition in postmenopausal women: insights from the multi-ethnic study of atherosclerosis

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The relationship between sex hormone levels and muscle composition in postmenopausal women remains underexplored. To address this gap, we conducted a cross-sectional observational study utilizing data from the Multi-Ethnic Study of Atherosclerosis. Our analysis included 682 postmenopausal women aged 45-84 years with complete data, with a mean age of 63.3 years. Using abdominal computed tomography imaging, we assessed abdominal muscle area (cm^2) and muscle radiodensity (Hounsfield units) in relation to serum levels of testosterone (total and free), estradiol, and sex hormone binding globulin, measured with radioimmunoassay's, in pmol/l or nmol/l. Multivariable linear regression models, adjusting for potential confounders, were employed to investigate these associations. In our fully adjusted models, higher levels of estradiol and free testosterone were found to be positively associated with total abdominal muscle area ($\beta = 1.41$, 95% CI 0.4, 2.4, $P = 0.007$ and $\beta = 18.5$, 95% CI 4.0, 33.1, $P = 0.004$, respectively), but not with muscle radiodensity ($p > 0.05$). Conversely, elevated levels of SHBG were associated with lower total abdominal muscle area and radiodensity ($\beta = -2.1$, 95% CI -3.2, -0.9, $P = 0.001$ and $\beta = -0.32$, 95% CI -0.6, -0.0, $P = 0.07$, respectively). Our study highlights significant associations between sex hormone levels and skeletal muscle area in postmenopausal women. Furthermore, the novel findings regarding SHBG, and muscle composition suggest a potential previously unrecognized role of SHBG in skeletal muscle adipose tissue accumulation. However, further validation in other cohorts is necessary to elucidate the potential role of SHBG in body composition.

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P988

JOINT869

High risk of type 2 diabetes in klinefelter syndrome irrespective of hypogonadism and testosterone replacement therapy

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Background
Testosterone replacement therapy (TRT) in Klinefelter syndrome (KS) is associated with reduced mortality. A potential mechanism behind this could be overall positive effects of TRT on metabolism in KS.
Aim
We investigated whether TRT in KS was associated with risk of type 2 diabetes (T2DM) as a proxy for metabolism.
Methods
We conducted a cohort study with riskset sampling based time of TRT in KS. Using Danish registry data, we estimated the risk of T2DM in KS. We computed the cumulative incidence and hazard ratios (HR) for incident T2DM in KS at three different life-stages: a) undiagnosed, b) diagnosed with no TRT, and c) diagnosed with TRT. We also included a male population control group. Lastly, we evaluated hemoglobin A1c levels (HbA1c) at diagnosis of T2DM and after two years of living with T2DM.
Results
We studied 895 men with KS and 50,110 controls from January 1994 until December 2022. The incidence of T2DM in KS was not associated with diagnosis- or TRT status ($P > 0.2$). The overall risk of T2DM was increased in KS at all life-stages compared with controls ($P < 0.001$). Similar data was seen for 5 and 10-year risk of T2DM. Compared with TRT treated KS, the incidence of T2DM was almost 75 % lower among controls (HR (95 CI), 0.27 (0.14-0.52). Maximum levels of HbA1c at diagnosis and lowest obtained values after two years of T2DM were not different among KS life-stages or comparing KS and controls ($P > 0.2$).
Conclusion
The risk of T2DM in KS is increased and not alleviated by TRT. These data indicate that the unfavorable metabolic profile in KS is only to a lesser extend explained by hypogonadism, and that specific genetic alterations as a consequence of the 47,XXY karyotype could contribute substantially to metabolic risk in the patients.

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P989

JOINT2733

Precocious puberty and risk of psychiatric disorders: a nationwide register-based cohort study

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Background
Early menarche within the general population has previously been linked to increased risk of mental health disorders. Therefore, extremely early puberty (precocious puberty (PP)) is likely to influence risk of long-term disease. However, little information about the risk of mental health disorders among individuals with PP exist.
Aim
To investigate the prospective association between PP and psychiatric disorders.
Methods
A register-based cohort study including all individuals with a diagnosis of PP in the National Patient Registry (NPR) from 1995 to 2020 ($n = 9,315$ (girls, $n = 8,289$, 89%)) using International Classification of Disease, tenth revision, including a diagnosis of central precocious puberty, premature puberty, premature

thelarche, and premature adrenarche. We included boys and girls with a diagnosis of PP before 10 years of age and 9 years of age, respectively. All individuals with a diagnosis of PP were matched with 5 randomly selected references from the background population (n = 46,566) according to age, gender, and calendar time (at diagnosis). The study population was followed-up in NPR, the Psychiatric Central Research Registry, the National Prescription Registry, and the National Cause of Death Registry for incident psychiatric disorder (addiction, attention deficit hyperactive disorder (ADHD), anxiety, autism spectrum disorder, bipolar disorder, depression, eating disorder, schizophrenia, and suicide including attempt and completed). The minimum average follow-up time was 7.9 years. The association between PP and psychiatric disorders was analyzed using Cox Proportional Hazard models, with strata for matched PP cases and references.

Results

PP was associated with a statistically significant increased risk of ADHD (Hazard Ratio (HR): 1.55, 95% confidence interval (CI): 1.32-1.82), anxiety (HR: 1.60, 95% CI: 1.46-1.76), autism (HR: 1.85, 95% CI: 1.57-2.19), depression (HR: 1.46, 95% CI: 1.33-1.61), eating disorders (HR: 1.32, 95% CI: 1.08-1.61), and schizophrenia (HR: 1.66, 95% CI: 1.31-2.11) but not addiction, bipolar disorder, and suicide (attempt and completed) when compared to matched references. Similar results were observed when stratifying by sex but generally with a larger effect size for boys than girls. However, the association between PP and eating disorders and schizophrenia was only statistically significant for girls.

Conclusion

Our large register-based cohort study highlights a markedly increased risk of psychiatric disorders amongst individuals (boys and girls) with a diagnosis of PP compared to their matched references from the background population. This has important implications for prevention and early intervention.

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P990

JOINT3324

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) reliability compared to immunometric assay (IA) for testosterone (T) assay in a clinical laboratory setting for male hypogonadism management

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Background

Testosterone Replacement Therapy (TRT) in Hypogonadism (Hy) is started when total testosterone (TT) levels fall below 3.5 ng/ml in presence of a suggestive clinic, therefore the technology used to measure serum T levels is relevant. LC-MS/MS is the gold standard for sex steroids measurement, but it is mainly used for research, while IA is routinary used for clinical purpose. The use of LC-MS/MS in clinical labs is increasing, but its impact in the clinics remains unclear. We aimed to investigate the role of LC-MS/MS compared to IA in the diagnosis and management of male Hy.

Methods

A total of 116 Hypogonadotropic (70) or Hypergonadotropic (46) Hypogonadic men were enrolled irrespective of their treatment status, serum TT was assessed by LC-MS/MS and IA, together with SHBG for calculated free testosterone (cfT). Hy was defined according to the Italian Society of Andrology and Sexual Medicine (SIAMS) threshold: serum TT $\leq$3.5 ng/mL and/or cfT $<$6.5 ng/dl. TT was quantified using CMIA DxI800 Beckman Coulter (IA) and Chrosystems MassChrom® Steroids in Serum/Plasma kit on Sciex CitrineTM (LC-MS/MS); cfT was calculated with the Vermeulen formula.

Results

Untreated and those patients under TRT were respectively 48 and 68, with a mean $\pm$ SD age of 45.98 $\pm$ 17.56 years and a mean $\pm$ SD BMI of 28.09 $\pm$ 5.36 kg/m^2. Serum TT and cfT assessed with LC-MS/MS were directly related to serum TT (R^2 = 0.6748, $P < 0.001$) and cfT (R^2 = 0.8787, $P < 0.001$) assessed with IA, but the R^2 did not show a precise concordance. Accordingly, the prevalence of biochemical Hy was significantly higher with IA than LC-MS/MS, for all Hy patients TT (59.5% vs 46.6%, OR 1.69, P = 0.025) and those untreated (87.5% vs 64.58%, OR 3.84, P = 0.011). A similar result was found even for cfT in all Hy (53.4% vs 39.7%, OR 1.75, P = 0.018) and the untreated ones (79.17% vs 58.33%, OR 2.71, P = 0.030). Correlation between serum TT measured by LC-MS/MS and IA was higher in the low ($\leq$3.5 ng/mL) (R^2 = 0.6877, $P < 0.001$) than in the normal to high (R^2 = 0.4396, $P < 0.001$) range of serum TT, suggesting incongruence between the two in patients under T therapy.

Conclusions

IA compared to LC-MS/MS in hypogonadal men overestimates significantly both the prevalence of biochemical Hy and TRT compensation both for TT and cfT. These results highlight the role of LC-MS/MS and SHBG assessments in every day clinical practice in the diagnosis and TRT monitoring of male Hy, avoiding unnecessary medication.

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P991

JOINT1739

Girls with high hormonal steroids, BMI and stress reach puberty early

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Background

There are ongoing concerns about declining age of puberty in females and what is driving the decline. We aimed to identify patterns in the hormonal steroid metabolome associated with accelerated pubertal development in girls, and to determine if this association was modified by body mass index (BMI), markers of stress, and breast cancer family history.

Methods

In the LEGACY Girls Study, we measured 36 metabolites of glucocorticoids, androgens, progesterone, and estrogens in two urine specimens collected before (pre, n = 327) and during puberty (pubertal, n = 115). Parents assessed the age at breast development (thelarche) through the Pubertal Development Scale. Girls aged $\geq$10 years self-reported age at menarche. Study staff measured participants' height and weight and administered the Internalizing Composite Scale (a parent proxy of child stress). We estimated hazard ratios (HR) and 95% confidence intervals (CI) for the association between a doubling in steroid metabolites (µg/mL per mg of creatinine) and age at thelarche, pubarche and menarche using Weibull survival models, testing for interactions with stress BMI z-scores, and family history using cross-product terms. We also used 12 principal components of pre-pubertal steroid metabolite data as predictors in Weibull models.

Results

Higher pre-pubertal levels of urinary metabolites of glucocorticoids (HR = 1.9, 95% CI 1.5-2.5), androgens (HR = 3.9, 95%CI 2.7-5.6) and progesterone (HR = 6.7, 95%CI 4.1-10.9) were associated with accelerated thelarche. Higher pre-pubertal (HR = 0.2, 95%CI 0.1-0.5) and pubertal (HR = 0.4, 95%CI 0.2-0.9) levels of estrogen metabolites were associated with delayed menarche. Higher levels of pubertal androgen (HR = 0.3, 95%CI 0.1-0.8) and progesterone (HR = 0.2, 95%CI 0.07-0.7) metabolites were associated with longer pubertal tempo. Girls with high glucocorticoid metabolites, BMI ($\geq$15.6 kg/m^2) and stress ($\geq$ 46) reached thelarche 7 months earlier than girls with low glucocorticoid metabolites, BMI ($<$15.6 kg/m^2) and stress ($<$ 46). There were no interactions with family history. There were 12 primary principal components that explained 95% of the variation in the steroid metabolites and 3 of these were significantly associated with earlier age at thelarche including scores either high glucocorticoids, or high in androgen and progesterone metabolites and low levels of glucocorticoid metabolites, or high progesterone metabolites, specifically high 17a-hydroxypregnanolone, pregnenediol, but low 11-oxo-androsterone.

Conclusion

Elevated metabolites of glucocorticoids, androgens and progesterone are associated with accelerated pubertal onset, and BMI and stress modify this

association. Previous studies focus on estrogens, menarche and BMI; our results suggest that androgens and stress impact age at thelarche with implications for our understanding of pubertal development.

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P992

JOINT1677

Modelling polycystic ovary syndrome *in vitro* with endometrium epithelial organoids and stroma cell culture

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Objective

Women with polycystic ovary syndrome (PCOS) experience reduced fertility associated with implantation failure, miscarriage and endometrial cancer, all linked to endometrial dysfunction[1]. Recently, we have created a single-nuclei transcriptomic atlas of the endometrium of women with PCOS[2]. Creating *in vitro* endometrial models is essential for studying PCOS-related dysfunction and treatments. This study develops three-dimensional (3D) endometrial epithelial organoids (EEOs) and single-layer stromal cells from endometrial biopsies of PCOS patients and controls to assess phenotype retention. Transcriptome profiling of EEOs and decidualized stromal cells is also included.

Methods

The 3D EEOs and the single-layer endometrial stromal cells are established from fresh endometrial biopsies of women with and without PCOS. Immunofluorescence staining showed that the EEOs consist of an intact proliferative basolateral epithelial membrane integrity. EEOs ($n = 4$ PCOS, $n = 4$ control) were subjected to hormone treatment (estrogen, progesterone and cyclic adenosine monophosphate, cAMP) over six days, with bulk RNA sequencing performed at day 0, day 2 and day 6. Similarly, single-layer endometrial stromal cells ($n = 3$ PCOS, $n = 3$ control) were treated with estrogen, progesterone and cAMP for 14 days and analysed for transcriptomic changes and cellular respiration using Seahorse XFe.

Results

EEOs displayed proliferative basolateral integrity and hormone responsiveness but lacked a strong PCOS signature in a static hormonal environment. To better mimic physiological conditions, a microfluidic system is being developed to simulate normal and anovulatory PCOS cycles. In contrast, stromal cells retained more PCOS-specific traits, exhibiting altered decidualization responses and differences in progesterone receptor expression. Metabolic assays showed lower maximum respiration rates in PCOS stromal cells, and transcriptomic analysis revealed disruptions in progesterone signaling, mitochondrial function, and inflammation—potential contributors to implantation failure and adverse pregnancy outcomes.

Conclusion

These preliminary findings indicate that under a static hormonal environment *in vitro*, EEOs lose their PCOS phenotype, whereas stromal cells retain more PCOS-specific characteristics. This suggests that the *in vitro* conditions do not fully replicate the dynamic hormonal environment of the menstrual cycle. Integrating insights from the altered decidualization response in PCOS will further refine *in vitro* modeling, helping to elucidate the mechanistic underpinnings of endometrial dysfunction in PCOS and identify potential therapeutic targets.

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P993

JOINT713

Unveiling the genetic architecture of testicular volume: a population-based GWAS using machine learning-based mri segmentations

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Background

The genetic basis of male fertility remains poorly understood. Previous studies, including those using ICD-10 codes and small-scale datasets, have failed to identify genetic loci associated with male fertility with consistent reproducibility. Testicular volume, a reliable proxy for quantitative spermatogenesis and male fertility, presents distinct challenges for population-level assessment. Traditional measurement methods are invasive, often introducing selection bias and restricting the scalability of studies. Despite its pivotal role in reproductive health, the genetic architecture of testicular volume has not been systematically explored at population level.

Methods

Using machine learning-based segmentation techniques, we analyzed bi-testicular volume in a total of 22,499 male UK Biobank participants with abdominal DIXON MRI data. A subset of 350 scans was manually segmented by a medical professional to train a fully convolutional network (U-Net model), generating 22,149 segmentations. Of these, 859 were excluded by an algorithm for incomplete segmentations, and 2,182 were excluded after manual review for not meeting quality standards. Additionally, 460 participants with male-specific ICD diagnoses that could potentially affect segmentation were excluded. By adding the manually segmented scans, this resulted in 18,998 participants remaining for population level analysis. The segmented volumes were subsequently used for a genome-wide association study (GWAS) of bi-testicular volume, conducted using linear regression in PLINK and adjusted for age and the first ten genetic principal components.

Results

The U-Net used for MRI segmentation achieved a median Dice score of 0.87, demonstrating human-level performance and ensuring accurate volume quantifications used in the analysis. The mean (SD) bi-testicular volume was 52 (16) mL. Our population-based GWAS identified 14 genome-wide significant loci ($P < 5\times10^{-8}$), revealing key genetic determinants of testicular volume and male fertility. The strongest signal was observed at rs12271187 in the *FSHB* locus on chromosome 11 ($P = 1.33\times10^{-41}$), alongside a significant association at the *FSHR* locus on chromosome 2, highlighting the central role of the follicle-stimulating hormone, including its ligand and receptor, in male reproductive biology. Functional annotation revealed that many significant SNPs are enriched in regulatory regions, such as UTRs and intronic sequences, suggesting their involvement in transcriptional regulation.

Conclusion

Our study demonstrates the potential of machine learning for population-level analysis of testicular volume, addressing key challenges in male reproductive health research. It provides a foundation for future exploration of the genetic determinants of male fertility.

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P994

JOINT1057

Changes in circulating small non-coding RNAs after castration

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Background
Small non-coding RNAs (sncRNAs) are found in circulation and are effective disease biomarkers. Some sncRNAs are actively secreted into circulation and may carry an endocrine signal to target tissues. Here, we identify circulating sncRNAs originating from the testis by mapping circulating sncRNAs before and after castration.
Methods
A cohort of 57 men with prostate cancer were randomised to either subcapsular orchiectomy (O-arm, $n = 28$) or GnRH-analogue (G-arm, $n = 29$) as part of a previous study. Blood samples were taken at baseline (W0), 12 weeks (W12), and 24 weeks (W24). RNA from 169 longitudinally paired serum samples was isolated and sequenced using the RealSeq-Biofluids Small RNA library preparation kit and sequenced on an Illumina NextSeq 550. Data from samples of suboptimal quality ($n = 5$) were excluded.
Results
JOINT analysis of sncRNA reads at W12 and W24 in contrast to W0 identified 81 and 175 circulating sncRNAs that were present at significantly different levels in the O-arm and G-arm, respectively. Most sncRNAs were found in lower levels (67 and 150 in the O- and G-arm, respectively) and only a few at higher levels (14 and 25 in the O- and G-arm, respectively). The most prevalent type of sncRNA identified to be differentially present after castration was piRNAs contributing to 44% (36 piRNAs) in the O-arm and 58% (101 piRNAs) in the G-arm. We identified 16 sncRNAs that were differentially present in both the O- and G-arm. Of the 16 overlapping sncRNAs, 5 have previously been reported in RNAseq from the testes and 8 (50%) were piRNAs, indicating that a testicular origin is likely.
Discussion
We identified several circulating sncRNAs that were significantly altered in serum from men after castration. The sncRNAs likely originate from the testis and could be novel markers of testicular function that potentially carry an endocrine message. However, the study was based on older men with prostate cancer who likely did not possess optimal testicular function at baseline, and we cannot rule out confounding effects from the treatment of prostate cancer.

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P995

JOINT2822

Maternal urinary paracetamol is associated with reduced uterine size and breast tissue diameter at infancy: a COPANA cohort study of 302 healthy girls

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Background
Maternal self-reported use of paracetamol during early pregnancy is associated with impaired ovarian function and reduced uterine size in female offspring. A single study reported urinary paracetamol (U-paracetamol) levels above 4000 ng/mL post-consumption – remaining over 1000 ng/mL for up to two days. However, no standardized cutoff for recent use exists. An alternative source of paracetamol is Aniline (textiles and pesticides), which is metabolized in the liver to paracetamol. Due to potential recall bias in self-reported data, urinary paracetamol levels may offer a more objective exposure assessment.
Aim
The first study evaluating associations between maternal U-Paracetamol measurements and ovarian activity in offspring.
Design
Prospective, observational pregnancy and birth cohort; The Copenhagen Analgesic Study (COPANA). (ClinicalTrials.gov NCT04369222).
Setting
Copenhagen University Hospital - Rigshospitalet (2020-2022).
Methods
Healthy, singleton pregnant women, enrolled in first trimester of pregnancy ($n = 685$), 589 infants (302 girls) examined. All pregnant women provided a urine sample in gestational week 14.1 (1.8) mean ($\pm$SD). Urinary levels of total paracetamol (free and conjugated) were measured (LC-MS/MS) and adjusted for urinary osmolarity. To ensure sufficient statistical power, girls whose maternal U-paracetamol levels exceeded 1500ng/mL ($n = 21$) were defined as highly exposed. Girls examined (age 3.4 months (0.4) mean ($\pm$SD)): breast tissue diameter ($n = 300$), ovarian volume ($n = 203$), total follicle count, ($n = 203$), uterine length ($n = 257$) and volume ($n = 230$) by transabdominal ultrasound. Blood samples ($n = 269/302 = 89\%$): AMH, FSH, LH, Inhibin B (immunoassays), E2 (LC/MS-MS).
Results
Paracetamol was measurable in all urine samples median (IQR) 64.5ng/mL (34.6-141.8), 14/21 women with U-paracetamol >1500ng/mL reported use of paracetamol in the first trimester. Uterine length and volume as well as breast tissue diameter were reduced in girls highly exposed to paracetamol in early fetal life; maternal U-paracetamol ≥ 1500ng/mL vs. <1500ng/mL, uterine length: 22.5 cm (20.4-26.7) vs. 25.5 cm (23.6-27.4) median (IQR) $P = 0.012$, uterine volume: 9.7 cm^3 (8.0-11.8) vs. 12.2 cm^3 (9.8-15.1), $P = 0.038$, mamma tissue diameter: 8. 0 mm (0-10.6) vs. 9. 6 mm (7.1-11.9), $P = 0.049$. Additionally, there was a trend towards reduced ovarian volume: 2.1 cm^3 (1.39-3.47) vs. 2.8 cm^3 (1.7-4.5), $P = 0.095$.
Conclusions
Including novel, objective assessment of paracetamol exposure in early fetal life, high levels of maternal U-paracetamol was associated with reduced sizes of estradiol-targeted organs, specifically the uterus and breast tissue. A trend of smaller ovarian volume suggests lower estradiol production, though single estradiol measurements showed no clear association, possibly due to individual fluctuations during minipuberty. Despite relying on a single U-paracetamol evaluation, findings align with self-reported data, reinforcing concerns about maternal paracetamol use affecting offspring ovarian function.

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P996

JOINT1611

Central precocious puberty in males, whether GnRH analog-treated or untreated, is not associated with fertility or general health problems in mid-adulthood

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Context
Knowledge is limited about the long-term health implications of idiopathic central precocious puberty (ICPP) in males, treated or untreated.
Objective
To assess the general health status and metabolic outcomes of men who had ICPP in childhood.
Design
A case control study of an historical cohort from a tertiary pediatric care center.
Patient
The study group comprised 118 men with ICPP aged 29-48 years, of whom 68 had been treated with GnRH-analog (GnRHa) and 50 were untreated. The control group comprised 351 men who were matched for age, year of birth and community clinic: 204 for the GnRHa-treated and 147 for the untreated group.

Methods
We extracted from the computerized database of a health management organization, demographic data, medical history, medications dispensed, recorded anthropometric measurements and laboratory data.
Outcome Measures
The prevalences of fertility issues, cardio-metabolic disorders (obesity, hypertension, dyslipidemia, diabetes), osteoporosis, malignancy and emotional problems.
Results
The median (interquartile range) current ages of the GnRHa-treated and untreated ICPP groups were 40 (29,44) and 44 (40,46) years, respectively. The prevalence of fertility issues was not statistically different between the study and control groups (11.8 vs. 16.2%, $P = 0.3$), nor between those with ICPP who were treated and untreated (11.8 vs. 18.4%, $P = 0.3$). For the study and control groups, the rates of obesity, metabolic disorders and cardiovascular diseases were similar. For the study group, both treated and not treated, the rates of osteoporosis and malignancy were less than 10%, and comparable to those of the control group. Emotional problems presented similarly, in less than 20%, of the study and control groups.
Conclusion
ICPP in males, treated or untreated, was not associated with increased fertility problems, cardio-metabolic disorders, malignancy or psychopathology in mid-adulthood. The health status of men who had ICPP was comparable to that of the general population.

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P999

JOINT1556

Testosterone to estradiol ratio in men with acute coronary syndrome

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Introduction
Sex hormones are believed to be responsible for gender difference in cardiovascular disease incidence and morbidity. The ratio between testosterone (T) and estradiol (E2) in men is associated with some health outcomes and behavioral traits.
Aim
We decided to investigate the ratio between T and E2 in the acute period after the onset of the acute coronary syndrome (ACS). It was hypothesized that the T to E2 ratio rather than the separate values alone may better reflect the severity of the cardiovascular event or relate to established risk factors.
Methods
For a period of three years 72 male patients with ACS, mean age 56.75, and 35 controls, mean age 54.22, were recruited. Student t-test, Mann-Whitney U-test and correlation analysis in SPSS v24 were applied.
Results
Lower values of both total and free T were found in the ACS group compared to controls (8.97 vs. 10.98 nmol/l, p=.001 for total T and 0.189 vs. 0.223 nmol/l, p=.006 for free T). Patients with myocardial infarction with ST-elevation (STEMI) had significantly lower T fractions compared to ACS without ST-elevation (NSTEMI). E2 values did not differ in both groups ($P > .05$) The T to E2 ratio on the other hand was significantly lower in the ACS group compared to the control subjects. The patient group had a more estrogenic hormonal environment with a mean value of T to E2 ratio 51.7 compared to 71.7 in the controls. ($P < .001$). The same tendency is valid when comparing ACS with ST-elevation to ACS without ST-elevation with lower value in the STEMI subgroup (T/E2: 46.9 vs. 64.1, p=.014). In the ACS group higher body mass index was associated with higher T/E2 ratio (r=-.277, p=.024). Free T was associated with GRACE risk and mortality risk score after adjusting for age (r=-.25, p=.043) but not T/E2 ratio (p=.97) or total T (p=.49).
Conclusion
Lower T/E2 ratio (more estrogenic environment) is observed in patients with ACS. Decrease in the substrate for E2 production as well as an increase in aromatization are possible mechanisms. Comparable to the decrease of T in ACS this may represent an adaptive response, but the significance of this finding is unclear. Free T on the other hand correlates with the cardiovascular risk even after correction for age. These results are in favor of sex hormones interrelation with the onset of acute cardiovascular events.

Keywords
acute coronary syndrome, testosterone, estradiol, ratio.
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P1000

JOINT917

New era: the pioneering journey of the GloBE-Reg database of long-acting growth hormone in china

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Introduction
The Long-Acting Growth Hormone Database in China, a brunch of the international GloBE-Reg (https://globe-reg. net/) project, was launched in 2023. It aims to establish the first database focusing on long-acting growth hormone (LAGH) in China and even globally, providing clinical data on the long-term efficacy and safety of PEGylated recombinant human growth hormone (PEG-rhGH)in the clinical practice for children with short stature.
Method
The GloBE-Reg database of LAGH in China has three layers of datasets. The first dataset is the core dataset applicable to any short stature indication, another dataset that allows the selection of a specific therapy and diagnosis, and the third dataset includes a therapy and diagnosis-specific minimum dataset (MDS) which collects information on diagnosis, therapy, clinician reported outcomes, patient reported outcomes and adverse events.
Results
Up to January 9, 2025, 29 hospitals have completed ethical reviews and 25 have been initiated across 17 provinces and cities in China, successfully recruiting 616 patients(male: female, 368: 248). The median age at the start of treatment was 6.42 years (range 0.68-16.00), baseline height was 109.94 cm (range 60.00-152.00), height Standard Deviation Score(Ht SDS) was -2.64±0.73, and baseline weight was 19.48 kg (range 5.30-54.00), -1.4±0.80 SDS. Currently approved indications for PEG-rhGH in China include growth hormone deficiency (GHD), idiopathic short stature (ISS) and Turner syndrome (TS).A total of 569 cases (92.4%) have been recorded for indications, including GHD 373 cases (60.6%), ISS 147 cases (23.9%) and TS 49 cases (8.0%). There are 47 off-label cases, including 22 cases of (3.6%) small for gestational age (SGA), Noonan syndrome(NS) 8 cases(1.3%), Silver-Russell syndrome (SRS) 8 cases (1.3%) and 9 cases of other rare causes of short stature including mixed gonadal dysplasia, 46 XX ootestis and Wiedemann-Steiner syndrome and so on. The initial dose of PEG-rhGH for GHD/ISS/TS/SGA/NS was 0.18/0.18/0.18/0.18/0.17 mg/kg/w respectively, with a mean duration of 2.39 years (range 0.44-7.40). In the 616 cases, 244 were followed up for >6 months, and the Ht SDS increase was 0.54±0.28,199 were followed up for one year, and the Ht SDS increase was 0.88±0.44.
Conclusion
The GloBE-Reg database of LAGH in China has been active. The analysis of large amount of data will provide treatment recommendations and decision support for long-term safety and efficacy studies of PEG-rhGH.

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P1001

JOINT369

The Effects of isotretinoin on male reproduction

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Introduction

The vitamin A derivative, isotretinoin, is known for its efficacy in the treatment of acne vulgaris. Isotretinoin use among young men is increasing. In 2023, the number of users in Denmark had risen to 10,015 (3.40 per 1,000), with the highest incidence observed among men aged 18–24-years (12.51 per 1,000). Isotretinoin is a stereoisomer of retinoic acid, which has a crucial role in spermatogenesis. Recent studies on isotretinoin exposure and male fertility remain inconclusive, suggesting both positive and negative effects. Therefore, we aimed to further investigate the potential side-effects of isotretinoin on male reproductive health.

Methods

The effects of isotretinoin and retinoic acid were investigated 1) *in vitro* on human sperm cells using a Ca^{2+}-fluorometric assay, and 2) *ex vivo* in hanging drop cultures of human testis tissue (for 96 hours). Germ cell proliferation and apoptosis in cultured testicular tissue were assessed through BrdU incorporation and c-PARP antibody detection with IHC staining. Steroid hormones, secreted by the cultured testis tissue, were measured using isotope-diluted on-line Turbo-Flow-LC-MS/MS, and Inhibin B was detected by ELISA. Additionally, 3) a cross-sectional analysis of the *in vivo* data from the Danish Young Men Study (DYMS) cohort compared reproductive hormones and semen parameters between isotretinoin users and non-users.

Results

Isotretinoin and retinoic acid (in concentrations of 12.5-100μM) induced Ca^{2+} signals and inhibited progesterone- and prostaglandin-initiated signals through the CatSper Ca^{2+} channel in sperm cells. In testicular cultures, neither isotretinoin nor retinoic acid significantly affected germ cell proliferation or apoptosis. However, assessment of hormones in the culture media revealed changes in secreted androgens, progestins and corticoids. Testosterone and androstenedione were significantly increased, while DHEAS decreased, after exposure to the highest isotretinoin concentrations (15-25 μM). Dihydrotestosterone (DHT) and inhibin B were significantly decreased under varying isotretinoin and retinoic acid concentrations (10-25μM). Progesterone and 17-hydroxypregnenolone increased across all isotretinoin and retinoic acid concentrations (10-25 μM), as did the corticoids, 11-deoxycorticosterone (DOC) and 11-deoxycortisol (11-DOC). Analysis of the DYMS cohort revealed significantly higher estradiol in isotretinoin users ($n = 51$) compared to non-users ($n = 6{,}498$), but no differences in semen parameters.

Conclusion

Our preliminary results indicate effects of isotretinoin on several male reproductive parameters. To establish its definitive role, further *in vitro* and *ex vivo* studies are needed, alongside more comprehensive investigations of the *in vivo* DYMS cohort data. These efforts are crucial to determining the potential side-effects of isotretinoin on male reproductive functions.

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P1002

JOINT4029

Childhood gonadectomy in ireland in differences of sex development (DSD)/intersex: clinical characteristics, historical and current practices, and incidence of gonadoblastoma

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Background

Differences of sex development(DSD)/Intersex are a heterogeneous group of congenital conditions affecting human sex determination and differentiation, classified based on karyotype and include: sex chromosome DSD, 46XX DSD and 46XY DSD. There is a risk of gonadal tumour development with an estimated prevalence of germ cell cancer (GCC) ranging from 0.8 to 40% depending on age and underlying condition. Gonadoblastoma (GB), is the precursor lesion of GCC in the dysgenetic gonad. Clinical recommendations and practice in DSD gonadectomy have evolved over time. International practice in DSD gonadectomy varies and optimal management of gonads is currently not well established.

Objectives

To determine the frequency and indication for childhood gonadectomy in DSD in Ireland over the last 25 years; and the incidence and clinical features of GB during this period.

Methods

From 1999 to 2024, all paediatric patients with DSD who underwent gonadectomy at the national referral centre for DSD at Children's Health Ireland were included. Patients' demographics, karyotype, sex of rearing, genetic results, and gonadal tissue histopathology were collected; retrospectively between 1999-2022 and prospectively between 2022-2024 as part of the International DSD registry study.

Results

A total of 57 patients with DSD (46 females) underwent gonadectomy. The main indications were risk of gonadal tumour development (41/57; 71%), GB identified on biopsy (5/57; 8%), incongruent hormone production (9/57; 15%) and concordance to sex assignment (2/57; 3%). The mean age at gonadectomy was 7.75 years (2 weeks to 18 years). GB was confirmed in 30% (17/57) of cases on histopathology of gonadal tissue, with 3 cases associated with dysgerminoma. GB was most frequently reported in 46XY complete gonadal dysgenesis (CGD) (8/17; 47%), followed by Turner syndrome Y chromosome material (7/17; 41%), and partial gonadal dysgenesis (2/17; 11%). The mean age of tumour diagnosis was 6.96 years (2 weeks to 17 years). The majority of tumours were unilateral (9/17; 52%) and located intra-abdominally (16/17; 94%). For all cases of dysgenetic gonads, the calculated risk of developing gonadal tumours was 38% (16/42). Patients with 46XY CGD demonstrated the highest risk of developing gonadal tumours (8/11; 72%).

Conclusion

The majority of gonadectomies were performed in dysgenetic gonads, either to mitigate tumour risk or remove gonadal tumours. The high incidence of gonadal tumours in dysgenetic gonads, particularly in 46XY CGD, highlights the importance of early prophylactic gonadectomy which should be performed only after multidisciplinary team discussion, which will be informed by these findings.

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P1003

JOINT656

Testicular index: a simple, clinically applicable tool to predict pregnancy outcomes in men with idiopathic infertility undergoing follicle-stimulating hormone treatment

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Background

Follicle-stimulating hormone (FSH) therapy has been shown to improve spermatogenesis, sperm quality, and reproductive outcomes. However, variability in patients' response and limited data on pregnancy rate complicate its extensive application in male idiopathic infertility.

Aim of the Study

To identify predictors of FSH efficacy in men with idiopathic infertility in terms of pregnancy obtainment.

Materials and Methods

A multicenter, retrospective, observational study was conducted at two Italian outpatient clinics from June 2019 to October 2024. We enrolled men with idiopathic infertility and FSH serum levels < 8 IU/l treated with FSH. Data from two visits were analyzed: baseline (V0) and the final follow-up visit (V1) when FSH treatment was discontinued. Predictors of pregnancy achievement were

searched among the data collected, such as semen parameters, hormonal levels, and testicular volumes. Different "testicular indexes" were calculated using V0 FSH and testosterone serum levels, bi-testicular volume and semen parameters.
Results
443 men were included, of which 84 achieved pregnancy (19%). One testicular index ((FSH + Total testosterone) / bi-testicular volume) was directly related to V0 semen parameters and entered in subsequent analyses. Significant improvements in sperm concentration, motility, and total sperm count were observed following FSH treatment regardless of whether or not pregnancy was achieved. However, men who achieved pregnancy had higher baseline testicular index, larger testicular volume, and lower FSH levels. Multivariate analysis identified patients' age and testicular index as significant predictors of pregnancy success.
Conclusion
This large, multicenter, real-life study identified a novel testicular index that predicts response to exogenous FSH stimulation, overcoming limitations of conventional semen analysis. The index assesses the interstitial compartment function (indicated by testosterone levels), spermatogenic potential (reflected by FSH levels), and target tissue amount (indicated by testicular volume). We demonstrate that low baseline testicular index correlates with a higher likelihood of achieving pregnancy through exogenous FSH stimulation.

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P1004

JOINT3801

Puberty induction in adolescents with primary ovarian failure: a single center study over a 10-year period

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Background
Effective and timely induction of puberty is crucial to ensure optimal physical development, psychosocial well-being, and long-term health outcomes in patients with primary ovarian insufficiency(POI). Turner Syndrome (TS) and chemo or radio-induced damage are the main causes of POI in adolescents. The aim of this study is to evaluate and compare the approaches and outcomes of puberty induction in a cohort of patients affected with POI, secondary to TS or who had undergone hematopoietic stem cell transplantation (HSCT) for oncological or hematological conditions.
Methods
Medical records of patients with POI who received hormonal replacement therapy (HRT) between 2012 and 2021 were retrospectively reviewed. Auxological data and estrogen replacement schedules were recorded from baseline(T0) until the initiation of progestin treatment. Data were collected at intervals of 6(T1), 12(T2), 18(T3), 24(T4) and 36 months(T5). Information on bone age, bone mineral density (BMD) and pelvic ultrasonography findings were gathered.
Results
53 patients (29 TS and 24 HSCT) were included. No significant differences in auxological parameters were observed between the groups, except for stature. The mean duration of puberty induction was similar in both groups (2.68 ± 0.98years in TS vs. 2.53 ± 1.03years in HSCT), with a shorter duration of HRT in patients who were already at a pubertal stage beyond S1 at T0 (2.20 ± 1.1 vs. 2.80 ± 0.90years, $P = 0.04$). All patients received transdermal HRT, except for 8 patients with TS who received oral therapy. Across the entire cohort, a positive correlation was observed between the progression of sexual characteristics and the estrogen dose ($r = 0.515$), which remained significant when analyzing the two groups separately. Growth velocity(GV) mimicked a physiological pubertal spurt in all patients. However, from 18 months onward, TS patients exhibited a more pronounced decline in GV compared to HSCT patients (3.9 ± 1.8 vs 4.7 ± 1.9 cm). At T1, GV showed a weak negative correlation with estrogen dose (r:-0.205), which was more evident in the TS group (r:-0.333). By T2, this association became positive (r:0.293; stronger in TS r:0.388). At other timepoints, no significant associations were observed. Age and estrogen dose at T0 were negatively correlated with final BMD ($r = -0.019$), but they were positively associated with the magnitude of BMD's improvement during therapy ($r = 0.333$).
Conclusions
Our results confirm the importance of starting treatment at a physiological age of puberty, independently of POI origin. Comparable outcomes were observed in the two groups in terms of evolution of puberty, growth velocity, at least in the first year, and bone density.

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P1005

JOINT1725

Risk of advanced chronic kidney disease in transgender individuals undergoing gender-affirming hormone therapy compared with the general population

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Background
An increasing number of individuals worldwide identify as transgender, and many undergo gender-affirming hormone therapy (GAHT) to align their physical characteristics with their gender identity. Feminizing GAHT typically involves estradiol, with or without an antiandrogen, while masculinizing GAHT involves testosterone. Simultaneously, the worldwide prevalence of chronic kidney disease (CKD) rises, presenting a significant global health challenge. Men in the general population have a higher risk of advanced CKD than women, potentially due to differences in sex hormone concentrations. Previous studies in transgender individuals confirmed this role for sex hormones, as estimated glomerular filtration rate (eGFR) increases with feminizing GAHT and decreases with masculinizing GAHT. However, these studies were limited to short-term follow-up, leaving long-term effects of GAHT on CKD risk unclear. This current study aimed to fill these knowledge gaps, by investigating the long-term risk of advanced CKD in transgender individuals undergoing GAHT, compared with the general population.
Methods
This retrospective cohort study included individuals who visited the gender identity clinic at Amsterdam University Medical Centre (1972–2018). Their records were linked to a nationwide registry (2012–2022). Advanced CKD was defined as eGFR <30 mL/min per $1.73m^2$ or chronic dialysis. Individuals who did not use GAHT or died before 2012 were excluded. Standardized incidence ratios (SIRs) were calculated for transgender women and -men using general population incidence rates stratified by age and socioeconomic status (based on education, income and employment).
Results
The study included 2,694 transgender women (follow-up: 22,759 person-years) and 1,612 transgender men (follow up: 12,970 person-years). Median age at GAHT initiation was 30 years (IQR 24–41) for transgender women and 24 years (IQR 20–32) for transgender men. Seventeen transgender women developed advanced CKD, with no increased risk compared with men (SIR 1.6; 95% CI, 0.9–2.5), but a significantly higher risk compared with women (SIR 2.5; 95% CI, 1.4–3.9) in the general population. Eight transgender men developed advanced CKD, with significantly higher risks compared with both women (SIR 3.8; 95% CI, 1.5–7.0) and men (SIR 2.6; 95% CI, 1.0–4.9) in the general population.
Conclusion
Transgender women undergoing feminizing GAHT are at higher risk of advanced CKD compared with women, but not with men in the general population. Transgender men undergoing masculinizing GAHT are at higher risk compared with both women and men. These findings underline the need for tailored clinical care to address the unique health risks faced by transgender individuals.

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P1006

JOINT1441

Oligogenicity associated with the adrenal phenotype of individuals with NR5A1/SF-1 variants

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Background
NR5A1/SF-1 variants cause differences of sex development (DSD) and manifest with a broad phenotype. Many individuals with DSD and *NR5A1*/SF-1 variants have anomalies in other organs, predominantly the spleen, rarely the adrenals. Oligogenicity could contribute to the variable phenotype. This study aimed at investigating individuals with *NR5A1*/SF-1 variants presenting with DSD and adrenal anomalies for additional genetic variants that may promote their exclusive adrenal phenotype.
Methods
Within the framework of the SF1next study, we had four patients with a DSD phenotype and adrenal anomalies. These individuals were investigated by whole exome sequencing (WES); after filtering, variants were classified according ACMG guidelines for pathogenicity assessment. Of patient 3 (Table1) and a healthy donor, we differentiated human fibroblasts-derived induced pluripotent stem cells (iPSCs) into adrenal-like cells (iALC) and assessed the model by liquid chromatography–mass spectrometry (LC-MS). Analysis of the transcriptome (RNA-seq) was performed to compare differentially expressed genes (DEG) between *NR5A1*/SF-1 mutant and wild-type (wt) iALC.
Results
Table1 summarizes the phenotypic and genetic characteristics of the four patients. Besides the *NR5A1*/SF-1 variants, we found additional (likely) causative variants in *NNT* and *CDKN1C* genes with established involvement in adrenal disorders in two patients. In the other two patients, filtering revealed one potentially deleterious variant in *ADCY1* and *ABLIM3,* respectively. RNAseq showed that expression levels of 1480 genes were significantly different (up or downregulated) in the mutant *NR5A1*/SF-1 in comparison to wt when investigated within the background context of patient and control-derived iALCs. We observed higher expression levels of NR5A1/SF-1 in mutant than in wt iALC, while ABLIM3 expression levels were similar across samples.
Conclusion
Our study indicates that individuals with DSD and rare adrenal anomalies who have *NR5A1*/SF-1 variants, harbor other deleterious gene variants that may explain their adrenal phenotype. Thus, variants in *NR5A1*/SF-1 may not suffice to cause an adrenal phenotype. Our in-vitro model is a potent tool to study adrenal anomalies and the molecular effects of novel genes proposed to be disease-causing.

Patient (Karyotype)	DSD phenotype; adrenal anomaly	Other anomalies	Genetic findings (zygosity)
1 (46,XY)	Opposite sex; adrenal insufficiency		*NR5A1*, p.(R427W) (hom) *CDKN1C*, p.(A202_P205del) (het); *ABLIM3*, p.(L555Q) (het)
2 (46,XY)	Severe; adrenal insufficiency		*NR5A1*, p.[(E7Ter);(T296M)] (comp het) *ADCY1*, (p.L719Q) (het); *SULT2B1*, (p.G187R) (het)
3 (46,XX)	Typical; adrenal hypoplasia	Asplenia	*NR5A1*, p.(R92Q) (hom) *ABLIM3*, p.(L649Q) (het)
4 (46,XY)	Severe; partial adrenal insufficiency	Polysplenia	*NR5A1*, p.(P14CfsTer19) (het) *NNT*, p.(R693H) (het)

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P1007

JOINT350

Reproductive hormones at 7-10 years of age in children born after assisted reproductive technology

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Background
The global rise in the use of assisted reproductive technology (ART) reflects the declining fertility rates. Investigation of the long-term health of children born after ART is therefore important. A former registry-based study found a higher risk for early puberty in girls and late puberty in boys conceived after ART.
Methods
Pubertal development and serum concentrations of reproductive hormones were evaluated in 606 singletons (292 boys) aged 7-10 years from the Health in Childhood following Assisted Reproductive Technology (HiCART) cohort. The HiCART cohort included children conceived after ART with frozen embryo transfer (FET) $n=$ 200, fresh embryo transfer (Fresh-ET) n = 203 and natural conception (NC) $n=203$. Concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and sex hormone-binding globulin (SHBG) were measured by immunoassays, and concentrations of estradiol (E2), testosterone (T), dehydroepiandrosterone sulfate (DHEAS), androstenedione and 17-hydroxyprogesterone (17-OHP) were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS).
Results
Mean age at examination was 8.53 years (0.55 standard deviation [SD]). BMI (SDS) did not differ significantly between the three groups. Stratification for sex revealed a significantly higher weight (SDS) (adjusted mean differences 0.35, 95% CI (0.03; 0.67)) and height (SDS) (0.43 (0.11; 0.76)) in the girls conceived after FET vs. NC. Among girls, clinical signs of puberty (Tanner $\geq$ B2) were found in 14% (16/107) in the FET-group, in 16% (15/98) in the fresh-ET-group and in 23% (23/98) in the NC-group, with no difference between the three groups (Chi-square P = 0.35). Clinical signs of puberty below the age of 8 years were found in 6/314 girls (median age 7.79 [range 7.46-7.87]), of whom three were in the FET-group and three in the NC-group. The concentration of LH was below 0.3 IU/l in all six girls, while four out of six girls had measurable estradiol. Among boys, clinical signs of puberty (testicular volume >3 ml) were absent in boys in the FET-group (0/86), while present in 2% (2/99) in the fresh-ET group and in 1% (1/101) in the NC-group. No significant difference was found in concentrations of hormones (LH, FSH, SHBG, E2, T, DHEAS, Androstenedione and 17-OHP) when comparing respectively girls and boys born after FET, Fresh-ET and NC, neither in the entire cohort nor after excluding pubertal children.
Conclusion
Pubertal development, reproductive hormones, and the prevalence of precocious puberty was not altered in the children conceived after ART. This is re-assuring on an individual and societal level as there is an increasing need for ART.

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P1008

JOINT1208

Habitual activity and muscle strength in children of mothers with, or without, polycystic ovary syndrome

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Background
Maternal free testosterone (FT) in 3rd trimester is higher in women with polycystic ovary syndrome (PCOS) compared to women without PCOS. In Odense Child Cohort, maternal FT was inversely associated with handgrip strength in boys and girls at age 5 years. Furthermore, higher maternal FT was associated with more body fat in boys at 7 years of age.

Aim
To investigate associations between 3rd trimester FT in women with and without PCOS and child physical activity engagement and isometric muscle strength at 7 years of age.
Hypothesis
Children exposed to higher maternal FT exhibit less physical activity engagement and reduced isometric muscle strength, with possible sexual dimorphism.
Methods
In the prospective Odense Child Cohort, Denmark, 146 of 976 mothers (9%) had a PCOS diagnosis during pregnancy. Maternal FT was calculated from total testosterone analyzed by mass spectrometry and sex hormone binding glubulin measured at gestational weeks 28-30. In their 7-year-old children, we assessed physical activity engagement by 24-hour/7-days accelerometers (n = 695, counts/min (overall activity volume) and time spent in light/moderate/vigorous physical activity), and isometric muscle strength (n = 976, Newton/kg bodyweight), measured by maximal voluntary contraction of the abdomen. Multiple linear regression models were adjusted for maternal age, parity, educational level and accelerometer non-wear.
Results
In boys, maternal PCOS in pregnancy was associated with less overall physical activity engagement, with 265 fewer counts/min on weekends (p=0.02) and 154 fewer counts/min on all days (weekend and weekdays) (p=0.04), whereas no association was found on weekdays. Maternal PCOS was also associated with less moderate (β=-6.7 min/day, p=0.05), vigorous (β=-6.3 min/day, p=0.03) and moderate-vigorous physical activity (β=-12 min/day, p=0.03) on weekends. Maternal FT was not associated with isometric muscle strength in boys. In girls, maternal PCOS was not associated with physical activity engagement. However, one nmol/l increase in maternal FT was associated with an 8.5 Newton/kg bodyweight decrease in isometric muscle strength (p=0.003).
Conclusion
Boys born of mothers with PCOS had less physical activity in weekends. In girls, prenatal exposure to higher 3rd trimester FT was linked to lower isometric muscle strength.

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P1009

JOINT2773

Childhood body mass index trajectories in women diagnosed with polycystic ovary syndrome

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Background
Most adolescent girls and young women diagnosed with polycystic ovary syndrome (PCOS) have an increased body mass index (BMI) compared to the general population. However, the detailed BMI trajectories during childhood among women later diagnosed with PCOS remain poorly understood.
Methods
This retrospective register-based study retrieved data on anthropometric measurements during childhood in women diagnosed with PCOS between 2003 and 2022. Data were obtained from the Danish registries; The National Patient Register, The Children's Database and The Danish Medical Birth Register. Latent class analysis (LCA) was used to identify distinct BMI trajectories. Additionally, BMI standard deviation score (SDS) was analyzed at 5-10 years of age and at 13-18 years of age. Birth characteristics were investigated by assessing the mean birth weight, mean birth weight (SDS) and mean gestational age.
Results
We identified 16,322 women diagnosed with PCOS between 2003 and 2022. Of these, 1,143 women had ≥3 measurements of height and weight, including birth weight and length, and they were included in the LCA. The LCA revealed three distinct BMI trajectories, all characterized by an early increase in BMI leading to overweight or obesity already during childhood, which persisted into adolescence. However, the trajectories differed in growth pattern, timing, and intensity of BMI change. Median BMI (SDS) was 1.1 (0.2-2.1 IQR) in the 5-10-year age group (n = 599) and 1.2 (0.2-2.1 IQR) in the 13-18-year age group (n = 1,619), suggesting that women later diagnosed with PCOS are overweight throughout childhood and adolescence. Birth characteristics in 16,123 women with PCOS did not differ from the WHO growth standards.
Conclusion
Women with PCOS experience an early and sustained increase in BMI during childhood, which continues into adolescence. The strong correlation between being overweight early in life and later development of PCOS underlines the need for preventive strategies already early in childhood.

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P1010

JOINT1899

Inflammatory stress in leydig cells: implications for steroidogenesis and mitochondrial dysfunction

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The global prevalence of infertility and subfertility has increased significantly, affecting both men and women. Growing evidence suggests that inflammation is a common feature of various pathological conditions and plays a critical role in male reproductive dysfunction by disrupting steroidogenesis and spermatogenesis. Leydig cells (LCs) are essential for sustaining testicular steroidogenesis, a process that relies heavily on mitochondrial function. Mitochondria mediate the initial steps of cholesterol processing and provide the energy required for testosterone synthesis. Although inflammation is known to impair LC steroidogenic function, the precise mechanisms underlying this disruption remain unclear. In this study, we investigated the link between inflammation, steroidogenic dysfunction, and mitochondrial impairment in LCs. Using a Mus musculus Leydig cell line (TM3), we exposed the cells to bacterial lipopolysaccharide (LPS) for 24 hours to induce an inflammatory response. Mitochondrial function was assessed by measuring the oxygen consumption rate (OCR) after mitochondrial modulation. The expression of key steroidogenic genes (STAR and CYP17A1) was analyzed by qPCR, and total testosterone levels in the post-treatment culture medium were quantified using electrochemiluminescence immunoassay. Our findings demonstrate that exposure to an inflammatory stimulus significantly reduces mitochondrial respiration and impairs steroidogenic activity, as evidenced by decreased gene expression and testosterone production. These results provide compelling evidence that local inflammation, independent of systemic inflammatory conditions, disrupts both steroidogenesis and mitochondrial energy production in LCs, highlighting a potential mechanism contributing to male reproductive dysfunction.

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P1011

JOINT2827

Gonadectomy in individuals with differences of sex development – a two year prospective i-dsd registry study

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Introduction
The appropriateness of gonadectomy in people with differences of sex development (DSD) is increasingly contested yet reports of contemporary practices are lacking. This study aimed to determine the frequency of gonadectomy and associated care pathways in individuals with DSD internationally.
Methods
A 2-year prospective study was undertaken through the I-DSD Registry (Dec 2022-Dec 2024). Participating centres reported gonadectomies undertaken in individuals with DSD in response to a monthly automated email survey. Where an individual had given informed consent for inclusion in the I-DSD Registry, a secondary survey captured additional clinical information.
Results
Over the 2-year study period, 30/74 (41%) centres reported no gonadectomy, while 173 individuals from 44 centres had gonads removed; median (range) / centre: 1 (0,18). Secondary survey data are available for 82/174 (47%) cases to date; 80% were female. Median (range) age at gonadectomy was 11.7 (0.1,20.0) years. All had specialist multidisciplinary team involvement prior to gonadectomy: endocrinology (98%), genetics (82%) and psychology (67%) were most frequent. Differences of gonadal development (36/82 [44%]) and chromosomal DSD (including Turner syndrome, 24/82 [29%]) were the most frequent underlying diagnoses. Gonads were intra-abdominal in 65/82 (79%). Pre-gonadectomy investigations included: hormonal testing (77/82 [94%]), imaging (73/82 [89%], direct laparoscopic visualisation (29/82 [35%]) and gonadal biopsy (17/82 [21%]). Bilateral gonadectomy was undertaken in 57/82 (70%). Mitigation of future malignancy risk in the context of gonadal insufficiency was the most common primary indication for gonadectomy (55/82 [67%]). Concerning clinical (3/82 [4%]) changes and/or imaging or biopsy findings (8/82 [10%]) were uncommon. Histopathology confirmed neoplastic change in 24/82 (29%) individuals: age range 0.8- 17.0 years. Nine (11%) had precursor lesions alone; 15/82 (18%) had gonadal tumours, of whom 3 had precursor lesions also present. Two individuals had evidence of extra-gonadal metastases. Surveillance imaging pre gonadectomy raised no suspicion for gonadal neoplasm in 18/23 (78%).
Conclusions
This prospective I-DSD surveillance study offers important contemporary insights into the practice of gonadectomy in individuals with DSD internationally. Overall gonadectomy appears relatively infrequent. Multidisciplinary care provision prior to gonadectomy is standard; however, our data confirm variation in care pathways and significant challenges for decision-making regarding gonadal management. The limitations of imaging for reliable gonadal surveillance and the presence of gonadal neoplasms in young children demonstrated here must be measured alongside considerations to defer gonadectomy to prioritise personal autonomy. These findings should inform future shared decision-making resources and clinical care for gonadal management in individuals with DSD.

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P1012

JOINT815

Changes in reproductive hormones in the years before diagnosis of testicular cancer

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Testicular germ cell tumors (TGCTs) are the most common malignancy found in young men. They arise from the precursor cells, germ cell neoplasia *in situ*, which are hypothesized to be present in the testes already at birth. Since reproductive hormone levels are affected in patients with a TGCT, we hypothesized that changes in reproductive hormone levels were detectable even before their primary TGCT diagnosis. We measured the concentrations of reproductive hormones (FSH, LH, inhibin B and AMH) in plasma samples from 72 Danish blood donors and participants in the Danish Blood Donor Study (DBDS), 1-20 samples from each, donated up to 11 years before they were diagnosed with a TGCT. We also measured reproductive hormones in 72 sex- and age-matched controls from DBDS. Within one year prior to the primary diagnosis, we found significantly higher concentrations of FSH ($P = 0.033$) and lower concentrations of inhibin B ($P = 0.009$) and AMH ($P = 0.019$) in patients compared with controls. In patients with the histological subtype seminoma, FSH standard deviation (SD) scores were higher ($P < 0.001$) and inhibin B SD scores lower ($P = 0.001$) compared with controls. In patients with non-seminomas, LH SD scores were significantly lower ($P = 0.021$) compared with controls. Significant differences in FSH, inhibin B and AMH SD scores were evident up to three years before diagnosis of a TGCT compared with controls. Lastly, higher FSH and LH and lower inhibin B SD scores ($P = 0.003$, $P = 0.047$, and $P = 0.032$, respectively) were observed in patients with seminomas compared with patients with non-seminomas. In conclusion, changes in reproductive hormone concentrations and sex- and age-adjusted SD scores are evident in patients several years prior to a primary diagnosis of a TGCT, suggesting a gradual reduction in testicular function prior to diagnosis. The observed changes are dependent on the histological subtype of the TGCT.

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P1013

JOINT1403

Effects of selected pre-treatments prior to denosumab administration on germ cell proliferation in ex vivo cultured testicular tissue from humanized RANKL mice

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Novel treatment options for male infertility are highly warranted, as male-factor infertility is involved in up to 50% of all infertile couples. Yet for the vast majority (90%) of affected men no treatment options exist. The RANKL/RANK/OPG signaling pathway, known for its role in bone resorption, is also active in the testis of both men and mice. In previous studies, we have demonstrated that inhibition of RANKL with denosumab in mice resulted in higher sperm count and testis weight. Additionally, increased germ cell proliferation was found in *ex vivo* cultures of adult mouse testis tissue following denosumab treatment and a randomized control trial showed that denosumab treatment enhanced sperm concentration in infertile men with serum AMH levels above 38 pmol/l. These findings suggest that RANKL inhibition may be a potential treatment option for some infertile men. Here, the potential beneficial effects of pre-treatment with selected compounds (e.g. prostaglandins, gonadotropins) prior to denosumab treatment was examined. A humanized RANKL mouse model enables the use of the RANKL inhibitor denosumab in mice, and testicular tissue fragments (1.5 mm^3) from these mice were cultured *ex vivo*. The first 24 hours with agents such as hCG, and Ibuprofen, followed by treatment with 100 ng/mL denosumab for 48 hours. Germ cell proliferation was assessed via quantification of BrdU incorporation. Pre-treatment with vehicle, hCG, ibuprofen, or dexamethasone was

examined, and a significantly increased germ cell proliferation was found after pre-treatment with hCG (82%, $P = 0.0042$) and ibuprofen (92%, $P = 0.0017$) when compared to vehicle treated tissue. No effect on germ cell apoptosis was observed. This study suggests that pre-treatment of adult testicular tissue with hCG and ibuprofen prior to denosumab administration may enhance the stimulatory effect of denosumab on germ cell proliferation. However, further research is needed to understand the effects of RANKL inhibition on the interplay between Sertoli and germ cells and the implications for improvement of spermatogenesis.

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P1014

JOINT3178

Hypophosphatemia is a frequent finding in infertile men and is associated with semen quality

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Background

Phosphate is available in fluid from all segments of the male reproductive tract in concentrations manyfold higher than in serum. However, the role of phosphate in male fertility is largely unknown. Here, the associations between serum phosphate, semen quality, and reproductive hormones were assessed in infertile men.

Methods

A cross-sectional study of 1,488 men, referred due to infertility. Each man underwent a physical examination, had semen parameters assessed, and had blood analyzed prospectively for concentrations of phosphate, ionized calcium, alkaline phosphatase, PTH, 25OHD, and reproductive hormones. 246 were excluded due to serious comorbidities, leaving 1,242 for the analyses.

Results

Infertile men have a high prevalence of mild (25.5%, 0.66–0.80 mmol/l), and moderate hypophosphatemia (10.9%, 0.32–0.65 mmol/l). The percentages of motile spermatozoa and progressively motile spermatozoa were lower in men with moderate hypophosphatemia than in men with mild hypophosphatemia or normophosphatemia (44%, 49%, 51%, $P = 0.040$, and 32%, 35%, 41%, $P = 0.036$, respectively). The total numbers of motile and progressively motile spermatozoa were also lower (13, 12, 18 million, $P = 0.009$, and 9, 9, 14 million, $P = 0.006$, respectively). Serum concentrations of total and free estradiol were highest in men with moderate hypophosphatemia (97.5 pmol/l, 96.2 pmol/l, 92.1 pmol/l, $P = 0.004$, and 2.4 pmol/l, 2.3 pmol/l, 2.2 pmol/l, $P = 0.034$, respectively).

Conclusion

Hypophosphatemia is frequent in infertile men and is associated with lower number of motile sperm. The precise mechanisms through which hypophosphatemia may impact sperm motility remain to be clarified.

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P1015

JOINT428

Changes in quality of life and intimate experience after 10 years in young women with mayer-rokitansky-kuster-hauser syndrome

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Backgroud

MRKH syndrome is a cataclysmic diagnosis with a heavy psychological burden. In a previous national study (T1, $n = 131$, mean age 26.5y), we reported similar global and sexual quality of life to the general population (GP), except for lower psychosocial health and social relationship scores in younger patients, alongside high sexual distress. In an additional qualitative psychological analysis ($n = 40$), we reported traumatic handicap experience, unexpected eating/addictive disorders, and fertility distress. All self-defined heterosexual (T1).

Objective

To study their psychological evolution ten years later (T2), using the same methodology.

Study design

25 patients were included; 8 lost to follow-up, 7 declined. All completed WhoQol-bref (general QoL), FSFI, and FSDS-R (sexual QoL) scales. Qualitative psychological functioning was assessed using clinical interviews, Rorschach and TAT tests. T2 results were compared to previous data T1, after a median 9.6-year interval [IQR 9.2;10].

Results

Median age was 35.7y [32-38.3], (25-35y:$n = 11$, 35-45y:$n = 14$). All were sexually active, two self-defined bisexual. Quality of life decreased only in the physical dimension (T1:78,6 – T2:75, difference -7.1 [-14.3;0], $P = 0.004$) and remained lower than that of the GP ($P = 0.008$), which was not the case at T1. Eleven patients had new health issues between T1 and T2 (only 2 related to MRKH). Psychological health was much lower than in the other dimensions (scores 66.7 vs 75 to 78.1). Besides, compared to GP, the psychosocial score was significantly lower only in the younger group (62.5 vs 70.8 $P = 0.036$), similarly to T1. Sexual quality of life and sexual distress were not different between T1 and T2 (FSFI score: T1:26.2 – T2:27.7, difference 1.2 [-0.9;4], $P = 0.13$), (FSDS-R score: T1:16 – T2:13, difference -2 [-14;4], $P = 0.14$)). Fourteen (56%) had dyspareunia, which was significantly associated to lower WhoQol psychological scores at T2 (60.4 [58.3;69.8] vs 79.2 [64.6;79.2], $P = 0.044$), 14(56%) had cyclic pelvic pain. All patients expressed at Rorschach tests perseverant and erroneous ideations on internal genitals including ovaries as a missing organ. Eating disorders disappeared in 2/5 patients who had them at T1. Sports addiction disappeared in 4 patients who had them at T1. Five patients (20%) had children (3 adopted, 2 surrogated). Motivation for parentality declined from 88% ($n = 22$) to 44% ($n = 11$) and considering uterine transplantation dropped [T1:36% ($n = 8/22$) T2:18% ($n = 2/11$)].

Conclusions

Quality of life remained good after 10 years, except in the psychological domain, especially among younger individuals. Qualitative assessment revealed a higher complex psychosocial impact of uterovaginal aplasia. Dyspareunia was frequent and associated to poor psychological health.

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P1016

JOINT3160

Inhibin b- an important marker to screen testicular function in CAIS patients?

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Introduction and objective

Gonadectomy was carried out for a long time after the diagnosis of complete androgen insensitivity syndrome (CAIS). It is now recommended to leave the gonads *in situ* in order to guarantee endogenous hormone production. It is unclear how to best clinically monitor testicular function. The aim of the study was to investigate whether inhibin B can be used as a future follow-up parameter to screen for gonadal function in CAIS patients.

Material and Methods

A total of 57 adolescent and adult CAIS patients who presented to two DSD centers (Lübeck and Pisa) were included. Hormonal parameters were retrospectively evaluated. Ideally, we included different time points: during puberty (12-16 years), in early adulthood (17-21 years) and later adulthood (22-50 years). We evaluated the testosterone/lH ratio as a measure of Leydig cell function and the inhibin B/FSH quotient for Sertoli cell function.

Results
Testosterone levels were elevated and within the typical male reference range (6.20 ng/ml +/- 3.08). FSH values increased with age. Inhibin B levels were high and even above the male reference range (383.8 pg/ml+/- 206.5 SD). In adulthood, inhibin B levels decreased by 52.53% ($P = 0.0030$) and the inhibin B/FSH ratio by 75.56% ($P = 0.0103$).
Conclusion
Our data show that inhibin B and the inhibin B/FSH ratio is a suitable functional marker for gonadal function and in particular for Sertoli cell function. In CAIS patients from adolescence onward, these parameters may be useful to examine gonadal function and to possibly detect a loss of function that may necessitate hormone replacement therapy.

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P1017

JOINT3750

The effect of treatment on matrix metalloproteinases levels and endothelial function in women with polycystic ovary syndrome. association with metabolic and hormonal abnormalities of the syndrome

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Introduction
Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorder affecting women of reproductive age. Insulin resistance and consequent cardiometabolic disorders are the main components of PCOS. The data regarding the presence of clinical or subclinical cardiovascular disease in PCOS, are controversial. Moreover, the impact of potential treatment intervention in markers of hormonal, cardiovascular and endothelial function in PCOS has not yet been fully elucidated.
Objective
The aim of the present study is to investigate a) the association between subclinical markers of cardiovascular and endothelial integrity with insulin resistance and hormonal profil in women with PCOS and b) the impact of potential treatment interventions on these markers.
Methods
In total, 40 women with PCOS recruited in the study and received metformin ($n=20$), GLP1-agonists ($n = 10$), or oral contraceptive pills ($n = 10$). At baseline and six months after treatment, 75g-oral glucose tolerance test (OGTT) was performed in all patients. At 0, 60, and 120 min of glucose load insulin, glucose, and the perfused boundary region of sublingual microvessels (high PBR values represent reduced glycocalyx thickness) were measured. Insulin resistance was evaluated using Matsuda index and HOMA index. At baseline and six months after treatment, androgen levels and matrix metalloproteinase 9 (MMP9) concentration were also assessed.
Results
The mean age of all the participants was 30 ± 3years old. At baseline, the percentage change of PBR was associated with the percentage change of glucose at 120min of OGTT ($r = 0,42$, $P < 0.05$). At baseline, Matsuda Index, Homa Index and Testosterone levels were associated with PBR ($2.91\pm0.1\mu m$) at 120min OGTT ($r = 0.41$, $r = 0.38$ and $r = 0.28$, respectively). Moreover, MMP9 levels were associated with Matsuda and Homa Index ($r = 0.45$, $P < 0.05$ and $r = 0.41$, $P < 0.05$ respectively). Six months after treatment, all the participants presented improvement of Matsuda Index (7 ± 0.31 vs 9.1 ± 0.2), Homa Index (5.3 ± 0.8 vs 2.91 ± 0.1), MMP9 (210 ± 30 vs 178 ± 28ng/ml) and testosterone levels (44.2 ± 5 vs 39.1 ± 2ng/dl) compared to baseline ($P < 0.05$ for all the comparisons). Six months post treatment, no association was observed between markers of insulin resistance and testosterone levels with PBR or its change during OGTT. Six months post-treatment, patients received GLP-1 agonists presented the greatest improvement in MMP9 levels compared to baseline.
Conclusion
Postprandial hyperglycemia, insulin resistance and testosterone levels are associated with impaired glycocalyx thickness in women with PCOS. The different treatment options resulted in the improvement of insulin resistance and biochemical markers of atherosclerosis, with GLP-1 agonists presenting the most prominent Results.

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P1018

JOINT2117

Sex steroids measurement by immunometric assay (IA) compared to liquid chromatography-tandem mass spectrometry (LC-MS/MS) in patients with klinefelter syndrome (KS)

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Background
KS is a genetic condition characterized by an extra X chromosome in male individuals associated with an increased risk of primary hypogonadism, which requires testosterone replacement therapy (TRT) when suggestive signs, symptoms and low serum Testosterone (T) are present. While IA remains the standard method for T measurement in the clinic, LC-MS/MS is increasingly being utilized also in clinical laboratory settings.
Aim
The aim of this study is to analyze the accuracy of IA compared to the gold standard LC-MS/MS for the diagnosis and monitoring of hypogonadism in patients with KS.
Materials and Methods
A total of 67 measurements (33 untreated and 34 under TRT) in KS patients were accrued: serum total T (TT) was assessed by both LC-MS/MS and IA, together with SHBG for calculated free testosterone (cfT). Hypogonadism was defined according to the Italian Society of Andrology and Sexual Medicine (SIAMS) threshold: serum TT $\leq$ 3.5 ng/mL and/or cfT $<$ 6.5 ng/dl. TT was quantified using CMIA DxI800 Beckman Coulter (IA)and Chrosystems MassChrom® Steroids in Serum/Plasma kit on Sciex CitrineTM (LC-MS/MS); cfT was calculated with the Vermeulen formula.
Results
The overall cohort and the subgroup not under TRT showed similar results, with only some minor differences. Serum TT measured by IA showed a strong positive correlation with LC-MS/MS measurements (respectively $R^2=0.891$, $P < 0.001$ and $R^2=0.849$, $P < 0.001$) similarly to cfT (respectively $R^2=0.853$, $P < 0.001$ and $R^2=0.638$, $P < 0.001$). However, a higher prevalence of biochemical hypogonadism was observed with IA compared to LC-MS/MS for TT both in all (41.17% vs 23.53%, OR 1.94, $P = 0.059$) and in untreated KS (75.75% vs 60.61%, OR 2.03, $P = 0.190$). A similar but significant result was found for cfT in all (54.69% vs 34.38%, OR 2.16, $P = 0.033$) and in untreated KS (75.75% vs 45.46%, OR 3.75, $P = 0.014$). Finally, in the subgroup of patients not under TRT a higher concordance between the two methods, LC-MS/MS and IA, ($R^2=0.950$, $P < 0.001$) was observed for total testosterone levels $>$ 3.5 than $\leq$ 3.5 ng/ml, highlighting some challenges in discriminating hypogonadal subjects.
Discussion
In accordance with what discovered in the overall population at risk for hypogonadism, even in KS patients IA seems to overestimate significantly both the prevalence of hypotestosteronemia and TRT compensation for TT and cfT when compared to LC-MS/MS. Hence, LC-MS/MS and SHBG assessments in every day clinical practice are probably crucial to detect and to correctly address to treatment KS patients, as well as for monitoring TRT.

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P1019

JOINT1330

Exposure to high anti-müllerian hormone (AMH) levels during mini-puberty in mice induces polycystic ovary syndrome-like defects in both sexes

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Polycystic Ovary Syndrome (PCOS) is the most common endocrinopathy affecting women worldwide, leading to various long-term cardio-metabolic repercussions. Despite its significant impact, there is currently no cure, emphasizing the urgent need for effective treatments. Gestational excess of androgens and anti-Müllerian hormone (AMH) is common in women with PCOS and preclinical studies have demonstrated that abnormal exposure to these hormones during prenatal development can cause PCOS-like traits in adult female offspring. However, it is unclear if there is also a critical period of susceptibility to PCOS during early postnatal life. Interestingly, AMH levels have been found to be significantly higher during mini-puberty in both daughters and sons of mothers with PCOS compared to infants of non-PCOS women. To elucidate whether elevated AMH levels during infancy in offspring of women with PCOS are a byproduct or a driving force behind the condition, we developed an innovative mouse model by exposing otherwise healthy mice to AMH during mini-puberty. We showed that such treatment induced PCOS-like reproductive and metabolic defects in females and males alike. Additionally, we developed a pharmacological approach that showed beneficial effects on both reproductive and metabolic PCOS-related defects. These findings suggest that exposure to elevated serum AMH levels during mini-puberty plays a causal role in the pathophysiology of PCOS. They also identify a window of opportunity for developing novel therapeutic preventive strategies for PCOS.

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P1020

JOINT183

Visfatin (Nampt) siRNA induced knockdown effect on blastocyst transcriptome, implantation rate and offspring ovarian function. Studies on normal weight and obese mice

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Objectives
Adipokines regulate reproduction in dependence of metabolic conditions. Visfatin, upregulated in obesity, improves oocyte maturation in obese and old individuals. Our previous studies showed that lack of visfatin leads to decrease in blastocyst number in obese mice. The aims of this study were to determine the effect of visfatin on the blastocyst transcriptome in normal weight and high-fat-diet induced obese mice, as well as blastocyst implantation rate and ovarian function of offspring.
Methods
We knockdowned the mRNA expression of *Nampt* at the 1 cell stage embryo (siRNA electroporation) and cultured it until the blastocyst stage, then we isolated RNA and evaluated blastocyst transcriptome (RNASeq, padj <0.05), DEGs ontology and pathways were analyzed in qProfiler and DAVID software. As a next step the blastocyst implantation rate/offspring number were calculated and offsprings (17.5 dpi) ovaries were collected to measure steroidogenesis (*Star, Cyp11a1, Cyp17a1, Hsd3b, Cyp19a1*), folliculogenesis/oogenesis (*Gdf-9, Bmp-15, Figla, Dnmt1*) and proliferation/apoptosis (*Pcna, Bax, Bcl2*) related genes level (real-time PCR, $n = 5$). Statistical analysis was performed in GraphPad Prism software.
Results
Transcriptomic analysis showed 73 upregulated and 24 downregulated genes in the blastocyst from normal weight mice after *Nampt* silencing. Ontology and pathways analysis classified these genes to biological processes (cell death, glycolytic process, metabolic process, anatomical structure development) and cellular components (cytoplasm, cytoskeleton, cell junction). According to KEGG we noted estrogen signaling, p53 and progesterone mediated oocyte maturation pathways. In obese mice group only 2 genes were upregulated (*Gm10052, Tspan7*) and 1 (*Tmem^{2}54c*) downregulated. Visfatin silencing does not affect the implantation rate and offspring number in normal weight mice. However, we observed the changes in the expression of marker genes of proper ovarian function in offspring including stimulation in *Bmp-15 and Cyp17a1* and inhibition in *Hsd3b* transcripts.
Conclusion
Visfatin is an important factor in early embryogenesis, and the effect of its absence in early embryonic life is long-lasting and affects the fertility of female offspring. It also indicates that visfatin may play a compensatory role in reproduction during obesity.
Keywords
visfatin, early embryogenesis, siRNA induced gene knockdown, transcriptome.
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P1021

JOINT2335

Fibrosis is an early marker of subcutaneous adipose tissue dysfunction in polycystic ovary syndrome (PCOS)

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Prenatally androgenised female sheep are a clinically realistic model of PCOS. In adolescence (11 months of age) there is reduced subcutaneous adipogenesis and in adulthood (30 months of age) there is increased subcutaneous adipose tissue (SAT) dysfunction with inflammation. We hypothesised that analysis of adipose tissue in young adults (20 months of age), after adipogenesis is complete but before inflammation is manifest, would give insights into the evolution of adipose tissue dysfunction in PCOS. Pregnant Scottish Greyface sheep were treated intramuscularly with testosterone propionate (100 mg) or vehicle control twice weekly from day 62-102 of gestation (147 days) and their female offspring were studied. Two cohorts of weight-matched PCOS-like sheep and contemporaneous controls were investigated. At 20 months of age the SAT of young adult PCOS-like sheep ($n = 10$) and control sheep ($n = 10$) was examined by RNAseq and fixed for histochemical analysis. At 30 months of age PCOS-like sheep SAT ($n = 4$) and control sheep SAT ($n = 4$) underwent histochemical analysis. In addition, SAT was collected from obese adult women with PCOS ($n = 12$) and obese adult women without PCOS ($n = 12$) for histochemical analysis. RNAseq analysis of young adult PCOS-like sheep SAT showed that a total of 792 genes were differentially expressed when compared to control sheep (406 upregulated; 386 downregulated). Ingenuity pathways analysis highlighted upregulation of fibrosis signalling pathways, extracellular organisation pathways and the assembly of collagen fibrils in the SAT of PCOS-like sheep. RT-PCR confirmed that *POSTN*, which is associated with tissue remodelling and fibrosis, was increased ($P < 0.05$) in PCOS-like sheep SAT as were *COL1A1* ($P < 0.05$), *COL1A2* ($P < 0.05$) and *COL3A1* ($P < 0.01$). Masson's Trichrome stain showed an increased area of fibrosis in SAT of PCOS-like sheep ($P < 0.05$) when compared to controls. This increased fibrosis was also seen in both adult PCOS-like sheep ($P < 0.05$) and obese women with PCOS ($P < 0.05$) when compared to controls. Early fibrotic changes in SAT occurs in young adult PCOS-sheep and this change is also seen in adulthood and in adult women with PCOS. In young adult PCOS-like sheep SAT fibrosis is present before SAT inflammation is detected. SAT fibrosis might provide a barrier to healthy adipocyte expansion and have a mechanistic role in the development of the detrimental inflammatory environment in PCOS.

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P1022

JOINT1354

TSH concentration does not affect metabolic and reproductive hormones in euthyroid women with pcos

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Introduction
Thyroid function is central to the regulation of human metabolism and reproductive function; abnormal thyroid function tests (TFTs) have been

associated with unfavourable metabolic and hormonal changes in women with PCOS. However, it is not known if slight variations in TSH concentration affect these parameters in euthyroid women with PCOS. If a significant association is present, one may suggest thyroxine treatment in this population, even with TFTs within reference values.
Subjects and Methods
Cross sectional data of 1762 European women of Caucasian origin (age: 24.57 ± 5.54 years, BMI: 26.34 ± 6.88 kg/m^2) diagnosed with PCOS by Rotterdam criteria were analysed. All subjects had both normal TSH values (0.4-4.7 IU/ml) and either T4 or FT4 values. None of the subjects was on treatment with Thyroxine. Anthropometric parameters (age, BMI, WHR, FG Score), metabolic indices (glucose, lipids, liver function, HOMA-IR) and hormonal (gonadotropins, testosterone, SHBG, DHEAS, D4, FAI, estradiol, insulin) values were evaluated. Data were stratified by TSH values (higher or lower of 2.5IU/ml) forming two groups: Group A (TSH $<$ 2.5 IU/ml) and Group B (TSH $<$ 2.5 IU/ml). In addition, data were stratified according to TSH quartiles (Q1, TSH 0.4-1.5, Q2 1.5-2.5, Q3, TSH 2.5-3.5, Q4, TSH$>$ 3.5-4.7 IU/ml).
Results
The comparison between Groups A and B reached significant difference ($P <$ 0.05) in TSH values (1.49 ± 0.58 vs. 3.98 ± 0.56IU/ml) as expected. However, except for SHBG (40.78 ± 19.55 vs.37.96 ± 19.64 nmol/l) and DHEAS values (3.03 ± 1.35 vs. 2.84 ± 1.32 nmol/l), no difference was observed in any other parameter evaluated (Table 1). When data were analysed based on TSH quartiles, statistically significant differences were found between subgroups regarding LH, FSH, SHBG and DHEAS values.
Conclusions
Our findings originating from a large European PCOS cohort suggest that TSH values in euthyroid women with PCOS are not significantly associated with any metabolic and hormonal parameters except for SHBG and DHEAS. The association between TSH and these hormones warrants further evaluation but our findings advocate against thyroxine use in women with PCOS and TSH values within the reference range for metabolic or hormonal purposes.

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P1023

JOINT2897

Remission of polycystic ovary syndrome based on the recovery of ovarian morphology identified by three-dimensional power doppler ultrasonography:a retrospective cohort study

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Objective
Polycystic ovary syndrome (PCOS) is a high prevalence chronic disease. Limited studies have explored the issue of remission PCOS indicated by regular menstrual cycles or natural pregnancies. As 90% of women with PCOS showed polycystic ovary morphology (PCOM) on ultrasound examination, the aim of this study was investigated the rate of achieving remission of in patients with PCOS, which was based on the recovery of ovarian morphology in PCOS patients using three-dimensional (3D) ultrasound techniques after pharmacological approaches.
Methods
This retrospective study included 727 reproductive-aged women with PCOS recruited in the PCOS-specialized outpatient clinics at Shanghai Tenth People's Hospital from May 2020 to August 2024. Since the initiation of medication, anthropometric parameters, biochemical variables, reproductive indicators at baseline and post-treatment period were collected at every three months. During the follow-up period, 3D ultrasonography was used to assess the presence of polycystic morphology.
Results
A total of 296 participants were eligible for the study, and 28 participants (9.46%) achieved remission of PCOS with regularized menstrual cycle, normalized ovarian morphology. The mean time to achieve remission of PCOS was 14.1 ± 13.2 months. The remission group had significantly higher waist circumference (WC), waist-to-hip ratio (WHR), and higher follicle number in both ovaries than the non-remission group ($P <$ 0.05) at baseline. In the remission group, significant reductions were observed post-treatment in body mass index (BMI), waist circumference, alanine aminotransferase (ALT), aspartate aminotransferase (AST), low-density lipoprotein cholesterol (LDL), progesterone, and total testosterone (TT). Meanwhile, there was a significant reduction in ovarian volume and follicle numbers of both ovaries in the patients with PCOS remission. Medication promoting insulin resistance and weight-loss (GLP-1 agonists, metformin, SGLT-2 inhibitors) were widely taken in the remission group.
Conclusion
Our study demonstrated that 9.46% patients with PCOS could achieve remission of PCOS with normalized ovarian morphology after taking medications for improving metabolism and weight loss.

Keywords
polycystic ovary syndrome, remission, three-dimensional power doppler ultrasonography.
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P1024

JOINT1659

Paternal use of paracetamol prior to conception is associated with elevated adrenal steroid levels in female infants - a copana study

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Background
Growing evidence suggest that maternal paracetamol use impairs fetal ovarian development. In animal studies, paternal preconceptional use of paracetamol has been suggested to affect fetal development, possibly through mechanisms including epigenetic changes, altered non-coding RNAs, oxidative stress, or hormonal disruption in the sperm's paracrine environment. The female HPG and HPA axis is functionally established in early infancy enabling assessment of ovarian and adrenal activity.
Aim
Evaluate associations between paternal use of paracetamol and ovarian and adrenal function in female offspring.
Design
Prospective, observational pregnancy and birth cohort; The Copenhagen Analgesic Study (COPANA) (ClinicalTrials.gov NCT04369222).
Setting
Copenhagen University Hospital – Rigshospitalet, Denmark (2020-2022).
Methods
Healthy, singleton pregnant women enrolled in first trimester of pregnancy (n = 685) and 589 children (302 girls) examined in infancy. Fathers (n = 245) reported their paracetamol use (yes/no) prior to conception and girls were categorized as exposed if their father used paracetamol three months prior to conception (exposed = 133, unexposed = 112). Girls were examined at age 3.4 ± 0.4 months (mean(±SD) including transabdominal ultrasound: ovarian volume (n = 161/245). Infant serum hormones (n = 218/245): FSH, LH, AMH, Inhibin B (immunoassays), 16 steroid metabolites (LC/MS-MS). Age and sex specific SD-scores were calculated. Mothers reported their paracetamol use every two weeks during pregnancy (yes/no), and delivery mode (vaginal/elective section/emergency section) was obtained from medical records.
Statistics
Mann Whitney U-test and linear regression models.
Results
There was a trend towards reduced ovarian volume; median (IQR) 236.3 mm^3 (153.1–419.08) vs 316. 0 mm^3 (204.9–458.5) P = 0.069 in exposed girls at

infancy compared to unexposed. Furthermore, paternal use of paracetamol was associated with increased levels of several steroid metabolites (Table 1). The associations were not affected after adjusting for maternal use of paracetamol in early pregnancy or delivery mode, respectively. Paternal use of paracetamol was not associated with levels of reproductive hormones in infancy.

Conclusion

Paternal paracetamol use before conception appears to affect ovarian development in a manner comparable with effects observed after maternal prenatal use of paracetamol. Furthermore, circulating levels of several adrenal steroids were linked to paternal use of paracetamol. This reinforces concerns about the effects of paracetamol on fetal development, likely involving multiple biological mechanisms.

Table 1

	Median (IQR)		*P*-value
	Unexposed (n = 96)	Exposed (n = 122)	
17-alpha-hydroxyprogesterone SDS	-0.21 (-0.91– 0.57)	0.09 (-0.66– 0.82)	0.068
11-deoxycortisol SDS	-0.03 (-0.85– 0.60)	0.17 (-0.51– 0.89)	0.047
Cortisol SDS	-0.11 (-0.68– 0.51)	0.27 (-0.45– 0.81)	0.004
11-Deoxycorticosterone SDS	-0.45 (-1.26– 0,48)	-0.08 (-0.87– 0.78)	0.020
Corticosterone SDS	-0.48 (-1.11–0.82)	-0.04 (-0.76– 0.77)	0.035

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P1025

JOINT25

Outcomes and fertility in men with PAIS worldwide: lessons from an I-DSD registry platform cohort

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The androgen receptor (AR) sensitivity is an important determinant of male phenotype expression in XY individuals during fetal life and from the onset of puberty. Partial Androgen Insensitivity Syndrome (PAIS) is a spectrum of various genital phenotypes and gonadal impairments affecting approximately 1 birth in 130,000 individuals. However, there is still very little information on fertility in men with PAIS in the medical literature. Fertil'PAIS is an international, retrospective, multi-centre, observational study still in progress, evaluating fertility in PAIS men over sixteen years from the I-DSD Registry platform, as well as their genital phenotype at birth, pubertal development, psychological well-being, gender identity, and hormonal replacement therapy. Currently, 68 patients with PAIS from 11 different countries have been included, with a median age of 20.2 (16,3-69) years. Ninety-seven percent were identified as male gender, and among the 2 patients who were identified as female at birth, 1 underwent gender transition to male at 16, and 1 had a legal sex change facilitated by parents. External Genitalia Score at birth was around 8.5 out of 12: 79% had a genital tubercle beneath 30 mm, 20% no labioscrotal fusion, 55% a scrotal meatus, and 30% inguinal or impalpable gonads. Most patients had not undergone gonadectomy or gonadal biopsy and had testes identified by ultrasound. Additionally, among the 22% for whom we had information, all of them, except one, experienced spontaneous puberty at a median age of 12.7 years and 90% had gynecomastia around 13.4 years. More than 50% had high FSH, LH, AMH and total testosterone at 20 years old and we found low inhibin B in only 2 patients. Finally, we found information about fertility desire in only 39% of the 18 patients who had more than 16 years at last assessment, of whom 71% had desired fertility. Only 6 patients had sperm assessment with count - all abnormal-, none of them had sperm cryoconservation, and only one was able to father twice thanks to medically assisted conception (MAP). In conclusion, the phenotype of PAIS men at birth varies greatly, but they mostly exhibit severe variations in genital development and gynecomastia. While most undergo spontaneous puberty and have normal inhibin B levels, fertility remains poorly monitored, and cryoconservation or MAP is not well considered. Therefore, we need to obtain more information about fertility in these patients to better understand their desires and provide them with follow-up and assistance according to their needs.

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P1026

JOINT228

Splenic structural and functional abnormalities in individuals with NR5A1/SF-1 variants

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Objective

Steroidogenic Factor 1 /Nuclear receptor subfamily 5 group A member 1 (SF-1/NR5A1) is essential for spleen development and function, and *NR5A1* variants have been linked to abnormal spleen development. Hyposplenism exposes individuals to severe complications with potential serious sequelae. This study aimed to determine the prevalence and main features of hyposplenim in a cohort of French patients with *NR5A1* variants.

Methods

Morphology and function of the spleen were assessed in 34 patients carrying a heterozygous *NR5A1* variant. Quantification of pocked-RBCs, the reference marker for splenic function, was performed in all participants along radiological examination.

Results

Functional hyposplenism was observed in 61.7% of patients, with 47% having severe forms. 44.1% of participants had morphological abnormalities of the spleen, including complete absence in 11.7%. All patients with splenic morphological abnormalities on imaging also showed functional hyposplenism. 28% of patients with functional hyposplenism did not have any morphological abnormality on imaging. No association between *NR5A1* genotype or gonadal phenotype and splenic anomalies was identified.

Conclusions

Functional hyposplenism is common in patients with *NR5A1* variants, regardless of genotype and gonadal phenotype. Hence, assessing splenic function becomes mandatory in managing these patients, and preventive measures are critical when hyposplenism is present.

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P1027

JOINT309

Low detransition rates among 709 gender-affirming therapy recipients and associated risk factors: results from a systematic follow-up study

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Background

The dramatic increase in individuals seeking Gender-Affirming Therapy (GAT) has sparked debates about gender dysphoria, including concerns about detransition rates, irreversible effects, and the contentious issue of access to treatment, particularly for minors. While reported detransition rates vary widely (0.5-30%), prior studies have lacked systematic efforts to track and interview individuals who discontinued attendance at specialized gender clinics.

Aim and Methods

This study evaluated detransition rates among individuals initiating GAT at Tel Aviv Sourasky Transgender Health Center between May 2014 and December 2022. Subjects who discontinued follow-up after $\geq$2 visits were contacted, and those who detransitioned participated in structured interviews to understand the motives and circumstances leading to their decision.

Results

Of 709 adults initiating GAT, 239 (33.8%) discontinued follow-up. All but 15 were successfully contacted, providing 694 subjects for analysis. Among the 224 subjects who discontinued clinic attendance, 13 had detransitioned, representing a detransition rate of 1.87% (CI 0.86-2.88). All other subjects, including the 470 who maintained clinic attendance, continued their gender-affirming process.

Focusing on the group of 224 individuals who had discontinued clinic attendance, we found no differences between the 13 detransitioners and those continuing treatment (usually under family physician care) in demographic (gender, age, ethnicity) or socioeconomic (education, profession, employment) parameters. Detransitioners had received GAT for a shorter duration (median 12 vs 79 months, $P < 0.001$) and had lower rates of surgical procedures (23.1% vs 58.8%, $P < 0.001$), with only one subject having undergone genital surgery. Additionally, detransitioners demonstrated markedly higher rates of complete lack of family support (38.5% vs 8.5%, $P = 0.003$), were less likely to reside in the Tel Aviv-Central area (38.5% vs 61.1%, $P < 0.001$), and more frequently had pre-existing psychiatric diagnoses (84.6% vs 41.7%, $P = 0.01$).
Conclusions
In this first systematic follow-up study of transgender individuals who discontinued clinic attendance, we found a notably low detransition rate of 1.87%. While detransitions occurred across various treatment durations, they rarely followed irreversible surgical interventions. Distance from specialized care centers, lack of family support, and pre-existing psychiatric conditions may influence detransition risk, emphasizing the importance of accessible care and comprehensive support systems.

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P1028

JOINT1442

Prevalence and predictive factors of bleeding disorders in adolescents with abnormal uterine bleeding

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Background
Abnormal uterine bleeding (AUB) is a frequent and potentially severe condition in adolescents, leading to anemia and impacting quality of life. While AUB is commonly attributed to anovulatory cycles, bleeding disorders may underlie a significant proportion of cases, warranting precise identification to optimize management.
Aim
This study investigated the prevalence and types of coagulation disorders in adolescents with AUB and identified potential clinical and biochemical predictors of these disorders.
Methods
A prospective longitudinal cohort study was conducted on 130 female adolescents (10–17 years) with AUB referred to a Tertiary Pediatric Hospital from 2012 to 2022. Patients with prior coagulopathy or endocrinopathy were excluded. Collected data included medical history, bleeding tendencies, laboratory tests and pelvic ultrasounds. Anemia was categorized as mild (Hb:10–12 g/dl), moderate (8–10 g/dl), or severe (<8 g/dl). A potential clinical risk score of bleeding disorder was identified.
Results
Among 130 female adolescents, 89% experienced AUB within 2 years of menarche (mean age: 11.6 ± 1.4 years). Anemia was found in 56%, with 42.4% of which, severe. Coagulation disorders were identified in 15.4% ($n = 20$), including von Willebrand disease (50%), thrombocytopenia (10%), and coagulation factor deficiencies (40%), predominantly Factor VII deficiency. Ferritin levels were significantly more reduced in the coagulation disorder group (11.8 ± 11.3 ng/dl VS 21.6 ± 18.6 ng/dl; $P < 0.005$). A personal history of bleeding at sites other than menorrhagia (20% vs 0.9%) and a family history of bleeding disorder (20% vs 0.9%) were more frequently reported in the coagulation disorder group compared to adolescents without bleeding disorders. A composite score, called the AUB-BDA-Score (Abnormal Uterine Bleeding - Bleeding Disorders Adolescent Score), was developed based on the statistically significant risk factors found. This score is calculated as the sum of three variables:.
1. Personal history of bleeding at other sites (0 = absent, 1 = present);.
2. Family history of bleeding disorders (0 = absent, 1 = present);.
3. Ferritin levels <12 ng/mL (0 = no, 1 = yes).
A score of 3 suggests the need of investigating a potential bleeding disorder.
Conclusions
In our cohort, the 15.4% of adolescents with AUB had a bleeding disorder, with von Willebrand disease and factor VII deficiency being the most prevalent. Predictors included bleeding history, family history of bleeding and ferritin levels below 12 ng/mL. The proposed AUB-BDA-Score needs to be verified in further studies in order to enhance diagnostic precision and improve patient outcomes.

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P1029

JOINT1632

Reference intervals for serum total testosterone, free testosterone and sex hormone binding globulin in middle-aged men; the impact of overweight and obesity

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Introduction
Reference intervals for serum total testosterone (TT), free testosterone (FT), and sex hormone-binding globulin (SHBG) are essential for diagnosing hypogonadism in men. Obesity influences androgen and SHBG concentrations, complicating the interpretation of hormonal changes. This study aims to establish reference intervals for serum TT, FT, and SHBG in middle aged adults and to calculate expected values for different BMI categories.
Methods
The Netherlands Epidemiology of Obesity study is a population-based prospective cohort study comprising 3156 male participants aged 45–65, with oversampling of individuals with a BMI >25kg/m^2. Fasting blood samples were analysed for testosterone and SHBG concentrations using LC–MS/MS and an automated immunoassay (Architect), respectively. FT was calculated using the Vermeulen formula. The reference population was defined by a BMI <25kg/m^2, no history of cardiovascular or hormone-affecting diseases, non-smokers, and no use of medication. Reference intervals were calculated, based on the 2.5th and 97.5th percentiles, for testosterone, SHBG, and free testosterone. The proportions of individuals of BMI groups falling within the reference intervals were assessed.
Results
Reference intervals for 216 men aged 45-65 years with a BMI <25 kg/m^2 were 8.3 – 28.7 nmol/l for TT, 139 – 422 pmol/l for FT, and 17.7 – 80.8 nmol/l for SHBG. As BMI increases, a greater proportion of men fall below the lower limit of the reference intervals. Specifically, among men with a BMI >35 kg/m^2, 24% fall below the reference interval for TT, 17% for FT and 11% for SHBG.
Conclusion
We present reference intervals for TT, FT and SHBG in middle-aged men. Men with overweight or obesity more often fall outside these reference intervals. Our findings can improve interpretation of abnormal laboratory results in individuals with overweight or obesity.

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P1030

JOINT2917

Sleep disturbances in adolescents with PCOS: does metabolic status have an impact beyond obesity?

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Background
Polycystic ovary syndrome (PCOS) is a complex endocrine disorder in adolescents, often linked to hyperandrogenemia, obesity, and insulin resistance. While metabolic dysfunction in PCOS is well-documented, the role of sleep disturbances remains underestimated. Emerging evidence suggests that poor sleep quality and increased obstructive sleep apnea (OSA) risk may worsen metabolic outcomes, independent of obesity. This study aims to explore the association between sleep disturbances, metabolic dysfunction, and obesity in adolescents with PCOS, with a particular focus on the independent contributions of hyperandrogenemia and insulin resistance.

Methods
A total of 74 adolescents and young adults diagnosed with PCOS (14-24 years) and 87 age-matched healthy controls were included in this cross-sectional study. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and Berlin Questionnaire for OSA risk. Anthropometric measures included BMI, BMI-SDS. Biochemical analyses covered LH/FSH ratio, testosterone, SHBG, androstenedione, DHEAS, glucose, insulin, HOMA-IR, and lipid profile. Analysis was made between PCOS and control groups, as well as within the PCOS cohort based on obesity status.
Results
PCOS patients had significantly higher BMI ($P < 0.001$) and BMI-SDS ($P < 0.001$) than controls. Moreover, 57% of PCOS patients were obese, compared to only 11% in the control group. Compared to controls, PCOS patients had significantly higher ESS scores ($P = 0.04$) and an increased risk of OSA ($P = 0.031$), while overall sleep quality, as measured by PSQI scores, did not differ significantly. Among PCOS patients, obese individuals had significantly higher levels of testosterone ($P = 0.017$), androstenedione ($P = 0.004$), insulin ($P < 0.001$), HOMA-IR ($P < 0.001$), and LDL cholesterol ($P = 0.018$) compared to non-obese PCOS patients. Poor sleep quality (PSQI >5) was strongly associated with an increased risk of OSA ($P < 0.001$). Correlation analysis revealed a weak but positive association between HOMA-IR and Berlin Questionnaire scores ($r = 0.272$, $P = 0.02$), suggesting a potential link between HOMA-IR and OSA risk. Similarly, the triglyceride/glucose ratio showed a weak positive correlation with Berlin scores ($r = 0.292$, $P = 0.015$).
Conclusions
This study highlights that sleep disturbances in PCOS are not solely driven by obesity but are also influenced by metabolic status. Poor sleep quality is associated with increased OSA risk. Given the potential long-term cardiometabolic consequences, integrating sleep health into PCOS management may be crucial, especially in obese individuals. Further research with objective sleep assessments, like polysomnography, is crucial to gaining deeper insights into the complex relationship between PCOS, sleep disturbances, and metabolic dysfunction.
Key words
PCOS, adolescent, sleep quality, metabolic status, OSA.

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P1031

JOINT2820

Baseline obesity classifications influence the impact of pharmacotherapy on weight and BMI in adolescents with PCOS: findings from the clinical adolescent polycystic ovary (CALICO) database

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Background
Estrogen-containing contraceptives (EC) and metformin are leading pharmacotherapies for polycystic ovary syndrome (PCOS), yet the impact of these medications on weight and body mass index (BMI) gains over time in adolescents are unclear. We sought to understand the effect of these treatments on the velocity of changes in weight and BMI over time in teens with PCOS, and if there was a differential effect based on preceding BMI category.
Methods
Participant ($n = 899$) information was extracted from the CALICO Database, a longitudinal chart review with data on adolescents with PCOS diagnosed using the 2018 international guidelines at 17 US sites. For this analysis, the primary outcomes were change in weight and BMI over time. As such, we excluded patients taking weight loss medications, atypical antipsychotics, and daily hormone therapies other than EC. Linear mixed effects models evaluated the differences in weight/BMI change trajectories over time between Ever EC Users (pill, patch, or ring, $n = 458$) vs Never EC Users ($n = 441$) and Ever Metformin Users ($n = 503$) vs Never Metformin Users ($n = 396$). All models were adjusted for age, race, and insurance status. Models were conducted by weight subgroup (BMI 5-84%, BMI 85-94%, BMI $\geq$95%). EC models were adjusted for metformin use, and vice versa. Analyses were performed using R version 4.4.2.
Results
For those with a BMI $<$85%ile, no group had an increase in weight trajectory over time. While taking medications, there was a decrease in both weight and BMI trajectories in those taking EC [-0.146(-0.257,-0.036)kg/mo, $P = 0.010$; -0.0627(-0.1055,-0.0198), kg/m^2/mo, $P = 0.005$] or metformin [-0.211(-0.349,-0.074)kg/mo, $P = 0.003$; -0.2112(-0.3485,-0.0738)kg/m^2/mo, $P = 0.003$]. For the overweight participants, no group demonstrated increases in weight velocities over time. Those taking metformin had a decrease in both weight [-0.382(-0.575,-0.189)kg/mo,$P = 0.0002$] and BMI [-0.113(-0.181,-0.0441)kg/m^2/mo, $P = 0.002$] trajectories while taking the medications. For girls with obesity, BMI increased over time for EC [0.026(0.006,0.049)kg/m^2/mo, $P = 0.013$] and metformin [0.0255(0.0008,0.0441) kg/m^2/mo, $P = 0.042$] groups, but not the non-treatment groups [No EC 0.0256(-0.0086,0.0599) kg/m^2/mo, $P = 0.142$; No metformin 0.0272(-0.0073,0.0617) kg/m^2/mo, $P = 0.122$]. There was no change in the positive weight ($P = 0.503$) and BMI ($P = 0.6840$) trajectories while taking EC, whereas during metformin use, the weight [-0.1453(-0.2506,-0.0401) kg/mo, $P = 0.007$] and BMI [-0.0532(-0.0898,-0.0166)kg/m^2/mo, $P = 0.005$] gain trajectories were significantly less positive.
Conclusion
The impact of EC and metformin on weight and BMI over time differ by baseline BMI category in adolescents with PCOS. Counseling of the weight effects of these medications should be guided by the patients' pretreatment BMI category.
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P1032

JOINT697

Effects of testosterone treatment on the morphology of female internal genitalia assessed by transabdominal ultrasound (TAUS) in trans boys

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Background
International guidelines for the healthcare of transgender youth include the possibility of hormone therapy. Recent concerns have been raised about testosterone treatment in trans men and its effects on their fertility potential as well as the risk of endometrial hyperplasia and cancer. To our knowledge, current studies are conducted in adult transmasculine individuals.
Aim
To investigate the effects of testosterone on the internal female genitalia assessed by transabdominal ultrasound (TAUS) in an unselected population of trans boys who initiated hormone therapy before the age of 18 years.
Methods
Trans boys were referred to a TAUS scan after approximately one year of testosterone treatment ($n = 48$). 2D ovarian and uterine TAUS were conducted by experienced gynecologists using the Voluson E10 Ultrasound System (GE Healthcare Medical Systems, Zipf, Austria) and a multifrequency transabdominal probe (C2-9). All TAUS findings are given as median (10th, 90th percentiles). Hormone serum concentrations are presented as median (IQR).

Results
At the start of testosterone treatment the median age was 16.9 years. Some of the trans boys had prior GnRH analog monotherapy ($n = 31$), and Tanner stage ranged from 3 to 5 before any treatment. Self-reported age at menarche was 12 years (range 9 – 15). The median age at TAUS was 18.0 after a median duration of testosterone treatment corresponding to 15.0 months. Serum concentrations were 0.8 IU/l (0.2 – 3.1) for LH, 3.2 IU/l (1.2 – 6.2) for FSH, 18.3 nmol/l (12.2 – 26.9) for testosterone, and 104.8 pmol/l (76.4 – 134.8) for estradiol. The mean ovarian volume, in trans boys with both ovaries visualized, was 8.9 cm^3 (3.4, 13.8). The median number of small follicles was 3 (1, 5), and the largest follicle measured 6.0 mm (3.3, 11.5). Uterine volume was 77.0 cm^3 (37.9, 104.9), uterine length was 6.7 cm (5.0, 7.8), and endometrial thickness was 4.0 mm (2.2, 6.0).
Conclusion
Our results indicate that testosterone monotherapy may not fully suppress the pituitary-ovarian axis in trans boys, and the aromatization of testosterone to estradiol may be sufficient to stimulate the endometrium. This could result in cyclic pain and breakthrough bleeding. Additionally, this may have implications for contraception in sexually active adolescents.

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P1033

JOINT2776

Long-term cardiovascular risk in women with subfertility: systematic review and meta-analysis

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Objective
Infertility and cardiovascular disease (CVD) are major global health concerns. While some studies suggest infertility may be an early marker of cardiovascular risk, others report no clear association. This meta-analysis (MA) aims to evaluate the relationship between female infertility and the risk of developing CVD later in life, with a focus on the possible impact of assisted reproductive technology (ART) exposure.
Design and Methods
We followed PRISMA guidelines to conduct a MA of 21 studies examining the link between female infertility and CVD outcomes. A total of 178,828 women with a history of infertility and 3,398,781 controls were included. Data on CVD incidence, coronary heart disease (CHD), and cerebrovascular events were extracted. Sensitivity analyses were performed to assess the impact of study design, participants' age at recruitment and ART exposure on the observed associations.
Results
Women with a history of infertility had a 14% higher risk of developing CVD compared to controls (HR = 1.14; 95% CI: 1.12–1.16; $I^2 = 89\%$). Infertility was also associated with a 17% increased risk of CHD (HR = 1.17; 95% CI: 1.12–1.23; $I^2 = 0\%$) and a 16% higher risk of cerebrovascular events (HR = 1.16; 95% CI: 1.11–1.21; $I^2 = 73\%$). Sensitivity analyses of prospective-only studies confirmed these associations, with a 4% increased risk of CVD (HR = 1.04; 95% CI: 1.01–1.08; $I^2 = 0\%$), a 15% increased risk of CHD (HR = 1.15; 95% CI: 1.07–1.24; $I^2 = 54\%$), and an 11% higher risk of cerebrovascular events (HR = 1.11; 95% CI: 1.05–1.17; $I^2 = 54\%$). Among 392,266 ART-exposed women and 33,630,919 controls, we observed a higher risk of CVD (HR = 1.18; 95% CI: 1.11-1.25; $I^2 = 97\%$), although a woman's prior exposure to ART did not significantly increase the risk of prevalent or incident CHD, cerebrovascular events, or heart failure. Studies evaluating infertile women aged < 40 years, when compared to controls, found a higher risk of CVD (HR = 1.20; $I^2 = 81\%$). On the contrary, studies evaluating infertile women over 40 years showed a comparable incident risk for CVD to controls (HR = 1.04; $I^2 = 29\%$).
Discussion
This study shows an increased risk of CVD, including CHD and cerebrovascular events, among women with a history of infertility. ART exposure was associated with higher CVD risk. However, the true magnitude of the effect of ART remains uncertain due to significant heterogeneity across studies, likely secondary to differences in study methodologies and ART protocols.

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P1034

JOINT3783

Genetic landscape and clinical spectrum of 46,XY differences of sex development: a retrospective study in a major saudi referral center

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Introduction
46,XY Disorders of Sex Development (DSD) encompass a spectrum of conditions characterized by atypical gonadal, hormonal, or phenotypic development in individuals with a 46,XY karyotype. The underlying etiologies of 46,XY DSD vary widely and may include genetic mutations affecting gonadal differentiation, steroid biosynthesis defects, or androgen insensitivity syndromes. Understanding the prevalence and diagnostic yield in specific populations is crucial for optimizing clinical management and genetic counseling. This study aims to evaluate the diagnostic outcomes and underlying causes of 46,XY DSD among patients in Saudi Arabia, providing insights into the regional distribution of these conditions.
Methodology
A retrospective review was conducted at King Faces Specialist Hospital Research Centre (KFSHRC), analyzing medical records of patients diagnosed with 46,XY Disorders of Sex Development (DSD) who were seen in the endocrine clinic between 2019 and 2024.Clinical, biochemical, and genetic data were systematically reviewed. The diagnostic yield was assessed based on the ability to establish a definitive diagnosis through genetic investigations. STATA version 18 was used for statistical analysis. Ethical approval was obtained from the ethics committee at KFSHRC (reference: 2231110).
Results
A total of 278 DSD patients were included. At birth, 24.4% were assigned female, while 75.6% were assigned male. Currently, 80.9% identify as male, and 19.1% identify as female. Genetic testing was conducted in 201 patients (72.30%), of which 168 (83.58%) yielded positive results with 42 distinct mutations. The most frequently identified genetic abnormality was SRD5A2 deficiency, found in 43 out of 168 cases (25.50%), Complete Androgen Insensitivity Syndrome (CAIS) in 21 (12.50%), Adrenogenital disorders 17 (10.11%), 17β-HSD deficiency in 15 (8.92%), Gonadal dysgenesis in 12 (7.14%), LHCGR in 7 (4.16%), CHARGE syndrome in 4 (2.38%) and 49 (29.16%) others.
Conclusion
This study highlights the high diagnostic yield (83.58%) of genetic testing in 46,XY DSD in the Saudi population, emphasizing its critical role in establishing definitive diagnoses. SRD5A2 deficiency (25.5%), Complete Androgen Insensitivity Syndrome (12.5%), and adrenogenital disorders (10.1%) were the most frequently identified genetic abnormalities among 42 distinct mutations. The findings underscore the genetic heterogeneity of 46,XY DSD and the importance of early genetic evaluation in guiding clinical management. Additionally, the observed discrepancies between assigned sex at birth and current gender identity reinforce the need for a multidisciplinary approach integrating genetic, endocrine, and psychosocial support to optimize patient outcomes.

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P1035

JOINT1292

Mini-puberty induction in male infants with congenital hypogonadotropic hypogonadism: a case series

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The aim of this study was to assess safety and efficacy of minipuberty induction with gonadotropin therapy for congenital hypogonadotropic hypogonadism (CHH). We recruited five male infants with clinical ± biochemical CHH. Treatment goal was penile and testicular growth, testicular descent, and normalisation of testosterone and inhibin B levels. Four cases had multiple pituitary hormone deficiency (MPHD); two each with pituitary stalk interruption syndrome and septo-optic dysplasia on MRI. The fifth case had Trisomy 21 with clinical hypogonadism. All five demonstrated micropenis with cryptorchidism noted in four. Clinical and biochemical picture was consistent with hypogonadotropic hypogonadism in all. Minipuberty induction was performed using subcutaneous injections of choriogonadotropin alfa (10-20μg twice-weekly) and recombinant FSH (25-50 IU thrice-weekly). Serial biochemical and clinical monitoring was performed. Age at induction was 11 ± 4.6 weeks for the MPHD patients and 26 weeks for case 5. Treatment duration was 16 ± 6.3 weeks All patients demonstrated good clinical response (**Table 1**). SPL increased from 1.0 ± 0.3 cm to 3.0 ± 0.4 cm ($P < 0.001$), TV (ultrasound) increased from

Table 1: End of treatment assessments

	Case 1	Case 2	Case 3	Case 4	Case 5
Treatment duration (weeks)	24	22	8	18	8
Testosterone LCMS (6-20nmol/l)	18.0	22	22	25	33
Inhibin B (300-500ng/l)	209	95	387	468	228
SPL (cm)	2.8	3.5	2.8	2.6	3.2
Testis location	R Inguinal | scrotal L Hi-scrotal | scrotal	R scrotal | scrotal L scro-tal | scrotal	R Inguinal | scrotal L Ingu-inal | scrotal	R Inguinal | scrotal L Ingu-inal | scrotal	R Inguinal | scrotal L Ingu-inal | scrotal
TV Ultra-sound (0.48-0.61mL)	R 0.03 | 0.1 L 0.04 | 0.13	*baseline only* R 0.34 L 0.2	R 0.22 | 0.36 L 0.12 | 0.27	R 0.13 | 0.43 L 0.18 | 0.44	R 01 | 0.42 L 0.2 | 0.22

Peak levels reported. Testicular position and volume reported as "initial | final". Hormonal ranges represent 0 to +2SDs (Busch 2022). TV-US range 50th to 90th for age (Goede 2011).

0.156 ± 0.09mL to 0.296 ± 0.31mL ($P = 0.09$), testosterone increased from 0 ± 0.1nmol/l to 22 ± 5.6nmol/l ($P < 0.001$) and inhibin B rose from 76 ± 29ng/l to 228 ± 148ng/l ($P = 0.02$) pre- and post-treatment. Testicular descent into scrotum was noted in 4 children. No adverse events occurred during treatment. This case series demonstrates successful induction of minipuberty with testicular descent seen in 80% cases obviating the need for surgery. Significant heterogeneity in response was observed highlighting the need for close monitoring and personalised treatment.

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P1036

JOINT1745

The global landscape of managing hypogonadotropic hypogonadism in male infants: results of an international survey

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Introduction

Congenital hypogonadotropic hypogonadism (CHH) impairs gonadotropic axis activation during mini-puberty, puberty, and adulthood. Severely affected males may present as neonates with micropenis and/or undescended testes, while milder cases exhibit delayed or absent puberty and infertility. Mimicking gonadotropin action using central hormone agents is standard for puberty and fertility treatments. However, no consensus exists on replacement therapy for mini-puberty, with strategies ranging from testosterone application to central agents like GnRH or gonadotropins via subcutaneous injections or pumps. Central agents are thought to not only improve penile size and testicular descent, but potentially also fertility outcomes, though supporting long-term data are lacking. Variability in regimens and drug access further complicates decision-making.

Aim

This survey aimed to identify global barriers in diagnosing and managing CHH during mini-puberty, providing insights for future guidelines.

Methods

An online survey using the Jotform platform was distributed via pediatric society networks, conferences, and email snowballing between June 2024 and January 2025.

Results

A total of 153 responses from 32 countries were analyzed, with Europe (85), South America (32), and North America (24) contributing most. Most respondents were paediatric endocrinologists (94%), also acting as primary patient managers (96.7%). Referrals occurred during mini-puberty for most cases (49.7% within the first 24 weeks), though 39.9% were referred later. Diagnostic testing during weeks 4–24 was considered optimal by 78%. Next-generation sequencing was performed by 60.1%, while 27.5% lacked access, predominantly in low- and middle-income countries. Hormone treatment was offered by 79.7%, with testosterone-only regimens used by 70.5%, central agents by 9%, and both by 20.5%. Limiting factors creating barriers toward hormone prescriptions included insufficient data (64.5%) and paucity of knowledge (25.8%). Two-thirds treated 0-2 patients with either testosterone or central hormone agents in the last 12 months ($n = 339$ receiving testosterone, $n = 111$ receiving central agents). Among testosterone prescribers, intramuscular administration (64.9%) over 3 months (68%) was most common, while the most common central hormone regimen was a hCG + recombinant human FSH combination (35.1%), followed by a hCG-only regimen (24,3%) given via subcutaneous injections (69.4%) for 3 or 6 months (47,2% and 33,3%, respectively). Central agents had lower treatment adherence and were more likely discontinued (16.6%) compared to testosterone (8%).

Conclusion

Despite evidence supporting central hormone agents for fertility outcomes, testosterone remains the more commonly used treatment globally. The findings underscore the need for consensus guidelines and long-term studies, particularly on fertility outcomes.

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P1037

JOINT69

A novel role of pregnancy-specific glycoprotein 1 in the maintenance of human chorionic gonadotropin secretion in human placental trophoblasts

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In pregnancy, the placental trophoblasts secrete a large amount of pregnancy-specific glycoprotein 1 (PSG1) into the maternal circulation. However, the exact role of PSG1 in pregnancy remains elusive. Human chorionic gonadotropin (hCG) is a hormone produced primarily by syncytiotrophoblastic cells of the placenta during pregnancy. The hormone stimulates the corpus luteum to produce progesterone to maintain the pregnancy. By using primary human placental trophoblasts, we demonstrated that like the expression of hCG, the expression of PSG1 was also significantly increased during syncytialization of placental trophoblasts. Knock-down of PSG1 expression did not affect hCG beta subunit mRNA levels, but increased intracellular hCG accumulation in trophoblasts while decreased extracellular hCG abundance, suggesting that PSG1 maintains hCG secretion in human placental trophoblasts. Induction of endoplasmic reticulum (ER) stress with thapsigargin (Tg) reduced PSG1 secretion along with increased intracellular hCG in trophoblasts and decreased extracellular hCG. In conclusion, we have demonstrated a novel of PSG1 in the maintenance of hCG secretion in human placental trophoblasts which may be impaired by ER stress. This novel function of PSG1 indicates that PSG1 participates in pregnancy maintainence by stimulating hCG secretion.

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P1038

JOINT3116

Follicular fluid from women with polycystic ovary syndrome and obesity impairs granulosa cell glycolytic function

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Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by exacerbated ovarian androgen production. When PCOS is accompanied by obesity and insulin resistance, reproductive dysfunction is usually even more pronounced. Granulosa cells (GCs) play a pivotal role in oocyte maturation, as key regulators of ovarian steroidogenesis and physiology. Consequently, GCs metabolic dysfunction can disrupt follicular development and potentially result in anovulation. However, the extent to which GC metabolic function is affected in the presence of PCOS remains

largely unknown. This study aim was to explore whether the follicular fluid (FF) microenvironment is able to influence GC glycolytic function. The study enrolled 24 women undergoing controlled ovarian stimulation for infertility treatment: 12 with PCOS and 12 controls. Each group was further subdivided according to BMI, normal weight ($n = 6$; BMI < 25 kg/m^2) and obesity ($n = 6$; BMI ≥ 30 kg/m^2). Human granulosa cells (HGrC1) were incubated for 24 hours in culture medium supplemented with 20% of FF collected during oocyte retrieval from women with PCOS or controls. Glycolytic function was assessed by measuring the extracellular acidification rate (ECAR). HGrC1 cells when exposed to FF from women with PCOS and obesity depicted a significantly lower glycolytic capacity when compared to those incubated with FF from normal-weight controls. Furthermore, non-glycolytic acidification of HGrC1 cells incubated with FF from women with PCOS irrespective of BMI was significantly lower than of those incubated with FF from normal-weight controls. These findings indicate that the FF from women with PCOS and obesity harbours the potential to impair granulosa cell glycolytic function, while suggesting that GC metabolic disruptions could underlie ovarian dysfunction in women with PCOS, particularly when associated with obesity.

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P1039

JOINT2221

The triglyceride-glucose (TyG) index and its relation to metabolic indices in women with PCOS: a phenotype-based analysis

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Introduction
Polycystic ovary syndrome (PCOS) is an endocrine disorder linked to insulin resistance (IR), dyslipidemia, and hyperandrogenism. The triglyceride-glucose (TyG) index is a proposed surrogate marker for IR, but its relevance across PCOS phenotypes remains unclear. This study aimed to assess the metabolic significance of TyG in women with PCOS from a Serbian population.
Subjects and Methods
A total of 160 women with PCOS, diagnosed using the ESHRE/ASRM criteria, were divided into four phenotypic groups with 40 patients each: A (oligo/anovulation-OA + clinical/biochemical hyperandrogenism-HA + polycystic ovarian morphology-PCOM), B (OA+HA), C (HA+PCOM), D (OA+PCOM). Fasting glucose, insulin, lipid profile, total testosterone and SHBG were analyzed, while HOMA-IR, FAI and the TyG index were calculated. Patients were stratified by the TyG median calculated from our cohort (7.9).
Results
Our patients had a mean age of 25.98±6.03 years, BMI 24.05±5.64 kg/m^2, and waist circumference (WC) 79.73±13.94 cm. Initial analysis showed significant differences in BMI, WC, fasting glucose, HOMA-IR, and androgens across phenotypes, while insulin, lipid indices, and the TyG index did not differ significantly. Stratification by the TyG median (7.9) revealed significant differences in all metabolic parameters except androgens, with insulin showing borderline significance ($P = 0.056$). Pairwise comparisons showed that the TyG was lower in phenotype D (7.92±0.37 mmol/l) than in A (8.16±0.51, $P = 0.027$) and B (8.19±0.62, $P = 0.030$), though these differences did not remain statistically significant after adjustment. In phenotypes A and B, TyG correlated positively with most metabolic parameters and negatively with HDL. Stratification based on the TyG median confirmed that individuals with higher TyG had significantly higher BMI, WC, impaired glucose homeostasis, and dyslipidemia. In phenotype D, TyG correlated only with triglycerides and HDL, with higher triglycerides in the high TyG group, whereas HDL levels were lower but did not reach statistical significance ($P = 0.051$). ROC curve analysis for TyG in relation to HOMA-IR cut-offs (2.5, 2.0, 1.5) showed AUC values of 0.617 (95% CI: 0.530-0.703), 0.641 (95% CI: 0.553-0.729), and 0.658 (95% CI: 0.552-0.764).
Conclusion
Our analysis confirmed that the TyG index correlates with anthropometric and metabolic parameters, showing phenotype-dependent differences. Larger cohort analyses are needed for the assessment of insulin sensitivity in PCOS phenotypes using this simple non-insulin index.

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P1040

JOINT1222

Morphometric and transcriptomic changes during early testicular development in pigs

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Both pigs and humans exhibit a triphasic pattern of Leydig cell development [1,2]. The second phase, termed "mini-puberty" in humans, is associated with penile growth, changes in body composition and cognitive development during the first six months of life [1]. In pigs, this phase begins around 2.5 weeks prenatally, peaks at 2.5 weeks after birth and ends seven weeks postnatally [2]. In contrast to humans, pigs have a functional gonadotropin-releasing hormone type II (GnRH-II)/GnRH-II receptor (GnRHR-II) system in the testes, the activation of which leads to luteinizing hormone (LH) independent testosterone secretion by Leydig cells [3]. This study aims to characterize the morphometric and transcriptomic changes in the porcine testes from 1 to 12 weeks of age to contribute to a better understanding of early testicular development and provide potential translational relevance. Testis samples were collected from pigs at 1, 3, 6 and 12 weeks of age ($n = 6$-10/group). The samples were fixed in Bouin's solution and prepared for histomorphometric analysis. In addition, a portion of each sample was snap-frozen in liquid nitrogen for subsequent qPCR analysis. Histomorphometric analysis revealed a marked decrease in Leydig cell surface area and a progressive increase in nucleoplasmic index in 6- and 12-week-old animals compared with animals aged 1 and 3 weeks. Distinct age-dependent expression patterns were established for androgen receptor (AR), estrogen receptor 2 (ESR2), follicle-stimulating hormone receptor (FSHR), GnRH-II, GnRHR-II, inhibin subunit alpha (INHA), steroidogenic acute regulatory protein (STAR) and betaine-homocysteine S-methyltransferase (BHMT). Expression levels of transcripts for steroidogenic pathway proteins, i.e., HSD3B1, increased with age, whereas the expression of STAR progressively decreased. Upregulation of FSHR, ESR2, GnRH-II and INHA was observed from week 6 and of GnRHR-II, AR and BHMT from week 12. Expression of the LH/choriogonadotropin receptor was comparable across groups. Observed morphometric changes are consistent with the three-phase developmental pattern of Leydig cells and are associated with a reduced requirement for steroidogenesis at the end of mini-puberty, as shown by the reduced expression of STAR. The expression data also suggests that the GnRH-II/GnRHR-II system is not activated in the porcine testis during mini-puberty. Taken together, these preliminary results emphasize the interplay between structural adaptations and transcriptome changes that control testicular maturation in pigs.
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P1041

JOINT1882

"Variable phenotypic expression of NR5A1 mutation in a family: sex development abnormalities and management challenges"

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Steroidogenic Factor 1 (*SF-1*/*NR5A1*) is essential for gonadal and adrenal development. Mutations in *NR5A1* are associated with differences in sex development (DSD), presenting a broad phenotypic spectrum from asymptomatic carriers to severe DSD. Despite extensive research, the factors influencing these varied clinical manifestations remain unclear. Oligogenic inheritance may contribute, with multiple genetic variants influencing the phenotype. This case highlights a family with a missense *NR5A1* mutation and marked phenotypic variability. Twin 2, from a dichorionic diamniotic pregnancy, presented with ambiguous genitalia, while Twin 1 had normal male genitalia. At birth, Twin 2 had Cilitorophallic enlargement (1 cm), a perineal urethral opening, posterior labioscrotal fusion, and bilateral labioscrotal gonads. The mother had an older phenotypically normal male child and a history of unilateral ovarian germ cell tumour. The maternal aunt, born with genital ambiguity, underwent feminizing genitoplasty and was diagnosed with 46XX ovo-testicular DSD

Twin 2 's Investigation Results.

QF-PCR	No evidence of SRY
Karyotype	46XX
(Day 30)	
LH	5.1 IU/l
FSH	9.3 IU/l
Testosterone	2.3 nmol/l
AMH	184.1 pmol/l (Reference female range < 25)
Synacthen test	Cortisol 871 nmol/l, ruling out adrenal insufficiency
DSD gene panel	Heterozygous *NR5A1* missense variant (NM_004959.5: c.274C>T, p.R92W) was identified in Twin 2, matching the maternal aunt's and later confirmed in the mother.
Examination Under Anaesthesia	Common channel leading to a normal urethra, bladder, and appropriately sized vagina, but no uterus. The gonads appeared abnormal, with a fallopian tube-like structure on the left and an epididymis on the right. Both were relocated to the pelvis, and bilateral inguinal hernia repair was performed.
Histology	Ovarian tissue with numerous primordial follicles

due to a heterozygous *NR5A1* variant. She underwent gonadectomy at age nine, with histology revealing intratubular neoplasia. A multidisciplinary team, in agreement with the parents, decided to raise the child as female. Gonapeptyl injections were given until nine months of age to prevent further virilisation. Genetic testing is ongoing for the patient's two male siblings and maternal grandparents. Future management will involve balancing the risks of malignancy and fertility preservation. The mother had both fertility and malignancy, while the maternal aunt showed malignancy at nine years. If the gonads are retained, a screening protocol will be necessary, along with monitoring for virilisation at puberty. Periodic adrenal function assessment will be required due to the risk of late-onset adrenal insufficiency. Additionally, splenic function will need to be monitored, with appropriate vaccinations, given *NR5A1*'s role in splenic development.

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P1042

JOINT2368

Evidence for bone marrow adipose tissue dysfunction in polycystic ovary syndrome (PCOS)

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There are three main functional fat depots in the body: subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT) and bone marrow adipose tissue (BMAT). In women with PCOS the SAT is dysfunctional with larger adipocytes and increased inflammation. This is recapitulated in the clinically realistic ovine model of PCOS using prenatal androgenisation. As BMAT is difficult to access and has not been studied in PCOS we aimed to use PCOS-like sheep to investigate the structure and function of BMAT. Pregnant Scottish Greyface sheep were treated with testosterone propionate (100 mg) or vehicle control twice weekly from day 62 to day 102 of a 147-day pregnancy. The female offspring exposed to increased prenatal androgens in utero develop the features of PCOS. BMAT was collected from adult offspring at 30 months of age (PCOS-like sheep $n = 4$; Control $n = 6$) and fixed for histological analysis and frozen for assessment of gene expression. The number of adipocytes per 3 mm^3 ($P = 0.78$) and size of the adipocytes ($P = 0.31$) in BMAT was no different in PCOS-like sheep when compared to contemporaneous controls. PCOS-like sheep had increased expression of the inflammatory markers *TNF* ($P = 0.0128$), *IL6* ($P = 0.0013$) and the macrophage marker *CD68* ($P = 0.0206$) in BMAT. We therefore performed an additional unbiased analysis of BMAT gene expression in PCOS-like sheep using RNAseq. There was differential expression of 604 genes when compared to controls (232 down and 373 up) in PCOS-like sheep BMAT. Ingenuity Pathway Analysis highlighted up-regulation of inflammatory pathways with significant increases in activation, recruitment and degranulation of leukocytes, synthesis and metabolism of reactive oxygen species, recruitment and migration of phagocytes and the immunogenic cell death signalling pathway. Interestingly the top two canonical pathways altered were related to bone health linked to osteoclast and chondrocyte function suggesting increased bone resorption and remodelling. These results suggest that in PCOS immune cells may be developing in a more inflammatory environment and they already show functional alterations. Additionally, there may be a local effect on bone health. This suggests a possible mechanistic link to the systemic adverse inflammatory environment in PCOS.

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P1043

JOINT752

PCOS in adolescent girls vs young women: similar distribution of body fat, different severity of PCOS phenotype

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In essence, polycystic ovary syndrome (PCOS) is an endocrine-metabolic mode driven by ectopic fat [1]. It is unknown whether similar degrees of total, truncal, abdominal, visceral and hepatic adiposity associate to similar PCOS phenotypes in adolescent girls vs young women. The baseline data of an international PCOS intervention study [2] (www.spiomet4health.eu; Horizon 2020 grant 899671) offered an unanticipated opportunity to answer this question. Indeed, adolescent girls with PCOS ($n = 129$; mean $\pm$ SD; 16 $\pm$ 2 yr) and young women with PCOS ($n = 183$; 22 $\pm$ 1 yr) in this study happened to have similar measures of body adiposity: BMI 27 $\pm$ 5 vs 27 $\pm$ 5 kg/m^2; total fat (by DXA) 29 $\pm$ 11 vs 28 $\pm$ 11 kg; truncal fat (by DXA) 14 $\pm$ 6 vs 13 $\pm$ 6 kg; non-truncal fat (by DXA) 15 $\pm$ 5 vs 15 $\pm$ 6 kg; abdominal thickness of subcutaneous fat (by MRI) 6 $\pm$ 2 vs 6 $\pm$ 2 cm; abdominal area of subcutaneous fat (by MRI) 218 $\pm$ 77 vs 219 $\pm$ 84 cm^2; visceral fat (by MRI) 48 $\pm$ 29 vs 52 $\pm$ 34 cm^2; and hepatic fat (by MRI-PDFF) 7 $\pm$ 5 vs 7 $\pm$ 2 %. However, the PCOS phenotype was more severe (all $P < 0.001$) in adolescent girls than in young women: hirsutism score (modified Ferriman-Gallwey) 13 $\pm$ 6 vs 10 $\pm$ 6; SHBG 32 $\pm$ 18 vs 41 $\pm$ 20 nmol/l; free androgen index 6.8 $\pm$ 4.6 vs 4.9 $\pm$ 3.0; HOMA-IR 3.3 $\pm$ 3.2 vs 2.3 $\pm$ 2.5; mean serum insulin during oGTT 437 $\pm$ 456 vs 253 $\pm$ 218 pmol/l; HDL-cholesterol 1.3 $\pm$ 0.3 vs 1.6 $\pm$ 0.4 mmol/l. In conclusion, the baseline data of an intervention study disclosed unexpectedly that a similar fat distribution associates with a more severe PCOS phenotype in adolescent girls than in young women. A differential secretion of growth hormone may be among the mechanisms underpinning the difference in PCOS phenotype [3,4]. In order to reverse PCOS, measures to reduce adiposity and/or to redistribute fat may thus be even more relevant for adolescent girls than for young women.

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P1044

JOINT1676

Health behaviours in women conceiving by medically assisted reproduction vs natural conception: a cross-sectional study of 23,334 nulliparous women

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Introduction

Women conceiving by fertility treatment have a planned pregnancy, easing adherence to preconception recommendations, which they are expected to be highly motivated to comply with. However, little is known about the actual adherence among these women. Thus, we investigate to what extent women conceiving by fertility treatment adhere to recommendations from the Danish Health Authority regarding preconception health behaviour and whether the adherence differs from that observed in women conceiving naturally. Secondly,

we elucidate differences in health behaviour in early pregnancy by mode of conception.
Material and methods
A cross-sectional study using clinical patient-reported questionnaire data from 23 443 nulliparous women collected in connection with their first-trimester nuchal translucency scan from 2012 to 2022 at Copenhagen University Hospital in Denmark. The women answered an online clinical questionnaire including information on whether they conceived by fertility treatment, which type of treatment, and their health behaviours before and in early pregnancy. This included alcohol consumption, smoking, exercise, and intake of dietary supplements. Differences in health behaviours by mode of conception were analysed using multiple logistic regression with adjustments of age and educational level.
Results
Overall, 91% of women responded to the questionnaire. Women who conceived by MAR (15%) had healthier preconception behaviours with significantly higher odds of taking folic acid supplements (aOR 11.04), smoking cessation due to planning of pregnancy (aOR 1.72), and avoiding smoking (aOR 4.67), passive smoking (aOR 2.02), and alcohol consumption (aOR 2.40) compared to women conceiving naturally. Despite these healthier behaviours, adherence among women conceiving by MAR was only 30.6% for alcohol avoidance and 42.7% for meeting the recommended hours of exercise per week. In early pregnancy, both groups generally exhibited healthy behaviours; however, women conceiving by MAR still had significantly healthier behaviours overall, except for exercise.
Conclusion
Women conceiving by MAR generally exhibited healthier preconception behaviours than women conceiving naturally, though they showed poor adherence to recommendations on avoiding alcohol and engaging in exercise. In early pregnancy, women conceiving by MAR also overall demonstrated healthier behaviours. Health professionals at fertility clinics may consider motivating women to engage in exercise and avoid alcohol.

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P1045

JOINT2354

Combining machine learning and metabolomics to identify the metabolic signatures of polycystic ovary syndrome patients according to body mass index

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Introduction
Polycystic ovary syndrome (PCOS) is frequently associated with metabolic disorders such as obesity and/or insulin resistance. A metabolic assessment is recommended by 2023 ESHRE PCOS guidelines in all patients, regardless of body mass index (BMI). However, in the literature, normal-weight PCOS patients are less explored and the increased risk of diabetes in this population is still in debates. The aim of this study was to identify the associated metabolic profile of normal-weight patients with PCOS.
Material and Methods
A retrospective study in the Pitié-Salpêtrière endocrinology department was conducted between January 2019 and December 2023. Clinical and biological data were collected during day hospital check-up. PCOS patients were classified into 3 BMI categories: 152 patients with a normal BMI (< 25 kg/m^2), 96 overweight patients (25-30 kg/m^2) and 149 obese patients (BMI ≥ 30 kg/m^2). All 76 control patients had a normal BMI. To identify metabolomic profile according to BMI, we used a combined mass spectrometry and machine learning approach. In addition to bioclinical parameters, we have also integrated blood steroidome (including 20 molecular species quantify thanks to mass spectrometry).
Results
HOMA-IR, to assess insulin resistance, was higher in the obese group than in the overweight and normal BMI groups ($P < 0.0001$) and HOMA-IR$>$ 2.5 was more frequent in obese PCOS patients. Lean PCOS patients presented a better metabolic profile with high HDLc, low LDLc and triglycerides, and normal liver function. In terms of hormonal assessment, due to a higher SHBG, lean patients have a lower bioavailable testosterone than obese PCOS patients ($P < 0.0001$). The LC-MS/MS circulating steroid profiles showed increase in delta5 steroids in normal-weight PCOS patients compared to obese PCOS women but there was no difference with control cohort. To identify a characteristic metabolomic signature, we used a combined approach including mass spectrometry data and machine learning modeling. We used this approach to characterize PCOS patients compared to control patients and to characterize PCOS patients according to their BMI. The resulting model showed a continuum between hormonal variables on the one hand and metabolic variables on the other hand. Interestingly, some obese patients were metabolically healthy and positioned on the hormonal side. In contrast, some lean patients had a more metabolic profile.
Conclusion
Metabolic profile of normal-weight PCOS patients is characterized by lower HOMA-IR, higher HDLc and bioavailable testosterone, and normal lipid and liver functions.

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P1046

JOINT528

Detection of piRNA-associated proteins as a diagnostic tool for spermatogenic arrest

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Introduction
Emerging evidence suggests that pathogenic variants in genes (like *MYBL*, *PIWIL1*, *TDRDs*) that are involved in the processing of PIWI-interacting RNAs (piRNAs) are a major genetic contributor to spermatogenic arrest. Studies suggest that the entire piRNA processing pathway is affected if one component of the piRNA biogenesis is missing.
Hypothesis
We hypothesize that the lack of single piRNA components may be indicative of a faulty piRNA biogenesis and cause spermatogenic impairment.
Methods
Testicular expression of piRNA-associated proteins were analyzed in 117 biopsies from 115 patients with impaired ($n = 87$) or complete ($n = 30$) spermatogenesis. Immunohistochemical (IHC) and *in situ* hybridization (ISH) stainings identified MYBL and PIWIL1 protein and transcript. Image segmentation was used for quantitative analysis. Statistical significance was determined using Mann-Whitney U and Fisher's exact tests.
Results
Biopsies from patients with complete spermatogenesis consistently expressed MYBL and PIWIL1 proteins in spermatocytes and round spermatids while 32% (37/117) of biopsies with impaired spermatogenesis showed absence of one or both of these proteins. Quantitative image analysis of a subset of the samples revealed a significantly reduced expression of MYBL and PIWIL1 proteins ($P<0.001$ and $P<0.001$, respectively) and transcripts ($P=0.002$ and $P<0.001$, respectively) in the biopsies with impaired spermatogenesis.
Conclusion
The observed lack of MYBL and PIWIL1 expression in 32% of biopsies with impaired spermatogenesis substantiates the critical role of piRNA-associated proteins for spermatogenesis. Whether the observed lack of PIWIL1 has an effect on the expression of piRNAs during spermatogenesis remains to be established.

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P1047

JOINT2960

Sexual health in women with type 1 diabetes – a qualitative study from the ReproDia study

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Background
Sexual health is a state of physical, emotional, mental, and social well-being related to sexuality, and it can be affected in women with type 1 diabetes (T1D). There is limited knowledge about how sexual health is perceived and experienced among women with T1D.
Objective
To explore thoughts and experiences related to sexual health among women with T1D.
Methods
Semi-structured individual interviews were conducted with women with T1D at a diabetes outpatient clinic in Norway. Data were analysed using thematic analysis.
Results
From June to November 2022, 24 women with T1D, aged 18–45 years, were contacted and invited to participate in the study, of which 17 accepted. Four main themes were identified: (1) Inadequate communication and information about sexual health; prompting reflections on the information healthcare providers should offer depending on the life stage. (2) The impact on women's relationships and intimacy; where decreased sexual desire, vaginal dryness, pain, as well as glycaemic variations and the intrusions from diabetes equipment were highlighted as significant factors. (3) The relationship between menstrual cycle and diabetes management; where varied experiences were reported regarding the regularity of menstruation and its impact on glycaemic variations, ranging from no influence on daily life to a marked impact. (4) Genitourinary infections; where different experiences and concerns were expressed. Hyperglycaemia was perceived as a risk factor, and the emotional burden of such infections was emphasized.
Conclusion
Women with T1D experience numerous challenges related to sexual health, indicating a need for improved follow-up from healthcare services. There was significant individual variation in experiences, underscoring the importance of empathetic communication and tailored information at relevant times throughout a woman's life stages.

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P1048

JOINT231

A novel variant in the NDNF gene in a 17-year old boy with hypogonadotropic hypogonadism and anosmia

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Introduction
Congenital hypogonadotropic hypogonadism (CHH), whether or not associated with anosmia (Kallmann syndrome), is a rare genetic disorder characterized by the absence of pubertal development and infertility, caused by GnRH deficiency. Recently, neuron-derived neurotrophic factor (NDNF) has been identified as a novel factor involved in GnRH neuron ontogeny. NDNF enhances the GnRH neuron migratory route during embryological development and plays a role in GnRH release in the median eminence, suggesting a possible role in GnRH neuron biology beyond embryonic development.
Clinical case
A 16-year-old boy was referred to endocrinology because of the absence of pubertal development and anosmia. Medical history revealed bilateral cryptorchidism, treated with orchidopexy at 12 years of age. Testicular volume was 1 ml bilaterally, with Tanner stage 3 for pubic hair. Morning serum testosterone, FSH and LH were undetectably low, whereas the other pituitary hormones were normal. Testicular ultrasound confirmed prepubertal volumes of 14x10x5 mm and 11x3x4 mm. MRI of the brain showed an absent olfactory bulb, and normal anatomy of the pituitary gland and stalk. Bone age was more than 2 years delayed. Family history revealed cryptorchidism and late puberty in his father, without fertility problems. The clinical diagnosis of Kallmann syndrome was made and pubertal induction with gonadotropins was started. Gene panel testing for hypogonadotropic hypogonadism revealed a heterozygous variant in the *NDNF* gene, NM_02457.4:c.509_513dup p.(Pro172Ilefs*13). This variant is predicted to cause a frameshift in the last exon, presumably escaping nonsense-mediated decay leading to a truncated protein missing both C-terminal fibronectin type III domains, crucial for its migratory function. No other relevant variants in known CHH genes were detected.
Discussion/Conclusion
We describe a novel variant in the *NDNF* gene in an adolescent with Kallmann syndrome, contributing to the evidence of Ndnf as a novel factor involved in GnRH neuron ontogeny. A previously published gene-based burden test in a cohort of 240 CHH patients revealed 4 other *NDNF* rare likely pathogenic variants in 4 patients with hypogonadotropic hypogonadism with anosmia (OMIM # 618841), with *in vitro* analysis showing a loss of function of these variants. Three of these probands' family members also carried the *NDNF* mutation and had partial and milder phenotypes, suggesting an autosomal-dominant inheritance with variable expression. Further research on the molecular role of *NDNF* on GnRH neuron migratory route and GnRH functioning is needed.

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P1049

JOINT3286

Testicular parenchyma inhomogeneity is a potential new marker for testicular dysfunction and subfertility in men born with hypospadias

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Introduction
Hypospadias is a common congenital urological condition associated with testicular dysfunction, such as reduced semen quality and subclinical hypogonadism. The severity of dysfunction varies, and is influenced by the degree of undervirilization and prenatal factors (e.g. being born small for gestational age). Despite these associations, testicular morphology—specifically parenchymal inhomogeneity and microcalcifications—remains understudied in men born with hypospadias. This study investigates testicular morphology in boys and men with hypospadias compared to controls using ultrasound. Specifically, we examine changes across puberty and their associations with clinical, prenatal, and lifestyle factors.
Methods
Cross-sectional case-control study: evaluation of testicular ultrasound studies of 244 boys/men born with hypospadias (Tanner 1: $n = 17$; Tanner 2-4: $n = 27$; Tanner 5: $n = 200$) and 51 controls (all Tanner 5) by three physicians (junior doctor, senior urologist and pediatric endocrinologist). Homogeneity and microcalcifications were scored on a 4-point and 3-point Likert scale, respectively. Associations were sought with clinical data (e.g. hormone assays, semen characteristics and physical exam) and maternal, dietary and substance factors (through a questionnaire).
Results
Substantial interobserver agreement was seen for microcalcifications ($\kappa = 0.735$, $P < 0.001$) and inhomogeneity ($\kappa = 0.647$, $P < 0.001$). Testicular inhomogeneity was more common in men born with hypospadias compared to controls ($P = 0.004$), also when divided in subgroups mild ($P = 0.006$), severe ($P < 0.001$), and complex hypospadias ($P < 0.001$). Descriptive analysis showed increasing abnormalities with puberty progression. Furthermore, associations were found between inhomogeneous testicular parenchyma and reduced semen quality, number of penile surgeries, shorter adult stretched penile length, being born small for gestational age and unhealthy lifestyle (i.e. smoking, drug use, high alcohol consumption and/or fast food intake). No difference in the prevalence of testicular microcalcifications was found between men born with hypospadias and controls ($P = 0.599$).
Discussion
More frequent testicular parenchymal inhomogeneity was found in men born with hypospadias and multiple associations were seen between testicular inhomogeneity and testicular and prenatal factors. We therefore hypothesize testicular inhomogeneity could serve as a relevant, non-invasive marker hinting towards possible impaired testicular function in men born with hypospadias. Screening may be recommended starting from late puberty as the first morphological changes are typically observed at this stage and could help determine which men need to be referred for endocrine or fertility work-up. Future research should explore long-term implications, particularly the link to sub- and infertility and potential risk to develop testicular germ cell malignancies.

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P1050

JOINT1811

The impact of organ specific autoimmunity on menopause onset in females with Graves' disease

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Introduction
Menopause is the permanent cessation of menstruation, as a result of inclining levels of ovarian hormones. Few studies demonstrate diminished ovarian reverse, fertility defects and menopause onset at a younger age, in female patients with autoimmune and inflammatory disorders. Aim of the study is to evaluate the potential effect of Graves' disease (GD) induced, organ-specific thyroid autoimmunity, on menopause onset.
Material and Methods
We recruited 140 menopausal women with GD, admitted in Autoimmune Endocrinopathies outpatient clinic, Department of Pathophysiology, Laikon General Hospital, between 2020-2023. The analyzed data were respectively collected from patients' medical record by a single investigator. We recorded demographic characteristics, comprehensive medical history, family medical history and smoking status. Medical history was focused on GD features. Moreover, we included past medical history related to reproductive and overall gynecologic health including age of menarche, mensuration irregularities, number of pregnancies, number of pregnancy loss and age of menopause onset. Patients underwent laboratory evaluation for autoantibodies (TPO-Abs, Tg-Abs, TSI, ANA, APCA) and biochemistry. The group of patients was compared to healthy control group of menopausal females (2:1).
Results
Mean patients age at the time of the study was 64.36 ± 8.56 years and mean BMI 27.13 ± 5.46 kg/m^2 . Age at menopause onset did not show statistically significant differences between the two groups, despite the fact that patients with GD had menopause onset at a slightly older age (49.42 ± 3.63 vs 48.88 ± 4.66 years, $P = 0.391$). Regarding menstrual irregularities during reproductive years, higher percentage of patients reported such disturbances compared to controls, without reaching statistical significance. Infertility issues were more commonly presented in patients with GD (32.1% vs 12,9%, $P = 0.006$). Pregnancy loss did not ascertain in 79.3% of patients with GD and in 82.9% of healthy controls ($P = 0.983$). Median menarche age was 12 years ($P = 0.20$) and it was the same for both groups.
Conclusion
From our study, a statistically significant impact of GD on menopause onset is not demonstrated, whereas we found significant difference in infertility issues between the two groups. Further prospective studies with higher number of participants should be conducted to establish potential correlation.

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P1052

JOINT3438

Luteinizing hormone/choriogonadotropin receptor (LHCGR)/G protein-coupled estrogen receptor (GPER) heteromers do not modulate reproductive signals in male and female gonadal cells

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The G protein-coupled estrogen receptor (GPER) forms heteromeric complexes with the gonadotropin receptors, reprogramming proliferative and anti-apoptotic signals. In the transfected HEK293 cell line, co-expression of GPER and luteinizing hormone (LH)/choriogonadotropin (hCG) receptor (LHCGR) specifically prevents LH- and hCG-dependent activation of Gq-mediated pathway and inhibits cell proliferation. In this study, we evaluated whether LHCGR/GPER heteromers modulate gonadotropin-dependent signals in gonadal cells endogenously expressing the two receptors. Expression level of genes coding G proteins (*GNAS, GNAQ*), and receptor (*LHCGR* and *GPER*) were quantified by digital droplet PCR, in native and GPER/Gper-coding cDNA transfected murine Leydig tumor cell line 1 (mLTC-1) and primary human granulosa cells (hGLCs). Receptor-receptor interactions were evaluated by proximity ligation assay (PLA). Cells were treated with LH/hCG, and signaling analysis was performed to evaluate intracellular calcium ion (Ca^{2+}), cAMP, inositol monophosphate (IP1) increase, and steroid production by bioimaging methods, and homogeneous time-resolved fluorescence (HTRF). Data was analyzed by Kruskal-Wallis test and Dunn's post-hoc test ($P < 0.05$; $n = 4$ to 6), as appropriate. Gene expression analysis confirmed that both cell lines have *LHCGR* and *GPER* transcripts, whose levels increased in transfected cells. PLA revealed the presence of LHCGR/GPER heteromers on mLTC-1 and hGLC cell surface. Receptor co-expression did not impair LH/hCG-dependent Gq-mediated pathway, as gonadotropins failed to activate it. In mLTC-1 and hGLC cells, Gs expression levels are higher than those of Gq, with LHCGR:G protein 10:1 e 0.5:1 ratio respectively, suggestive of preferential receptor occupancy by Gs, and only marginal Gq coupling. Therefore, LH/hCG-treatment activates intracellular cAMP response and steroid production but fails to trigger Ca^{2+}/IP1 activation in both gonadal cell types. IP1 response is restored in tranfected cells overexpressing Gq protein. In conclusion, endogenous GPER naturally interacts with LHCGR in Leydig and granulosa cells. However, GPER has no effect on Gq pathway, which is switched off by preferential LHCGR coupling to Gs.

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P1053

JOINT3386

A case of syndromic sexual dysgenesis caused by DAX1 gene duplication

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Background
The DAX1 (NR0B1) gene, located at Xp21.2, encodes a nuclear receptor critical for adrenal and reproductive system development. Its dosage sensitivity is documented, with duplications causing 46,XY disorder of sexual development (DSD) through testicular dysgenesis. This case report expands the phenotypic spectrum of Xp21 duplication syndrome and reinforces DAX1's role in sex determination pathways.
Clinical Case
A pediatric patient presented with syndromic features including hypertelorism, epicanthic folds, low-set ears, broad nasal bridge, and global developmental delay. Genital examination revealed ambiguous external genitalia (Prader stage II). Chromosomal microarray analysis identified two pathogenic copy number variations: a 37.2 Mb duplication at Xp22p21 (chrX:168,546-37,348,545) encompassing DAX1, and a 3.5 Mb duplication at Yp11.2 (chrY:24,985,261-28,458,663). Karyotype confirmation demonstrated 46,XY, dup(X)(p22p21). Endocrine evaluation showed elevated gonadotropins (FSH 18.7 IU/l, LH 12.3 IU/l) with low anti-Müllerian hormone (1.2 ng/mL), consistent with testicular insufficiency.
Conclusion
This case provides definitive evidence that DAX1 duplication alone suffices to cause 46,XY DSD, independent of Y chromosome anomalies. The identified Xp22p21 duplication (containing 63 OMIM genes including IL1RAPL1 and ARX) may explain the neurodevelopmental comorbidities. We propose that DAX1 copy number analysis should be integrated into first-tier genetic testing for 46,XY DSD, particularly in syndromic cases. These findings underscore the necessity of comprehensive genomic characterization to unravel complex genotype-phenotype correlations in sexual differentiation disorders.

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P1054

JOINT516

Follow-up of the pearl cycle app–evaluation: an integrated ovulation prediction kit (OPK) with urine test strips. fertility characteristics, number and course of pregnancies observed

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Fertility depends on the complex interaction of various factors. The most common causes include hormonal dysregulation or sperm abnormalities. The follow-up of the Pearl Cycle App study aimed to characterize fertility influencing factors (FIF), and the number and course of pregnancies observed. Women aged between 21 and 45, trying to conceive for up to 24 months and without hormone intake, were recruited in the gynaecological outpatient clinics of the Technical University Munich and the University of Ulm. After informed consent participants downloaded the app "Pearl Fertility" and received OPKs with lateral flow immunoassay test strips (LFIA) for LH, FSH, PdG and hCG for at home measurements. The LFIA colour change was analysed via camera detection and three algorithms calculated the ovulation date. Folliculometry was performed sonographically before and after the predicted day of ovulation. Participants were observed for up to three cycles and followed-up after one year. Three questionnaires assessed baseline characteristics, user experience, and later pregnancy outcomes and FIF. Out of 89 recruited women, 22,5% (20) and 11,2% (10) of their partners, had at least one FIF which became known before, during, or after participation. In 29,2% (26) of the couples at least one FIF was identified. In participants with hormonal dysregulation and/or irregular cycles, ovulation prediction was correct in 61,5% (16) of 26 cycles analysed. 15,7% (14) became pregnant after 1,3 (SD ± 0,5) cycles. Of these, 21,4% (3) had at least one FIF. 71,4% (10) of these pregnancies resulted in live births. 48/89 (53,9%) women responded to the follow-up. 50% (24) had become pregnant 11,1 (SD ± 8,3) months after participation. 14 (48,3%) of a total of 29 pregnancies post participation resulted in live births. 33,3% (8/24) were currently pregnant at the time of the follow-up. 37,5% (9/24) had used assisted reproduction technology and 8,33% (2/24) ovulation induction. The information on pregnancies and FIF is based on the patient surveys. Therefore, the true numbers might be even higher. The high proportion of couples with FIF and/or ART use after the study combined with the short participation period may explain why a pregnancy did not occur during participation or did not result in a birth. This could also reflect a selection bias as the app was likely used by women who had struggled to conceive. This information can also provide additional insights into the effectiveness of the ovulation prediction and highlights the need for medical evaluation of personalised approaches to fertility treatment.

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P1055

JOINT1243

Late bedtime was associated with increased androgen and reduced lean mass in women with polycystic ovary syndrome: a cross-sectional study

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Background
Despite limited evidence regarding the effect of bedtime on androgen and lean muscle mass, it is widely recognized as being associated with various metabolic diseases. The present study aimed to investigated the relationship between bedtime, androgen-associated traits, and dual-energy x-ray absorptiometry (DEXA)-based lean mass (LM) in polycystic ovary syndrome (PCOS).
Methods
This cross-sectional study recruited 899 reproductive-aged women with PCOS in the PCOS subspecialty clinic at Shanghai Tenth People's Hospital, and finally 636 women entered the study. Anthropometric, metabolic, sex and reproductive hormonal characteristics, and body fat and lean composition measured by DEXA were collected. The information on bedtime was adapted from the Pittsburgh Sleep Quality Index and bedtime was categorized into three aspects: early bedtime ($\leq$23:00), intermediate bedtime ($>$23:00 to 24:00), and late bedtime ($>$ 24:00) according to the time of falling asleep.
Results
There was 24.4% of participants fell asleep before 23:00, and 75.6% fell asleep after 23:00. After adjusting for age in covariance analysis, participants in both intermediate and late bedtime groups had fewer menstrual cycles and higher levels of anti-mullerian hormone (AMH) than those in the early bedtime group. Compared with early and intermediate bedtime, those with late bedtime had higher levels of total testosterone (TT) and androstenedione (AD). After controlling possible confounders, multiple liner regression analysis found that compared with early bedtime, late bedtime was independently associated with higher levels of TT and AD, meanwhile intermediate bedtime was independently associated with higher levels of AMH. Furthermore, late bedtime was independently correlated to reduced levels of muscle mass index LM/height^2 and appendicular muscle mass index appLM/height^2 compared with early bedtime.
Conclusion
This study provides novel insight that late bedtime (after 24:00) was independently related to elevated androgenic hormones and reduced LM in individuals with PCOS.

Keywords
polycystic ovary syndrome, sleep, bedtime, lean mass, androgen.
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P1056

JOINT1140

Impaired sperm quality in previous illicit users of anabolic androgenic steroids

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Background and Aims
Former use of anabolic androgenic steroids (AAS) may result in irreversible damage on testicular Leydig cell function. Impaired semen quality was reported in current AAS users but, the impact of long-term AAS usage is unclear. The primary aim of the current study was to assess semen quality in current and former AAS users compared with nonusers who had never used AAS.
Methods
Cross-sectional study including men involved in recreational training, grouped according to their AAS history. Medical records and AAS history were obtained during personal interviews. Each participant provided a semen sample to assess classical semen parameters. Impaired semen quality was defined as total sperm count below 39 million sperm, and oligospermia by a cutoff below 15 million sperm per milliliter semen, according to the World Health Organization 2021 guidelines.
Results
We included 46 former, 59 current AAS users, and 46 nonusers as controls. The mean (SD) age of all participants was 34.7 (8.5) years. The accumulated duration of AAS use, among current users was 153 weeks (114;207) (geometric mean (95% CI)), and among former users, 106 (77;145) weeks, $P = 0.092$. The elapsed duration since AAS cessation, was 1.3 (0.9;1.9) (geometric mean (95% CI) years in former users. A total sperm count $<$ 39 million was more prevalent among current and former users than in nonusers, 45 (76%) vs 13 (28%) vs 2 (4%), $P <$ 0.001. Furthermore, sperm concentration $<$15 million/ml was observed in 48 (81%) current vs 16 (35%) former users vs 5 (11%) nonusers, $P < 0.001$. Azoospermia was only present in current and former users (25 (42%) vs 2 (4%) vs 0 (0%), $P < 0.001$. The frequency of sperm immotility was increased among current 43 (23%) and former users 36 (20%) compared with nonusers, 26 (14%) (respectively $P < 0.001$, and $P = 0.005$) In a multivariable logistic regression model using men with previous use of AAS every doubling of duration since AAS cessation (log2) was associated with almost 50% reduction in the risk of total semen count below $<$ 39 million (odds ratio, 0.55, 95% CI, (0.33; 0.92), $P =$ 0.022) when adjusting for age and accumulated duration of AAS.
Conclusions
Anabolic androgenic steroids use is associated with impaired sperm count and motility among younger men with previous use more than one year after cessation. A potential improvement of sperm count over time following cessation was observed.

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P1057

JOINT3582

Establishing mouse ovarian ex vivo tissue culture

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Introduction
Infertility is an issue of increasing concern with an estimated 1 in 6 adults affected during their lifespan. This highlights the need for more comprehensive insight about the biological events that can affect the female fertility potential during a lifetime, and the importance of a more detailed understanding of ovarian physiology. Thus, this project aims to establish a foetal and a prepubertal mouse ovarian *ex vivo* culture model. These tissue culture models will be an essential tool to study the effects of selected manipulations on ovarian development, and early folliculogenesis.
Methods
Three *ex vivo* culture approaches were tested using ovaries from foetal and prepubertal mice including culture; on agarose gel fragments, in hanging drops, and on porous membranes. Ovaries were cultured for 48 hours, and 7 days. After the culture period, the three methods were evaluated, and overall tissue preservation was compared. Tissue morphology was evaluated using Periodic Acid-Schiff staining, while proliferation and apoptosis was investigated using BrdU incorporation and cleaved PARP staining, respectively. Subsequently, the established ovarian cultures will used to study effects of selected treatment given through the culture media. Analysis will include quantification of germ cells (Oct4-positive cells) and follicles (from PAS sections) and immunohistochemical stainings for cell lineage markers such as, granulosa cells (AMH, CYP19A1), and theca cells (CYP11A1, CYP17A1). +.
Results
The analysis of the three culture methods and culture lengths are currently ongoing. The optimal culture method will be determined based on preservation of morphology, minimal apoptosis, and sustained cell proliferation.
Conclusion
Preliminary findings suggest that *ex vivo* culture of foetal and prepubertal mouse ovarian tissue is feasible with the tested culture approaches. Ongoing analysis will identify the most appropriate culture approach for future studies examining the effects of manipulating various signaling pathways involved in the regulation of ovarian development and function.

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P1058

JOINT3323

The impact of estrogens on gut microbiome in post-menopause and premature ovarian insufficiency - a meta-analysis and systematic review

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Objectives
There has been a rising interest in the relationship between gut microbiome (GM) changes and women's reproductive health, with estrobolome taking a central role in the interplay. This meta-analysis aimed to systematically review and combine existing data to assess GM alterations in postmenopausal and women with premature ovarian insufficiency (POI) - hypoestrogenic women when compared to premenopausal (euestrogenic) women.
Design and methods
Medline, EMBASE and Cochrane Library were searched for relevant articles and selected according to the strict inclusion criteria. Studies comparing euestrogenic (premenopausal) to hypoestrogenic (POI or postmenopausal) women were considered. The inclusion criteria were: no use of hormonal replacement therapy (HRT) or hormonal contraceptives, no active infections, no active intestinal diseases and no actual history of cancer of any origin. Seven of 15 papers assessed for eligibility were included in the analysis, incorporating data from 1730 participants. The risk of bias was assessed using the Newcastle-Ottawa scale. This study was registered on the International Prospective Register of Systematic Reviews (PROSPERO), CRD42024497630.
Results
No statistically significant differences were observed in α–diversity ($P = 0.990$), Bacteroidetes (B) ($P = 0.440$), or Firmicutes (F) abundance ($P = 0.110$) between hypoestrogenic and euestrogenic groups. Similarly, the B/F ratio ($P = 0.400$) showed no significant difference between the groups. However, the results were highly heterogeneous in the current literature, with I^2 scores ranging from 68% to 99%.
Conclusion
This meta-analysis showed no differences in GM composition between postmenopausal and premenopausal women, nor between women with POI and premenopausal women. These findings should be interpreted with caution due to the high heterogeneity of the populations studied. Future research prioritizing the exclusion of already known GM disruptors is critical for women with POI and postmenopausal women. This meta-analysis challenges the assumed link between estrogen levels and GM alterations while stressing the need for rigorous, high-quality research to elucidate GM characteristics in estrogen-dependent states.

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P1059

JOINT2436

Health implications of self-reported PCOS in a developing country: the brazilian longitudinal study of adult health

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Context
The diagnosis of polycystic ovary syndrome (PCOS) remains challenging due to its heterogeneous clinical presentation and the absence of a single diagnostic marker. While clinical diagnosis integrates clinical, laboratory, and imaging assessments, population studies often depend on self-reported PCOS (srPCOS), leading to inconsistent findings regarding associated health risks. This study evaluates the prevalence of key clinical symptoms of PCOS, specifically oligomenorrhea (OA) and hirsutism, among women with self-reported PCOS (srPCOS) in a developing country and investigates their reproductive and cardiometabolic outcomes.
Methods
The ELSA-Brazil study integrates cross-sectional and prospective cohort analyses of 15,105 civil servants across Brazil. Participants underwent four longitudinal evaluations, including interviews, anthropometric assessments, and biochemical tests. This analysis included 7,623 women aged 35–74 years who participated in the first two evaluations (2008–2014). srPCOS was defined as a self-reported medical diagnosis based on clinical criteria, ultrasound findings, or unspecified parameters. Clinical symptoms assessed included OA (cycles >35 days) and hirsutism (self-administered questionnaire based on Ferriman–Gallwey score ≥ 5). Metabolic outcomes included obesity, central obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, metabolic syndrome, and hepatic steatosis on ultrasound. Reproductive outcomes included pre-eclampsia, gestational diabetes, and infertility/subfertility, while cardiovascular outcomes encompassed self-reported myocardial infarction, angina, myocardial revascularization, stroke, and heart failure. Statistical analyses were adjusted for age, race, education, smoking, alcohol intake, and physical activity, with significance set at $P < 0.05$.
Results
The prevalence of srPCOS was 11.7% ($n = 888$), with 12.3% reporting clinical diagnosis, 78% ultrasound-based diagnosis, 4.1% both, and 5.5% unspecified. Among women with srPCOS, 3.5% reported OA, and 21.9% reported hirsutism. The proportion of women with both OA and hirsutism was very low ($\leq 1\%$), while 22.5% reported either OA or hirsutism. srPCOS was associated with higher odds of obesity (OR 1.2), T2DM (OR 1.4), metabolic syndrome (OR 1.2), infertility/subfertility (OR 2.1), angina (OR 1.6), and heart failure (OR 2.3) (all $P < 0.05$).
Conclusions
In this large Brazilian cohort, most women with srPCOS reported an ultrasound-based diagnosis alone, and the prevalence of both hirsutism and OA was low—findings that differ from previous studies. srPCOS was linked to certain cardiometabolic and reproductive outcomes but not to others traditionally

associated with PCOS. This discrepancy likely reflects diagnostic heterogeneity in self-reported cases, emphasizing the need for improved classification methods in epidemiological studies.

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P1060

JOINT2309

Clinical and genetic overlap between congenital hypogonadotropic hypogonadism and cleft lip and palate

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Objective

Congenital hypogonadotropic hypogonadism (CHH) is a rare endocrine disorder characterized by absent or incomplete puberty due to deficient gonadotropin-releasing hormone (GnRH) function. A subset of affected individuals present with additional developmental anomalies, including cleft lip and palate (CLP). This study explores the clinical and genetic overlap between CHH and CLP.

Methods

A total of 336 CHH probands were evaluated for CLP. High-throughput sequencing was performed, and variant analysis focused on known CHH and CLP genes.

Results

Twenty-one patients (6%) had CLP. Genetic analysis identified pathogenic (P) or likely pathogenic (LP) variants in genes associated with both conditions (e.g. *FGFR1*, *CHD7*). Additionally, 17% of CHH probands without CLP carried deleterious variants in CLP genes (e.g. *DVL3*, *PLCB4, NIPBL* and *EDNRA*). Further, digenic inheritance involving genes from both conditions was observed in 4 cases. *FGFR1* was found in digenicity with 3 other genes in 3 patients (e.g. TP63, TGFBR2 and INTS1) and one case involved *PNPLA6* and *PIEZO2*.

Conclusion

These findings support a phenotypic continuum between CHH and CLP with genetic overlap, reinforcing the role of shared developmental pathways. Research into overlapping syndromes may improve diagnostic accuracy and personalized care for affected individuals.

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P1061

JOINT1084

Opposite degrees of virilisation in two individuals with 46,XY DSD and variants in NR5A1/SF1

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In 46,XY DSD with *NR5A1*/SF1 variants, genotype-phenotype correlations have failed to be found. SF1 is a nuclear receptor regulates early testis differentiation and the expression of steroidogenic enzymes, the androgen receptor (AR) and AMH. Variants affecting SF1 would be expected to result in gonadal dysgenesis and/or specific defects in androgen synthesis or action and/or in AMH expression, leading to various degrees of undervirilisation. This report describes two cases with 46,XY DSD and variants in *NR5A1* and opposite phenotypes, with hormonal and anatomic features that challenge the hypotheses on the potential pathogenic mechanisms. Case 1, assigned male at birth, was referred at 2 years of age, the phallus was 2.5-cm long, with penoscrotal hypospadias, partial labioscrotal fusion and labioscrotal gonads (External Genital Score-EGS: 7/12). Serum hormone levels were: FSH 5 mIU/mL (ref: 0.3-1.7), AMH 338 pmol/l (300-1800), LH 0.8 mIU/mL (0.1-0.3). At 6 years, testosterone post-hCG was 150 ng/dl. Altogether, these results indicated a mild primary hypogonadism. Müllerian remnants were absent in imaging studies. Gonadal histology, showing abnormally branching seminiferous tubules with typical Sertoli and premeiotic germ cells and a normal albuginea, was interpreted as mild testicular dysgenesis. Genetic analysis by NGS identified a heterozygous, missense, likely pathogenic variant NM_004959.5:c.259C>T, NP_004950.2:p.(Arg87Cys) in exon 4, corresponding to the DNA-binding domain (DBD), of *NR5A1*. Case 2, assigned female, was referred at 11 years of age for clitoromegaly. The phallus length was 3.5 cm, completely separated labia majora, a single urogenital opening and nonpalpable gonads (EGS 3/12). Hormone levels were: FSH 23 mIU/mL (ref for 46,XY: 1.3-6.5), AMH 10 pmol/l (40-400), LH 10 mIU/mL (0.7-5.2), testosterone 272 ng/dl (40-550), indicating mild primary hypogonadism. Surgical exploration showed the existence of abdominal gonads and absence of Müllerian remnants. Gonadal histology, showing normal albuginea, seminiferous tubules with typical Sertoli cells, absence of germ cells and thickened basement membrane, and interstitial tissue with typical Leydig cells, was interpreted as typical testicular tissue with changes associated with cryptorchid position. NGS identified a heterozygous, missense, likely pathogenic variant NM_004959.5:c.1210T>A, NP_004950.2:p.(Tyr404Asn) in exon 7 corresponding to the ligand-binding domain (LBD) of *NR5A1*. In conclusion, these two cases with very mildly affected testicular function showed normal Müllerian duct regression, as expected, but completely opposite androgen activity. These observations advocate against an effect of the *NR5A1* variants on testis differentiation and AMH expression, with potentially different effects on testosterone production and/or AR activity, and highlight the need for further functional explorations.

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P1062

JOINT1226

Reevaluating reference intervals for androstenedione in reproductive-aged woman

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Introduction

Reference intervals (RIs) for androstenedione should be specific to the population and immunoassay method. Generally, laboratories are responsible for verifying RIs established by an external source (e.g. a manufacturer) or determining their own. Initially, the laboratory adopted a manufacturer-defined RI for reproductive-aged women calculated by the direct method. As we noted many results above the upper reference limit, we needed to implement more suitable RIs for our population. We opted for an indirect approach using routine laboratory data stored in the laboratory information system. This study aims to compare (i) manufacturer-defined and calculated indirect RI and (ii) calculated indirect RIs from one and five years of data.

Methods

Manufacturer-defined 90%RI for reproductive-aged women was 1.71-4.58 nmol/l measured by Roche electrochemiluminescent immunoassay. All unique visits from women aged 20 to 45, with androstenedione, testosterone, sex hormone binding globulin (SHBG), and follicle-stimulating hormone (FSH) results, were extracted from the database. All patients with testosterone, SHBG and FSH outside the RI (0.29-1,67 nmol/l, 32-128 nmol/l, < 25.8 IU/l, respectively) were excluded. After the data-clearing step: (i) the initial data set included 520 subjects from one year of data, which is considered a small sample size for an indirect approach, and (ii) the subsequent data set included 2664 subjects from 5 years of data. Outliers were tested for each group separately and subsequently eliminated. RIs were calculated for the total age group (20 – 45 years) and subgroups (20-30 and 30-45 years) with the parametric method after Box-Cox transformation.

Results

For the first data set, the 95%RI in the total age group (20-45 years) was 2.48-8.89 nmol/l with a median of 5.13 nmol/l. The age-stratified 95%RIs were 3.02-9.43 nmol/l (20-30 years) and 2.23-7.75 nmol/l (30-45 years). The number of subjects was 518, 267, and 250, respectively. For the second data set, the 95%RI for the total age group (20-45 years) was 2,13-8,74 nmol/l with a median of 4.73 nmol/l.

The age-stratified 95%RIs were 2.81-9.25 nmol/l (20-30 years) and 1.88-7.96 nmol/l (30-45 years). The number of subjects was 2640, 1524, and 1391, respectively.
Conclusion
A larger dataset drawn from a broader data range showed RIs comparable to those calculated initially from a smaller sample size. This study confirms significant differences between calculated and manufacturer-reported RIs. Both calculated medians exceeded the manufacturer-declared upper reference limit, indicating that more than half of our subjects would have shown elevated androstenedione concentrations had the manufacturer-defined RI been applied.

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P1063

JOINT3391

Follicular fluid from women with polycystic ovary syndrome affects negatively the progressive motility of capacitating human spermatozoa

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Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by oligo-ovulation, clinical or biochemical hyperandrogenemia and polycystic ovaries, which affect reproductive function. Besides anovulation, there are several other hormone and metabolic factors that can have a negative impact in fertility outcomes of women with PCOS. Conception requires ovulation of a mature oocyte and the presence of mature spermatozoa. During ovulation, the oocyte is released into the oviduct along with follicular fluid (FF) that modulates its fluid composition, while within the oviduct spermatozoa undergo capacitation that is required for fertilization. The FF hormone and metabolic profile of women with PCOS is known to depict distinctive molecular fingerprints. However, whether the FF profile associated with PCOS affects spermatozoa capacitation is unknown, which this study aimed to disclose. For this purpose, spermatozoa were isolated from seminal fluid of men with normozoospermia ($n = 12$) and incubated with FF collected from women undergoing *in vitro* fertilization (IVF) treatments. FF was harvested from age-matched women with PCOS and normal weight (BMI $< 25 kg/m^2$; PCOS; $n = 6$), women with PCOS and obesity (BMI > 30 kg/m^2; PCOS + Ob; $n = 6$) and normo-ovulatory women with normal weight (BMI $<$ $25 kg/m^2$, CTRL; $n = 6$) submitted to IVF treatments due to tubal and/or male infertility factors. FF of each group was pooled before incubation with spermatozoa. Spermatozoa isolated from seminal fluid were incubated in capacitating medium (BWW) at 37ºC. After the first 2h of incubation, spermatozoa were treated with 20% pooled FF from each group (CTRL, PCOS, PCOS + Ob) for an additional 1h. Vitality and motility (total and progressive) were assessed hourly. While the FF did not affect vitality at all tested conditions, the progressive motility was significantly increased after incubation with FF from CTRL as compared to the pre-treatment conditions ($48.76 \pm 12.74\%$ vs $38.69 \pm 17.33\%$, $P = 0.0251$), which was not observed after incubation with FF from PCOS ($36.57 \pm 16.81\%$, $P = 0.8895$) nor PCOS + Ob ($35.69 \pm 16.17\%$, $P = 0.6560$). Moreover, progressive motility was higher after treatment with FF from the CTRL group as compared to the PCOS ($P = 0.0029$) and PCOS + Ob group ($P = 0.0009$). Overall, our results suggest that the FF from women with PCOS negatively impacts spermatozoa capacitation. While further studies are required to identify the molecular mechanisms, our study identified a potentially novel mechanism through which PCOS negatively impacts on fertility.

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P1064

JOINT3773

Perfluorooctanoic acid (PFOA) and male reproductive health: redox status imbalance in Wistar rat testes

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Per- and polyfluoroalkyl substances (PFAS) include several thousand compounds with a carbon chain and charged functional groups such as sulfonate or carboxylate. They are present in the environment mainly due to their widespread use and applicability in a large number of industrial sectors and consumer products. Due to their harmful effects on human health, the production and use of many compounds from this group have been banned, but due to their high persistence in the environment, these compounds are still present and represent a global problem. Previous studies have shown the harmful effects of these chemicals on the immune, metabolic, endocrine and reproductive systems. Among the long-chain PFAS, perfluorooctanoic acid (PFOA) is certainly one of the most important representatives of this group of compounds beingn abundant in the serum of the human population. The aim of this work was to examine the influence of PFOA on the parameters of oxidative stress and antioxidant protection in testicular tissue of Wistar rats. Groups M1 and m^2 were treated with doses that correspond to the lower (0.015 mg/kg b.w./day) and higher levels of exposure (0.15 mg/kg b.w./day) of the general population, respectively. Group M3 was treated with a dose that can be considered safe according to the literature (0.625 mg/kg b.w./day). PFOA solutions were prepared in a 0.5% solution of Tween-20 in deionized water. The experiment also included a control group that received a 0.5% solution of Tween-20 in deionized water. There were 6 animals in each group. After 28 days of exposure, the animals were sacrificed, testes tissue samples were collected, and IMA, MDA, SH groups, GSH, and SOD were determined by the spectrophotometric method. A statistically significant increase in MDA was observed in the m^2 group. Of the examined parameters of antioxidant protection, statistically significant decrease in the level of GSH compared to the control group was observed only in m^2 group. Probably, the decrease in GSH contributed to the increase in MDA in the m^2 group, as weakened antioxidant defense allows for greater lipid damage in cell membranes. The levels of SH groups and SOD were not significantly changed compared to the control. It has been shown that exposure to PFOA at doses that may reflect exposure in the general population can cause disturbances in the oxidative status of the testes, which can disrupt key hormonal pathways, leading to reproductive dysfunction and broader endocrine imbalances.

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P1065

JOINT3602

What matters most? gender diverse individuals' perspective in gender-affirming hormone therapy – the TRANSFORM study

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Background
Gender-affirming hormone therapy (GAHT) is guided by personalized patient objectives/goals, lab-based clinical monitoring, and safety considerations. Guidelines incorporate laboratory-based monitoring and safety data but encounter challenges when integrating patient goals into research, as patient goals are non-standardized and subjective. Key patient goals should be identified, integrated into clinical trials, and should be prioritized in endpoints of research; this could increase the relevance of research findings for clinical practice. This study aims to address this gap by exploring the personal goals and needs of transgender and gender diverse individuals regarding gender affirming hormone therapy, emphasizing the inclusion of gender diverse individuals' perspectives, which remain largely understudied.
Method
Following comprehensive literature research, we developed an anonymous, cross-sectional web-based online survey in collaboration with professionals and community representatives. Our target population was transgender and gender diverse individuals above age 16 who were currently undergoing, planned to start, or stopped GAHT. In addition to sociodemographic questions, participants rated predefined goals (physical changes, quality of life, sexuality, reduced gender dysphoria, safety) on a scale from 1 to 10 and then ranked them by priority (most

important, 2nd most important, etc.). If these goals didn't apply, they could specify a personal goal.
Result
Between May and September 2024, 738 individuals participated in the survey (407 transmasculine, 304 transfeminine, and 27 other gender identities). The median age was 25 [21-31] for transmasculine and 29 [25-39] for transfeminine participants. A total of 229 (56.3%) transmasculine and 106 (34.9%) transfeminine individuals identified as non-binary. Regarding hormone therapy, 75.4% of transmasculine and 86.8% of transfeminine individuals were currently receiving treatment. The most frequently reported primary goal of gender-affirming hormone therapy (GAHT) varied by gender identity. While **physical changes** were prioritized by binary transgender and gender diverse participants, non-binary transgender and gender diverse participants had more diverse goals, including **quality of life and reducing gender dysphoria**. Prioritization of treatment outcomes also reflected this variation, with sexuality and safety ranked lower across all groups.
Conclusion
Our findings help caretakers by guiding conversation with transgender and gender diverse individuals in terms of GAHT and informing future research priorities. Further, therapy goals differ significantly between binary and non-binary transgender and gender diverse individuals. Considering these diverse needs, especially those of non-binary individuals, can enhance gender-affirming care.

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P1066

JOINT2623

Hair mercury levels in children with central precocious puberty and healthy individuals from two distinct geographic regions of Brazil

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Background
The relationship between central precocious puberty (CPP) and endocrine disrupting chemical (EDCs) has been rarely demonstrated in children from different parts of the world. Longitudinal studies showed that mercury, a heavy metal considered an EDC, may increase the risk of CPP in American girls (Boston region). In Brazil, there are regions with high mercury environmental exposure, such as North region (Amazonian region) and a which may increase the risk of CPP.
Aim
To compare the hair mercury levels in children with CPP and control groups from two distinct geographic regions of Brazil (North and Southeast) with distinct levels of mercury environmental exposure.
Patients and Methods
This is a cross-sectional cohort study in which 127 children were evaluated: 71 from the North region (47 cases with CPP and 24 controls) and 56 from the Southeast region (34 cases with CPP and 22 controls). Sample collection followed a pre-established protocol with a small fraction of hair strands (about 20 strands) taken from the occipital region (1 to 2 cm away from the scalp). Hair mercury levels were analyzed using cold vapor atomic absorption spectrometry (CV-AASa) at the Carlos Chagas Foundation. The quantification limit of the method was 0.006 mg/g, and the reference values were 2-6 mg/g of hair mercury. Data were presented as the median (interquartile range), group comparisons were performed using the Mann-Whitney test in Stata program, and statistical significance was set at $p < 0.05$.
Results
In North CPP and control groups, the median hair mercury levels were 0.39 mg/g (0.06-1.72 mg/g) and 0.42 mg/g (0.08-1.6 mg/g), respectively. There was no statistically significant difference between these two groups. In Southeast CPP and control groups, the median hair mercury levels were 0.07 mg/g (0.01-0.77 mg/g) and 0.25 mg/g (0.17-0.45 mg/g), respectively. The comparison between these two groups showed a statistically significant difference ($P < 0.05$). Of note, the North CPP and control groups had higher median hair mercury levels compared to the South CPP and control groups ($p < 0.05$).
Conclusion
The higher hair mercury levels observed in both CPP and control groups from the North region confirmed an increased environmental mercury exposure in this part of Brazil. However, we could not identify an association between mercury exposure and CPP in this cohort.

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P1067

JOINT3366

Establishment of a foetal and prepubertal testis ex vivo mouse model

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Introduction
Previous research has demonstrated that inhibition of RANKL signalling with the monoclonal antibody denosumab results in increased sperm count and testis weight in a humanized mouse model. Additionally, when culturing adult testis from the humanized RANKL mouse, inhibition of RANKL resulted in an increase in germ cell proliferation. Based on these effects we hypothesized that RANKL signalling may also play a role in prepubertal and foetal testis. Therefore, this project aims to establish an *ex vivo* culture model for prepubertal and foetal mouse testis tissue to examine the involvement of RANKL signalling in testicular development and in the onset of spermatogenesis.
Materials and Methods
Three different *ex vivo* culture approaches were tested using prepubertal and foetal mouse testis tissue, namely hanging drop, porous membranes and agarose gel fragments. The prepubertal testis tissue was cultured for 48 hours, 4 days and 1 week. Foetal testis tissue was cultured for 48 hours or 1 week. After the culture period, the tissue was fixed, and paraffin embedded. Hematoxylin and eosin (H&E) staining was performed to evaluate tissue morphology, and immunohistochemical stainings and analyses was subsequently conducted to assess cell proliferation (BrdU incorporation) and apoptosis (cleaved PARP).
Results
Analysis of the three culture methods and culture lengths are currently ongoing. The optimal culture method will be determined based on preservation of tissue morphology, sustained cell proliferation, and minimal apoptosis.
Discussion
Preliminary results show that *ex vivo* culture of both prepubertal and foetal mouse testis tissue is feasible with the tested approaches. Ongoing analysis will identify the most effective culture method. The establishment of *ex vivo* models for both developmental stages will provide a crucial framework to investigate the role of RANKL signalling in testicular development.

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P1068

JOINT113

Neurocognitive function in males with 46,XX testicular disorder of sex development

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Background
46,XX testicular disorder of sex development (46,XX T-DSD) is a rare condition, in which individuals with a typical female chromosome pattern (46,XX) present with a male phenotype. Although previously considered to have minimal influence on neurocognitive function, recent research indicates an association with neurocognitive challenges, including lower educational attainment.
Objective
The aim of this study was to assess neurocognitive function in males with 46,XX T-DSD compared to 46,XY male controls, utilizing the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV). Cases and controls were matched on educational level.
Methods
A total of 47 participants were included in the study, comprising 25 males with 46,XX T-DSD and 22 46,XY male controls. All participants completed the

WAIS-IV. Based on subtest scores, we calculated Full-Scale IQ and the four index scores: Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index, and Processing Speed Index. T-tests or Wilcoxon rank-sum tests were used to compare Full-Scale IQ, index scores, and subtest scores, depending on data normality.
Results
Males with 46,XX T-DSD demonstrated significantly lower performance on the Working Memory Index (93.3 $\pm$ 15.7 vs. 104.3 $\pm$ 14.6, $P = 0.017$) compared to controls, with significantly lower scores on two out of three subtests. A trend towards lower performance was also observed in the Verbal Comprehension Index (91.6 $\pm$ 16.7 vs. 98.9 $\pm$ 11.4, $P = 0.092$), with significantly lower scores on two out of three subtests. Similarly, a trend towards lower Full-Scale IQ was observed (93.8 $\pm$15.6 vs. 100.7 $\pm$ 10.3, $P = 0.086$). Among males with 46,XX T-DSD, 56% scored in the low average range or below on the Full-Scale IQ, compared to only 13.6% in the control group. Additionally, two males in the 46,XX T-DSD group fell within the extremely low range, whereas none in the control group did.
Conclusion
These results indicate that males with 46,XX T-DSD exhibit certain neurocognitive challenges compared to 46,XY males. Significantly lower scores were found in the Working Memory Index and on two of three subtests in the Verbal Comprehension Index. In addition, a trend towards lower Full-Scale IQ suggests potential global cognitive weaknesses, warranting further investigation. These results emphasize the importance of early identification of neurocognitive challenges and the development of tailored interventions to support both educational and functional outcomes in this population. Future studies should focus on identifying strategies to minimize diagnostic delay, enabling timely intervention.

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P1069

JOINT213

Polycystic ovary syndrome in adolescent females with type 1 diabetes: a gonadotropins, leptin, insulin interplay

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Background
Menstrual irregularities and polycystic ovary syndrome (PCOs) are recognized morbidities among women with type 1 diabetes mellitus (T1DM) representing significant physical and psychological burden. Identifying the risk determinants of these morbidities and providing therapeutic interventions for them is of utmost importance.
Objectives
assess the frequency of PCOs among adolescent females with T1DM and correlate it with serum leptin, abdominal adiposity, insulin resistance, glycemic and lipid metrics.
Methods
Hundred-seventy five adolescent females with T1DM were assessed for diabetes duration, insulin therapy, menstrual regularity, manifestations of insulin resistance, hirsutism, anthropometric measures, systolic and diastolic blood pressure percentiles. Serum leptin, glycated-hemoglobin (HbA1c), fasting blood glucose and lipids, basal and stimulated follicle stimulating hormone (FSH) and luteinizing hormone (LH) were measured with calculation of the LH/FSH ratio and estimated glucose disposal rate (eGDR). Trans-abdominal pelvic ultrasound was done with measurement of the right and left ovarian size and endometrial thickness. Rotterdam criteria were adopted to diagnose PCOs.
Results
Sixty four adolescent females with T1DM had PCOs (36.6%). Adolescent females with T1DM having PCOs had significantly higher diabetes duration, total daily insulin dose, abdominal adiposity (waist/hip ratio z score), insulin resistance, serum leptin, LH/ FSH ratio and low density lipoproteins (LDL) than those without ($P < 0.05$). Multivariate-logistic regression analysis showed that diabetes duration (p-value = 0.030), waist/hip ratio (p-value = 0.030), LDL (p-value = 0.034), eGDR ($P = 0.008$), serum leptin (p-value = 0.009), and right ovarian volume ($P = 0.008$) were the most significant independent factors associated with PCOs among this vulnerable cohort.
Conclusion
PCOs is a prevalent morbidity among adolescent females with T1DM being associated with abdominal adiposity, insulin resistance, and hyperleptinemia.
Keywords
Adolescent females; Type 1 diabetes; Polycystic ovary; Leptin, Glycemic control.
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P1070

JOINT3427

Characterisation and evaluation of models of care for polycystic ovary syndrome (PCOS): a multinational study on clinical features, screening practices, and treatment outcomes

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Introduction
Recent research recognises Polycystic Ovary Syndrome (PCOS) as a multisystem condition that impacts several systems, including reproductive, dermatologic, metabolic, cardiovascular, and psychological health. Given the complexity of PCOS, a structured Model of Care (MOC) is crucial to reduce care variability. An evidence-based MOC should integrate clear referral pathways to tertiary care and align with international guidelines. The 2018 and 2023 international PCOS guidelines emphasise structured care models, yet a recent review indicated a lack of comprehensive data on implementing such models. This study aims to evaluate the characteristics of existing MOCs for PCOS care across multiple countries, assess their alignment with international guidelines, and analyse the outcomes of treatments.
>Materials and Methods
This multi-country study, conducted from May 2023 to March 2024, involved seven clinics from the United Kingdom, Turkey, Greece, India and Georgia. Clinics were invited to share their MOCs and first consultation management protocols for PCOS. Data were collected from patients seen between January 1, 2020, and December 31, 2023. The data included demographic information, clinical assessments (e.g., hirsutism, acne, metabolic screening), and biochemical tests (e.g., glucose, cholesterol, hormonal profiles). Adherence to the 2023 PCOS guidelines, including lifestyle advice and long-term risk education, was also evaluated. An online questionnaire was used to collect detailed MOC information. Data were analysed using the SPSS software version 29.0.1.1. Continuous data were assessed for normality using the Shapiro-Wilk test combined with graphical methods. Non-normally distributed data were presented as medians with interquartile ranges (IQR), while categorical data were expressed as absolute frequencies and percentages. All tests were performed at a 0.05 significance level.
Results
The study included 1,321 patients with a median age of 27 years (IQR 24-32). The most common clinical features at presentation were hirsutism (71.6%) and acne (28.7%). Screening for dermatology (86.9%), cardiometabolic health (80.9%), and reproductive health (75%) was commonly performed, but emotional well-being (37.1%) and long-term risk education (34.2%) were less frequently addressed. Biochemical testing varied widely, with hormonal (e.g., testosterone, FSH, LH) and metabolic parameters (e.g., glucose, HbA1c, lipid profile) being assessed in most cases. Significant differences were observed across countries in the types of parameters assessed and the proportion of patients diagnosed according to guidelines (overall $P < 0.001$).
Conclusion
This study highlights substantial variation in implementing PCOS care models across different countries, particularly in emotional well-being and long-term risk education. To improve patient outcomes globally, care practices must be standardised to align with international guidelines.

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P1071

JOINT24

Association of insulin resistance surrogate indices and erectile dysfunction: a systematic review and meta-analysis

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Background
Erectile dysfunction (ED), a condition impacting quality of life, is increasingly linked to insulin resistance (IR). This study aims to evaluate the relationship between IR indices and the incidence and severity of ED, providing insights into their diagnostic and predictive utility in practice.
Methods
A comprehensive search across PubMed, Embase, Web of Science, and Scopus was carried out. Required data were extracted and meta-analyzed. The Newcastle-Ottawa Scale (NOS) was employed to evaluate the studies' risk of bias. Sensitivity analyses and meta-regressions were conducted to explore heterogeneity and the impact of confounding variables.
Results
Seventeen studies with a total of 3810 patients with ED and 8252 without ED were included. Meta-analysis revealed that males with ED had significantly higher levels of Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) (SMD = 0.59, 95% CI [0.15, 1.03], I2 = 82%, P < 0.01), Triglyceride-Glucose Index (TyG) (SMD = 0.53, 95% CI [0.31, 0.75], I2 = 69%, P < 0.01), and Visceral Adiposity Index (VAI) (SMD = 0.45, 95% CI [0.25, 0.64], I2 = 76%, P < 0.01) compared to those without ED. However, there was no significant correlation between a one-unit increase in HOMA-IR (OR = 0.63, 95% CI [0.03, 13.69], I2 = 91%, P = 0.77) or TyG (OR = 0.53, 95% CI [0.02, 11.53], I2 = 88%, P = 0.68) and the odds of ED. Additionally, a one-unit increase in VAI was associated with more severe ED (SMD = 0.34, 95% CI [0.03, 0.64], I2 = 16%, P = 0.03). The diagnostic accuracy of these indices varied.
Conclusions
The results indicate a significant connection between insulin resistance and erectile dysfunction, as shown by HOMA-IR, TyG, and VAI. These indices highlight the potential role of metabolic dysfunction in the pathophysiology of ED, suggesting that IR may contribute to endothelial dysfunction and vascular impairment. Clinically, it is important to assess IR in men with ED, particularly in those with comorbid cardiometabolic conditions. Given the observed association between VAI and ED severity, targeting visceral adiposity through lifestyle modifications, weight management, and pharmacological treatments aimed at improving insulin sensitivity may concurrently alleviate ED progression. Future research should focus on standardizing IR assessment methods and exploring integrated diagnostic models that combine IR indices with other biomarkers to enhance predictive accuracy and clinical applicability. This approach could pave the way for personalized treatment strategies, ultimately improving both metabolic and sexual health outcomes in affected individuals.

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P1072

JOINT622

Identification of two novel likely pathogenic NR5A1 variants associated with DSD and infertility in two Kuwaiti families

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Background
Nuclear receptor subfamily 5 group A member 1 gene (*NR5A1*) plays a crucial role in adrenal and gonadal development. *NR5A1* mutations are associated with a wide phenotypic spectrum of differences of sex development (DSD). While, heterozygous inheritance is the prevalent pattern, *NR5A1* dosage significantly influences its biological function.
Case description
We report the first two Kuwaiti families with identifiable *NR5A1* mutations. **Case1:** A 13-years-10-month-old individual, raised as a female, and presented with delayed puberty. Clinical examination revealed Tanner stage 1 breast development, Tanner stage 4 pubic hair, posterior labioscrotal fusion, a 4.5 cm phallus and bilateral palpable inguinal testes (External genital Score was 6.5). Laboratory tests indicated hypergonadotropic hypogonadism, low anti-Mullerian hormone (AMH) and high testosterone levels. MRI pelvis confirmed bilateral small testes at external inguinal rings with no mullerian structures. Karyotype was 46, XY (SRY+). Whole exome sequencing (WES) and Sanger sequencing revealed a novel heterozygote in-frame deletion (c.1070_1075del; p.Gln357_Leu358del). The father, carrying the same mutation, had severe oligospermia and required assisted reproductive techniques (ART) for conception. **Case 2:** A 1-month-old 46, XY infant presented with penoscrotal hypospadias and bilateral undescended testes. Post-human chorionic gonadotropin (hCG) testing indicated an adequate testosterone response. WES and Sanger sequencing revealed a novel heterozygous missense (c.1105G > T; p.Val369Phe) variant in the NR5A1 gene. Although, parents were not genetically tested, the father also had severe oligospermia and required ART. Both cases have normal adrenal functions by ACTH stimulation test and a normal spleen on ultrasound.
Conclusion
Trio sequencing (patient and parents) is crucial to establish inheritance patterns. The broad phenotypic spectrum of *NR5A1* gene mutations within and across families may be related to the epigenetic modifiers or coinheritance of pathogenic variants in different testis/ovarian-determining genes. These findings expand the mutational spectrum of *NR5A1* and highlight the importance of genetic screening in DSD and infertility cases.
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P1073

JOINT3376

Disorders of sex development due to 17ß-hydroxysteroid dehydrogenase type 3 deficiency: searching for a phenotype-genotype correlation

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Introduction
Disorders of sexual steroid biosynthesis are the leading cause of disorders of sex development (DSDs) in non-Western societies. Molecular studies on cohorts have shown that testicular enzyme deficiency-related DSDs due to 17β-hydroxysteroid dehydrogenase type 3 (17HSD3) deficiency are more frequent than previously reported, particularly in the Middle Eastern and North African regions, and are underestimated due to very mild forms. This study aims to characterize, both phenotypically and genotypically, a Tunisian population with 17HSD3 deficiency.
Methods
This is a descriptive study including patients followed for 46,XY DSD secondary to 17HSD3 deficiency at the Department of Endocrinology, University Hospital of Sfax, Tunisia. Phenotypic evaluation was based on Tanner's sexual maturation staging and Prader's virilization grading of the genitalia. We measured a panel of sex steroids before and after stimulation with human chorionic gonadotropin (hCG). The molecular study was conducted at the Department of Genetics using next-generation sequencing (NGS).
Results
We identified seven patients, all assigned female at birth. The main reasons for consultation were pubertal virilization (4/7) and genital anomalies (2/7). None of the pubertal-aged patients exhibited signs of sexual maturation (Tanner stage S1). The mean genital differentiation score was 3 ± 1. The hormonal profile showed a low Testosterone/Δ4-Androstenedione ratio after hCG stimulation of < 0.8 in all patients. Genetically, we identified the nonsense mutation c.618C > A in the HSD17B3 gene, which was common to all seven patients, confirming its founder effect in our region. The phenotypic expression was variable, even among patients with the same genotype, indicating a weak phenotype-genotype correlation.
Conclusion
DSDs due to defects in the final step of steroidogenesis are common in North African populations, with an increasingly well-defined phylogeny. Phenotypic expression is highly variable and appears to be minimally influenced by genotype. This variability may be attributed to the presence of yet unidentified polymorphisms in the HSD17B3 gene, modifying genes, extragenic polymorphisms, alternative steroidogenesis pathways, environmental factors affecting 17βHSD3 protein activity, and the presence of other 17βHSD isoenzymes.

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P1074

JOINT3454

A case of 46, XY complete gonadal dysgenesis presenting with precocious peripheral puberty

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Introduction
46, XY complete gonadal dysgenesis, also known as Swyer syndrome, is a rare disorder of sex development characterized by a normal female phenotype at birth. Patients usually present in adolescence with complaints of menstrual failure or lack of breast development. This case presents a rare clinical presentation.
Case: A six-year and two-month-old female presented with breast enlargement observed three months prior. Her older sister had been examined for primary amenorrhea at 17 years, karyotyped as 46 XY, and underwent gonadectomy. The patient's height was 116.7 cm (-0.1 SDS) and weight 19.2 kg (-0.72 SDS). External examination showed no axillary hair, pubarche at stage 1, and thelarche at stage 3. Laboratory tests yielded: LH: 0.1 mIU/ml, FSH: <0.3 mIU/ml, estradiol: 13 pg/ml, total testosterone: 16 ng/dl, AFP: <0.9 IU/ml, and β-HCG: 88.8 mIU/ml. Gonadotropins were suppressed in GnRH stimulation test. Bone age was consistent with 6 years and 10 months. Ultrasonography revealed a uterus measuring 45x25x10 mm, with thin endometrium, and both gonads approximately 0.4 ml in volume. The patient was diagnosed with precocious peripheral puberty (PPP). Screening tests were performed considering elevated β-HCG as a cause. Cranial and sella MRI examinations were normal. PET-CT demonstrated calcific foci without fluorodeoxyglucose uptake in both adnexal areas. Contrast-enhanced pelvic MRI exhibited hypointense areas in both gonads, suggestive of dysgerminoma on the background of gonadoblastoma. The patient's karyotype was 46 XY. Bilateral gonadectomy was performed, with histopathological examination pending. Postoperative monitoring indicated regression of β-HCG and estradiol levels.
Conclusion
This case report presents a rare clinical finding in a patient with 46 XY complete gonadal dysgenesis. Patients typically show absence of pubertal signs in adolescence due to dysfunctional gonads. However, rare cases presenting with PPP have been documented, as observed in our patient. This presentation is thought to be due to high aromatase activity and tumoral hormone production in dysgenetic gonads. Since dysgenetic gonads can undergo neoplastic changes, they should be removed upon diagnosis regardless of patient age. This case report highlights atypical findings that may complicate diagnosis and delay urgent gonadectomy.

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P1075

JOINT1844

Testicular growth and sperm detection rates following combined hcg and rfsh therapy in adolescents with congenital and acquired hypogonadotropic hypogonadism

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Introduction
While testosterone monotherapy has traditionally been used in adolescents with hypogonadotropic hypogonadism (HH), there has been growing experience with hCG and rFSH therapies. Unlike testosterone monotherapy, these treatments offer a more physiological approach and enhance fertility potential. This study aims to present our treatment protocol and outcomes.
Method
This retrospective study included adolescent males who received combined rFSH and hCG therapy between 2018-2025. In all cases, 2-month rFSH regimen at 75 IU/day (Dwyer protocol) was followed by low-dose rFSH and hCG, gradually increased every 3–6 months up to 150 IU rFSH and 3000 IU hCG twice weekly (Sato *et al.*, 2015). After the Dwyer protocol, testosterone therapy was also initiated at 25 mg monthly and increased to 125 mg every 6 months. Testicular volumes were recorded quarterly, and semen analysis was performed after the third year.

Table 1. Increase in testicular volume during treatment.

	ΔTesticular volume (mL) from baseline		
	6th month	12th month	18th month
Complete congenital ($n = 11$)	1±0.6	1.8±0.6	3.1±1.3
Acquired ($n = 6$)	1.6±0.9	3.6±2	5.8±2.4
p	0.216	**0.027**	**0.036**
Partial congenital ($n = 2$)	1.2±0.7	3.5±3	9±5

Results
Twenty-one patients (15 congenital, 6 acquired) were included. Two genetically confirmed congenital cases with LH >5 IU/l but no pubertal progression were classified as partial HH. The mean age at treatment initiation was 16.6±2.1 years (13.1–19.8), and the median treatment duration was 32.8 months (12–82). Congenital cases included 3 with Kallmann syndrome and 12 with non-Kallmann HH, while acquired cases comprised 5 with craniopharyngioma and 1 with prior radiotherapy for nasopharyngeal carcinoma. Table 1 shows the increase in testicular volume from baseline in cases with an 18-month follow-up. In partial HH cases, a dramatic increase was notable at 18 months. In acquired HH cases, the increase became more pronounced compared to complete congenital cases from the 12th month. In the third-year semen analysis, sperm was detected in both partial congenital HH cases. The sperm detection rates in complete congenital and acquired cases were comparable (2/4 vs. 2/3, $P = 0.658$).
Conclusion
Combined therapy effectively increases testicular volume and, based on semen analysis, improves fertility potential in both congenital and acquired HH cases. Given the lack of evidence for adverse effects of testosterone at priming doses on testicular development, low-dose testosterone alongside conventional therapy may enhance bone mineral density and secondary sexual characteristics earlier, making treatment responses more visible and improving adherence. Further clinical experience will contribute to establishing an optimal protocol.

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P1076

JOINT1353

Multilingual menopause comics: combating misinformation and enhancing global health literacy through peer-reviewed educational videos

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Introduction
Women navigating menopause often face significant barriers to accessing reliable and accurate educational resources, which are exacerbated by the prevalence of misinformation online. Traditional, text-heavy resources frequently fail to engage modern audiences. The CoMICs (Concise Medical Information Cines) initiative produces short, engaging, evidence-based educational videos to address this limitation. However, these CoMICs are usually in English. Similar resources needed to be created in non-English languages to address health literacy and language barriers.
Objectives
• Develop peer-reviewed, evidence-based educational videos on menopause in multiple languages.
• Assess these educational videos' digital dissemination and engagement across social media.
Methods
This study was conducted in the UK between July and December 2024. A multidisciplinary team—including medical students, healthcare professionals,

and women with lived menopause experiences—collaborated to produce visually engaging, peer-reviewed videos. Using the five-phase CoMICs framework, the project involved script creation, video production, publication, evaluation, and impact analysis. The Menopause CoMICs in English were translated into 10 languages. Clinical experts and experts by experience rigorously reviewed the materials to ensure scientific and linguistic accuracy. The translated CoMICs were disseminated on social media between October 1 and 18, 2024. Full-length videos were uploaded to YouTube every other day, while shorter snippets tailored to platform-specific algorithms were shared on TikTok, Instagram, Facebook, and X (formerly Twitter). The engagement of these CoMICs across social media was tracked for three months. Views, likes, and shares were monitored to assess each video's reach and engagement.
Results
The initiative garnered 18,059 views, 112 likes, and 44 shares across all platforms. TikTok achieved the highest engagement with 5,891 views, followed by Instagram with 5,323 views and X with 6,845 views. A single video's highest view count was 1,600 on X, 1,500 on Instagram, and 1,092 on TikTok. Instagram led in likes, generating 52, followed by X with 46 and TikTok with 14. Stratified by language, the most viewed CoMIC videos were in Polish, followed by Serbian, Spanish, and Turkish, with the English video ranking sixth.
Conclusion
Menopause CoMICs successfully developed peer-reviewed audiovisual resources that overcame linguistic barriers. The preference for non-English videos highlights the importance of multilingual approaches in health education. By leveraging digital platforms, the initiative effectively promoted evidence-based education and combated misinformation about menopause. Future efforts will aim to expand content into additional languages and address a broader range of medical conditions, ensuring more inclusive and far-reaching health education.

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P1077

JOINT2324

Role of anti-TPO antibodies on ovarian reserve and early embryo development in assisted reproductive technology

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Introduction
Autoimmune thyroid disease (AITD) is among the most common endocrine disorders and occurs more frequently in women. Circulating antithyroid antibodies associated with AITD are known to affect various tissues, including the ovaries. As a result, this prevalent condition may influence female fertility, which is the focus of the present research. The aim of this study is to explore the role of anti-TPO antibodies in ovarian reserve and early embryo development in assisted reproductive technology (ART) based on the existing literature.
Material and Methods
Data regarding AITD and female reproduction, ovarian reserve and embryo development in ART were searched in MedLine, PubMed, WebofScience, Scopus, Google Scholar data base. Data were combined and presented as main conclusion.
Results
Infertility is a major global health concern, yet in-vitro fertilization (IVF) success rates remain low (8.6-46.2%). The molecular mechanisms linking reduced fertility to the presence of thyroid antibodies remain unclear. One important area of investigation is the role of immunological markers, specifically circulating autoantibodies, that impact female fertility. There are potential ways that anti-TPO antibodies could negatively affect the reproductive system, particularly ovarian tissue, can pass into the ovaries and have been found in the fluid surrounding eggs, targeting the zona pellucida in women with ovarian inflammation also reacted and suggests that ATPO might bind to the zona pellucida, potentially disrupting fertilization, embryo development, and implantation. Recent findings indicate a strong correlation between thyroid hormone levels in serum and follicular fluid. Additionally, the ratio of T4 to T3 in follicular fluid, along with serum TSH levels, showed a positive association with the number of retrieved oocytes, including mature ones, as well as the number of embryos. Relationship between ovarian reserve and the presence of anti-thyroid autoantibodies is limited. It is reasonable to suggest that fibrotic changes may develop in the ovary as part of the typical inflammatory response, potentially impacting ovarian reserve. Indeed, some studies have reported a decline in key markers of functional ovarian reserve in patients with AITD.
Conclusion
Although the impact of thyroid autoimmunity on natural conception and ART success rates is still a subject of debate, the current study suggests that the presence of antithyroid autoantibodies, including ovarian function, the composition of follicular fluid (which serves as the environment for oocyte maturation), as well as folliculogenesis and embryogenesis. Therefore, presence anti-TPO antibodies in the blood can reflect its follicular fluid level and can impact IVF outcomes.

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P1078

JOINT3168

Body composition and bone mineral density in adolescents with gender incongruence

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The number of adolescents with gender incongruence seeking for gender-affirming hormone treatments (GAHT) is increasing. There are a few studies about changes in BMI, body composition and bone mineral density (BMD) following treatment, often limited by small sample sizes and heterogeneous therapeutic protocols.
Objective
The aim of our study was to describe BMI, body composition and BMD of transgender adolescents before and after one year of GAHT.
Methods
We conducted a prospective study on 81 transgender adolescents, 34 assigned female at birth (AFAB) and 47 assigned male at birth (AMAB), aged 17 years (14.66-18.2), followed from 2019 to 2024. Anthropometric parameters, body composition, BMD were evaluated before and after one year of GAHT. Body composition was evaluated using Bioelectrical Impedance Analysis (BIA) to determine lean mass (FFM) and fat mass (FM). BMD was assessed using Dual Energy X-ray Absorptiometry (DEXA).
Results
At study entry mean BMI was within normal range in both AFAB (23.77 $\pm$ 5.95) and AMAB (22.79 $\pm$ 4.99). However, the rate of obesity was higher than in the region general population matched for age (19.7% vs 4.2%) as well as underweight (11% vs 1.4%). AFAB were more frequently obese (26.5%) than AMAB (14.8%) whereas AMAB were more frequently underweight (14.9%) than AFAB (5.9%). After one year of treatment, no significant changes in BMI were observed (AFAB 25.64 $\pm$6.53; AMAB 22.77 $\pm$4.96). Body composition showed significant changes after 1 year of treatment. FFM (%) was significantly reduced (72.77 $\pm$ 6.99) vs baseline (79.26 $\pm$ 10.14; $P = 0.026$) and FM (%) increased (27.23 $\pm$ 6.99) vs baseline (20,70 $\pm$10.14; $P = 0.022$) in the AFAB group. In the AFAB group, no significant changes in FFM (%) (68.09 $\pm$ 8.20 vs 67.32 $\pm$ 8.56) or FM (%) (31.91$\pm$8.20 vs 32.68$\pm$8.56) were observed. BMD z-score was within normal range in transgender adolescents. AMAB had significantly lower lumbar BMD-z score (-0.82 $\pm$0.85) compared to AFAB (1.17 $\pm$ 0.09; $P = 0.033$). After one year of treatment, no significant changes in BMD-z score were observed in both AMAB (-1. $\pm$0.76) and AFAB (-0.47 $\pm$0.73).
Conclusion
Transgender adolescents have a higher frequency of weight abnormalities before treatment, with a higher frequency of obesity among AMAB, and of underweight among AFAB. After one year GAHT, changes in body composition were observed aligning with the desired gender. No significant changes in BMI or BMD were detected.

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Thyroid

P28

JOINT1254

Familial papillary thyroid carcinoma: identification of 12 families and novel putative gene defects in the finnish population

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Background

Papillary thyroid carcinoma (PTC), the most common endocrine cancer, is usually sporadic and little is known about possible genetic determinants. However, we recently identified a truncating pyruvate dehydrogenase phosphatase (PDH) regulatory subunit gene variant segregating with familial PTC in the USA. Our aim was to identify PTC families and search for possible predisposing germline variants in the genetically homogenous Finnish population, an ideal population for the discovery of rare genetic defects of monogenic disorders.

Methods

We identified patients with familial papillary thyroid carcinomas from our University Hospitals and used whole-genome sequencing (WGS) to identify putative pathogenic variants. All patients were clinically characterized, including thyroid antibody measurements and careful histopathological examinations. Only gene variants shared by all PTC patients within the families were considered. Variants were confirmed by Sanger sequencing. Population frequencies were assessed with the gnomAD v.4.1.0 browser. *In-silico* protein prediction tools and databases were used for further analyses.

Results

We identified 12 families with PTC, 5/12 families have so far undergone WGS. A novel *DLD* c.100A>G (p.Thr34Ala) variant was found in family 1, and a novel *SIRT4* c.755A>C (p.Glu252Ala) variant in family 5. The corresponding allele frequencies in a global control population were 0.00086 and 0.00012, respectively. The *DLD* c.100 site is predicted to contain GATA4 and SMARCA4 transcription factor binding sites. In family 7, a protein truncating variant c.422-423 del (p.Leu141ProfsTer23), which leads to a premature stop codon in exon 2 in the *ZNF197* gene was found. The *ZNF197* c.422-423 site contains CTCF, CBX3 and SP1 transcription binding sites.

Conclusion

We have identified 12 Finnish families with PTC and three novel putative underlying gene defects. Two of them, *DLD* and *SIRT4*, regulate the pyruvate dehydrogenase complex (PDH) and one, *ZNF197*, is a VHL-associated KRAB-A domain containing protein, which is overexpressed in some thyroid cancer samples. We hypothesize that the mutations might destroy transcription factor binding sites and impair *DLD* and *ZNF197* gene expression. Further studies are needed to better understand the molecular mechanisms predisposing to PTC in these families.

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P29

JOINT515

THRIVE-2 phase 3 trial of Veligrotug (VRDN-001) in chronic thyroid eye disease (TED): efficacy and safety at 15 weeks

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Purpose

TED remains a condition with significant unmet needs, particularly in the chronic phase, where treatment options are limited. IGF-1R antagonism has emerged as a key therapeutic approach, addressing inflammation and proptosis. Veligrotug (veli), a full antagonist humanized monoclonal antibody targeting IGF-1R, previously demonstrated positive results in the ongoing phase 3 THRIVE trial for active TED. Here, we present efficacy and safety data from the ongoing phase 3 THRIVE-2 trial (NCT06021054) of veli in chronic TED at the primary timepoint of 15 weeks.

Methods

Adults with moderate-to-severe chronic TED (onset >15 months, proptosis ≧3 mm, with any clinical activity score [CAS]) were randomized (2:1) to 5 IV infusions 3 weeks apart of either 10 mg/kg veli or placebo. The following were assessed through 15 weeks: proptosis responder rate (PRR), defined as ≧2-mm reduction vs baseline by Hertel exophthalmometry; overall responder rate (ORR; PRR and no worsening in CAS); PRR by MRI/CT; mean change from baseline in proptosis; improvement and complete resolution on the Gorman subjective diplopia scale; and treatment-emergent adverse events (TEAEs).

Results

188 patients were randomized to veli ($n=125$) or placebo ($n=63$) and included in the intent-to-treat population. Baseline values for veli vs placebo were balanced including mean proptosis, 24.3 mm vs 23.8 mm; presence of diplopia, 52% vs 59%; and CAS ≧3, 57% vs 52%. 15-week results for veli vs placebo were as follows: Hertel PRR, 56% vs 8% ($P<0.0001$), with a mean reduction of 2.34 mm vs 0.46 mm ($P<0.0001$); MRI/CT PRR, 48% vs 3% ($P<0.0001$); ORR, 56% vs 7% ($P<0.0001$). In patients reporting diplopia on the Gorman subjective diplopia scale at baseline, 56% vs 25% ($P=0.0006$) reported improvement and 32% vs 14% ($P=0.0152$) reported complete resolution. Achievement of CAS 0/1 in patients with CAS ≧3 at baseline was nominally significant (54% vs 24%, $P=0.0060$). Most TEAEs were mild, with most common being muscle spasms (36% vs 6%) and menstrual disorders (33% vs 10% for menstruating women). Hearing impairment was 13% vs 3%. Serious TEAEs were 2% vs 3% (1 related to treatment in each group).

Conclusions

THRIVE-2, which assessed 5 IV infusions of veli vs placebo, is the first RCT in chronic TED to show statistically significant improvement not only in proptosis, but also in diplopia, with a generally well-tolerated safety profile. Results suggest the promising potential of veli in chronic TED. Follow-up through 52 weeks is ongoing.

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P30

JOINT1965

Atypia of undetermined significance (AUS) in pediatric thyroid nodules: Surgery after first fine needle aspiration (FNA) or follow-up?

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Introduction

The subsequent management of AUS in pediatric FNAs remains a controversial issue. While the 2015 American Thyroid Association (ATA) guideline recommends surgery after the initial AUS diagnosis, the 2022 European Thyroid Association (ETA) guideline advocates for performing a second FNA after 6 months. In the literature, the malignancy rates of pediatric patients diagnosed with AUS in FNAs present contradictory results. We aimed to investigate the follow-up and postoperative data of patients with AUS in FNA.

Methods

The medical records of 54 patients (F/M:36/19) with FNAs classified as AUS were reviewed retrospectively. Potential risk factors for malignancy predisposition in patients diagnosed with AUS and their follow-up were retrospectively examined (age, family history, previous diseases, nodule characteristics on ultrasonography).

Results

The mean age of patients was 14.1± 3.2 (5.7–21). Of the 54 patients, 49 underwent definitive surgery. Twenty-nine patients underwent surgery following the initial FNA, while 20 patients have surgery after subsequent FNA. The malignancy rate was 48.3% (14/29) after single AUS and 75% (15/20) after repeated FNA. Risk factors for thyroid cancer were similar in both groups. No

specific ultrasound findings indicative of malignancy was identified in the patients with AUS having malignancy. Patients with malignancy after single FNA of AUS were operated within 0.18 ± 0.08 years. However, patients with the second FNA diagnosis were operated within 1.2 ± 1.3 years, ($P < 0.05$).

Conclusion

Our study revealed that the rate of malignancy is high in pediatric patients with AUS. However, performing surgery after first AUS leads to unnecessary surgery in 51.7% of patients. To avoid unnecessary surgery or delayed diagnosis, molecular analysis and cytopathologic atypia subclassification should be performed in management of AUS in pediatric patients.

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P1080

JOINT3443

Diving into the shared genetics between hypothyroidism and its co-morbidities: Multi-trait meta-analyses and gene prioritization provide novel insights into the common genetic and biological factors

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Background

Hypothyroidism is a common endocrine condition affecting up to 10% of the general population. Patients experience a high degree of heterogeneity in symptoms, co-morbidities, and treatment effect. We aimed to investigate the shared genetic architecture of hypothyroidism and its co-morbidities for a better understanding of the disease mechanisms.

Methods

We leveraged publicly available genome-wide association study (GWAS) summary statistics to perform seven multi-trait GWAS meta-analyses (MTAG) based on four co-morbidity categories (Category 1 – Cardiometabolic; Category 2 – Psychiatric; Category 3 – Reproductive; Category 4 – Immune-mediated polyautoimmunity syndromes). MTAG boosts statistical power by JOINT analysis of multiple traits, enabling detection of new genetic associations. Thus, we aimed (1) to identify new genetic associations for hypothyroidism, and (2) to explore the genetic overlap across 26 genetically correlated conditions. Furthermore, we carried out gene prioritization, based on the new associations identified, to detect and characterize the potentially functional genes using two parallel combined SNP-to-Gene methods; (1) Otargen, a GraphQL-based R-package for tidy data accessing and processing from Open Targets Genetics, including nearest gene, variant-to-gene and locus-to-gene strategies, and (2) combined S2G-Framework (cS2G).

Results

MTAG analyses identified 114 new variants in 92 loci for hypothyroidism ($P < 5x10^{-8}$) compared to the input GWAS summary statistic data. Based on these new associations, a total of 1,134 genes were prioritized (1,114 genes by Otargen and 94 genes by cS2G). Out of 1,134 genes, 26 genes were prioritized as 'top-scoring' across the two methods, including 16 nearest protein-coding genes (*GLIS3, NFE2L3, NRG1, AFF3, TAGAP, S1PR1, CHN2, FOXK2, SWAP70, FCRL3, UBASH3B, SLC25A37, ABO, CD2, KCTD5, IL12RB2*). *GLIS3, NRG1, KCTD5*, and *SLC25A37* had significant expression or regulation patterns in the thyroid. Among the genes of interest, for instance, *GLIS3*, expressed in early embryogenesis with a role in multiple organ development, was highlighted as its variants have previously been associated with multiple co-morbidities of hypothyroidism including rheumatoid arthritis, type 1 diabetes, depression, as well as thyroid-related traits blood cholesterol and sex hormone levels. *GLIS3* loss-of-function mutations lead to hyperglycemia, hypoinsulinemia, and congenital hypothyroidism. Supporting our finding, it has also been briefly mentioned in a recent larger GWAS investigating the overlap between thyroid traits and the reproductive system.

Conclusion

Multi-trait analyses and gene prioritization approaches revealed new genetic associations and potential functional genes for hypothyroidism based on publicly available data, providing further fundamental insights into its genetic architecture and expanding the understanding of the common genetics and biological processes between hypothyroidism and its co-morbidities.

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P1081

JOINT664

Epithelial and tumor microenvironment changes driven by BRAF/RAS mutations in thyroid cancer progression

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Background

Thyroid cancer (TC) progression involves distinct mutation-specific pathways, primarily driven by BRAF and RAS mutations. These mutations influence epithelial cell states and tumor microenvironment (TME) dynamics, but their differential effects remain largely unexplored.

Methods

We conducted a multimodal genomic and transcriptomic analysis, integrating single-cell RNA sequencing, spatial transcriptomics, and bulk RNA sequencing across BRAF-driven (PTC-B, ATC-B) and RAS-driven (FTC-R, ATC-R) TCs. Additional validation was performed using public datasets.

Results

In ATCs, the proportion of epithelial cells decreased, while TME components expanded, as confirmed by multimodal transcriptomic analysis. Pseudotime analysis revealed distinct dedifferentiation pathways, with BRAF-driven TCs undergoing gradual dedifferentiation and RAS-driven TCs showing abrupt epithelial transitions, suggesting mutation-specific pathogenesis. Intracellular pathway activation also varied, with ATC-B exhibiting antigen processing/presentation and B-cell receptor signaling activation, while ATC-R displayed upregulation of EMT, hypoxia, and ECM-related pathways. TME-epithelial interactions, particularly those involving fibroblasts, were significantly increased in ATC-R, aligning with pseudotime trajectory shifts. Furthermore, receptor-ligand interactions differed between DTCs and ATCs, with those localized in stroma or ATC regions strongly correlating with poorer survival outcomes, emphasizing the role of mutation-driven TME remodeling.

Conclusions

Epithelial distribution, dedifferentiation trajectories, and TME interactions differ significantly between BRAF- and RAS-driven TCs, suggesting mutation-specific pathogenesis. These findings highlight the importance of considering epithelial states and mutation profiles when selecting TME-targeted therapeutic strategies, emphasizing the potential for personalized diagnosis and treatment.

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P1082

JOINT34

Thyroid eye disease: online medical education unveils knowledge gaps and barriers regarding targeted immunotherapy

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Thyroid eye disease (TED) has profound impact on quality of life. Several novel immunotherapies are in late-stage development. We aimed to identify learning needs on disease facts, diagnosis and management and attitudes towards novel treatment options. Physicians completed an online accredited 25-item clinical practice assessment of 20 knowledge and 5 attitudinal questions with evidence-based feedback on correct answers. Learning objectives were to increase knowledge regarding TED facts, treatment guidelines and self-assess learning needs on management. Launch Sep 6, 2024; data through Oct 22, 2024. Assessment completers: 139 ophthalmologists, 92 endocrinologists. Physicians showed a lack of knowledge using clinical activity score questionnaires for initial and follow-up assessments and had knowledge gaps on atypical TED presentations. Knowledge on immunotherapy targets for rituximab and teprotumumab was insufficient, most physicians were unaware of efficacy data showing proptosis reduction with teprotumumab. The role of selenium

supplementation for mild active TED was not known widely, instead steroids were seen as most appropriate for the majority of patients. The place of orbital decompression surgery in sight-threatening TED not sufficiently responsive to iv corticosteroids also required education. The majority of physicians stated that up to 50% of their patients are not adequately controlled on local therapy or corticosteroids, however less than half would be willing to prescribe a specific immunotherapy if available, due to cost concerns and lack of knowledge on safety and efficacy. Less than half of physicians felt confident (very or quite) about TED diagnosis and management. Physicians had a high interest for education on emerging therapies, in particular safety aspects. Online medical education is an effective method to identify TED learning needs to help the adoption of novel targeted immunotherapies for patients who can benefit from them.

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P1083

JOINT2119

Mental health, anxiety, depression, and the risk of incident thyroid dysfunction

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Background and Aim
Psychological stress has been implicated in the development of various autoimmune diseases. The relation between depression, anxiety and thyroid dysfunction (TD) remains poorly understood. The aim of the study was to investigate the longitudinal association between mental health, anxiety, depression, and the risk of TD. We also determined whether the relation between mental distress and the onset of TD was influenced by genetic predisposition.
Methods
A total of 418,622 TD-free participants from the UK Biobank were enrolled in the study. The mental health score was measured at baseline using the Patient Health Questionnaire-4 (PHQ-4), which has been shown to be a reliable and valid screening tool to assess psychological distress and in particular anxiety and depression in the general population. The diagnosis of TD, which included hyperthyroidism and hypothyroidism, was made using medical records. Polygenic risk score for hyperthyroidism and hypothyroidism was created. Survival curves with the Kaplan-Meier method was used to compare the differences in the cumulative incidence of TD according to mental health states. Cox proportional hazards models were used in multivariate models.
Results
During a median follow-up of 12.3 years, 2,242, and 9,419 new cases of hyperthyroidism and hypothyroidism were documented respectively. There was a graded association between mental health score at baseline and the risk of incident TD over the follow-up. The adjusted hazard ratio (HR) per SD increase was 1.13 (95% confidence interval [CI]: 1.08, 1.18) $P<0.001$ for hyperthyroidism and 1.11 (95% CI: 1.09, 1.13) $P<0.001$ for hypothyroidism. Individuals with severe mental health score had an increased risk of developing either hyperthyroidism (adjusted HR: 1.70, 95% CI: 1.09-2.65) or hypothyroidism (adjusted HR: 1.70, 95% CI: 1.36-2.12) compared with those with a low mental health score. Anxiety and depression as considered separately was each significantly associated with the risk of TD. Results were unchanged when considering clinical diagnosis of depression or anxiety instead of the PHQ-4 questionnaire. There was no significant interaction between the mental health and genetic risk score for the association with the incidence of TD.
Conclusion
Mental health, anxiety and depression were strongly and independently associated with the onset of both hyperthyroidism and hypothyroidism in general population. These findings suggest considering the potential risk of TD in individuals who experienced psychological distress, anxiety or depression.

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P1084

JOINT3716

Thyroid function and ultrasound morphology of the thyroid gland in a cohort of patients with rasopathies: an italian multicenter study

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Background
Subjects affected by RASopathies have an increased susceptibility to autoimmune diseases.
Aims
The aim of our study was to define the prevalence of antithyroid antibodies (ATAs) and ultrasound (US) abnormalities of the thyroid gland in a population of children and young adults with RASopathies.
Methods
Eleven Italian Pediatric Endocrinology Centers participated to this cross-sectional observational study. Inclusion criteria were molecular diagnosis of Rasopathies and availability of data on thyroid function (TSH, fT3, fT4), thyroid immune profile (anti-thyroglobulin, anti-thyroperoxydase, anti-TSH receptor antibodies) and thyroid doppler ultrasound.
Results
In this study data from 136 subjects with Rasopathies, 70 males (51.5%) and 66 females (48.5%), with an average age of 12.1 years, were collected. Among them, 127 patients (93.4%) were affected by Noonan Syndrome (NS) and 9 patients (6.6%) by other Rasopathies (3 Mazzanti Syndrome (MS), 2 Neurofibromatosis I (NF I), 2 Cardiofaciocutaneous Syndrome (CFCS), 2 Noonan Syndrome with multiple lentigines (NSML). The most prevalent genetic mutation was PTPN11, which was detected in 93 patients (68.4%). Further mutations were found in the following genes: SOS1/2, RAF1, NRAS, KRAS, LZTR1, SHOC2, BRAF, ERF, NF1, RIT 1, MEK1, MAP2K1, PPP1CB, PRMT6, NTNG1. ATAs positivity was detected in 23 out of 136 patients with an overall prevalence of 17.1% (7.7% of whom with double positivity), without a significant difference in gender or pubertal stage. Among patients with ATA positivity, 20 were affected by NS (17 PTPN11, 1 LZTR, 1 BRAF, 1 SOS1) and 3 were affected by MS (SHOC2). Four patients with NS (2 PTPN11, 1 LZTR, 1 SOS1) and positive ATAs presented a condition of hypothyroidism while 19 patients (16 NS and 3 MS) were in euthyroidism. Among patients with ATAs positivity, 69.2% presented with US abnormalities (thyroid nodules, increase or decrease in thyroid volume, abnormal echotexture) and 5.6% showed an US pattern of thyroiditis. Patients with positivity for at least one ATAs had a significantly higher prevalence of US abnormalities. No association was found between PTPN11 gene mutation and the biochemical profile of thyroid function, the ultrasound pattern of autoimmune thyroiditis, abnormalities of thyroid volume and echotexture or thyroid nodules.
Conclusions
Subjects with Rasopathies have a higher prevalence of autoimmune and nodular thyroid disease compared to the general population. Further studies are needed to define the genotype-phenotype correlation and to identify early risk factors for the development of autoimmune thyroid disease and thyroid nodules in these patients in order to prevent long-term complications.

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P1085

JOINT2781

Fatal carotid blowout syndrome induced by lenvatinib and nivolumab combination therapy in anaplastic thyroid cancer: a case report

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Anaplastic thyroid carcinoma (ATC) is an aggressive malignancy with a dismal prognosis despite multimodal treatment approaches. Tyrosine kinase inhibitors (TKIs), such as lenvatinib, and immune checkpoint inhibitors (ICIs), including nivolumab, have emerged as promising therapeutic options for ATC. Carotid blowout syndrome (CBS) is a rare but life-threatening vascular complication in patients with head and neck cancer, typically associated with prior surgical intervention and radiotherapy. Here, we report a fatal case of CBS following combination therapy with lenvatinib and nivolumab in an ATC patient who initially demonstrated a dramatic response to treatment. A 69-year-old male presented with a rapidly enlarging 6 cm right thyroid lobe mass and hoarseness. Total thyroidectomy and imaging studies confirmed ATC with tracheal and right recurrent laryngeal nerve invasion, along with synchronous lung and brain metastases (T4bN0M1, Stage IVc). Genomic profiling revealed NRAS (c.182A > G), TP53 (c.430C > T), TERT promoter (c.-146C > T) mutations with a high tumor mutational burden (23.4 mutations/Mb) and wild-type BRAF. The patient underwent external beam radiotherapy (EBRT; 6600 cGy in 30 fractions) followed by systemic therapy with lenvatinib (20 mg/day) and nivolumab (200 mg every 3 weeks). Two months after initiating systemic therapy, follow-up imaging demonstrated a significant partial response in pulmonary metastases and complete resolution of brain metastases, correlating with clinical improvement and weight gain. However, three months into therapy, the patient developed sudden-onset odynophagia. Neck computed tomography (CT) revealed a right tracheal wall defect with an exposed and unsupported right common carotid artery, indicative of impending CBS. Despite immediate cessation of systemic therapy and a recommendation for surgical intervention, rapid progression of tracheal necrosis led to acute carotid blowout, resulting in a fatal outcome. This case highlights the potential for severe vascular complications, such as CBS, in ATC patients receiving TKI and ICI combination therapy, even in the presence of an initial robust therapeutic response. Tracheal invasion and prior EBRT likely contributed to the pathogenesis of CBS, emphasizing the complex interplay between tumor biology, treatment modalities, and vascular integrity. These findings suggest that the administration of EBRT should be carefully considered or potentially omitted in ATC patients undergoing TKI and ICI combination therapy. Alternative treatment strategies should be explored to mitigate the risk of catastrophic vascular events.

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P1086

JOINT700

Timing of levothyroxine ingestion in the INFINITY-study: a randomized controlled trial comparing dose-adjusted, non-fasting and fasting levothyroxine ingestion

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Background
Levothyroxine (LT4) co-ingestion with food may lead to reduced absorption and increased thyroid-stimulating hormone (TSH) levels. Therefore, fasting ingestion is recommended. Yet, in a recent study we found that the majority of patients are burdened by fasting ingestion. Therefore, we aimed to investigate whether dose-adjusted, non-fasting LT4 ingestion could achieve stability of TSH levels comparable to fasting ingestion.
Methods
Patients were randomized to a fasting group, taking LT4 as usually recommended, or a non-fasting group, ingesting LT4 with breakfast after increasing the baseline LT4 dose by 15% to compensate for reduced absorption due to non-fasting ingestion. TSH, free T4 (FT4) and total T3 (TT3) levels were measured every six weeks until study completion. Patients were followed for 12 weeks in case two consecutive TSH levels fell within reference range. If TSH was out of range, follow-up was extended to 18 or 24 weeks. TSH stability was defined as a mean difference in TSH from baseline to study end ranging between -1 and +1mIU/l.
Results
Eighty-eight patients (80.7% female, median age 62y [IQR:49-69]) were randomized: 43 to the fasting and 45 to the non-fasting group. No significant differences were observed between the fasting and non-fasting group in mean difference of TSH (+0.22±1.00mIU/l vs. +0.22±0.92, p=NS), FT4 (-0.48±2.41 vs. -0.96±2.75pmol/l, p=NS) and TT3 (0.07±0.18 vs. 0.08±0.22nmol/l, p=NS), respectively. TSH stability was achieved in 71.8% of the fasting group and 73.2% of the non-fasting group (p=NS). By study end, 93.3% of the non-fasting group preferred to continue taking LT4 with breakfast.
Conclusion
Dose-adjusted, non-fasting LT4 ingestion achieved TSH stability comparable to conventional fasting LT4 ingestion. Therefore, this could be considered as an alternative to fasting LT4 ingestion.

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P1087

JOINT773

Natural course of subclinical hyperthyroidism in primary care in the netherlands

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Background
Subclinical hyperthyroidism (SHT) is characterized by a suppressed thyroid-stimulating hormone (TSH) concentration with normal free thyroxine (FT4) levels. While SHT has potential health implications, the epidemiology and contributing factors for its natural course and guideline adherence in primary care remain unclear.
Objectives
To investigate the incidence and natural course of SHT in primary care and assess guideline adherence to follow-up recommendations within Dutch primary care.
Methods
Using a retrospective cohort design, we analyzed data from the PHARMO General Practitioner database in the Netherlands (2012 to 2021). Patients with biochemically confirmed SHT were followed to assess progression to hyperthyroidism, recovery, or persistence. Adherence to the Dutch primary care guideline on SHT management was evaluated.
Results
The annual incidence of SHT was approximately 200 cases per 100,000 person-years, with a temporary increase in 2016-2017 coinciding with a national thyroid medication shortage. Among the 11,163 patients with SHT, 47% recovered, 11% persisted, and 8% progressed to overt hyperthyroidism over a median follow-up of five years. Female sex and baseline TSH <0.1 mU/l were associated with higher progression rates (1,69 (CI 1,32 - 2,17) and 2,36 (CI 1,97 - 2,83), respectively). Guideline adherence evaluation showed 33% received follow-up TSH measurement within six months, and 4% underwent TSH receptor antibody testing.
Conclusion
This study highlights that a small subset of SHT patients progresses to overt hyperthyroidism. Significant contributing factors of progression included lower TSH at baseline and female sex. In addition, our findings indicate a need for improved guideline adherence in follow-up and diagnostic testing.

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P1088

JOINT2171

Trends in thyroid cancer in the balearic islands, insights from 2000 – 2020 to 2021 – 2023

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Summary
Thyroid cancer (TC) incidence has been rising globally, including in the Balearic Islands. From 2010 to 2020, the spread use of neck ultrasound (US) by clinicians led to the detection of many subclinical cancers, causing overdiagnosis. Our aim is to assess the ongoing trends in TC during the 2021-2023 period.

Table 1. Trends in TC parameters in the Balearic Islands.

	Before US (2000-2009)	After US (2010-2020)	LU (2021-2023)
Disease crude incidence (x105 habitants)	3.35	8.39	7.46
Estimated annual percent change in incidence, %	3.05	11.37	-9.77
Incidence of MPTC, %	14.20	20.50	21.40
Incidence of aggressive histology, %	6.48	7.15	18.01
Anaplastic carcinoma, % (n)	0.93 (3)	0.66 (7)	2.48 (8)
Median tumor size (cm ±SD)	2.78 ±0.45	2.04 ±1.56	1.88 ±3.88
Lymph node at diagnosis, %	7.97	11.28	17.24
Distant metastases at diagnosis, %	1.38	1.91	4.19
Initial Lobectomy, %	1.93	5.13	33.55
Initial I-131 ablation therapy, %	87.21	74.61	54.04
Initial thermal ablation therapy, % (n)	0	0.56 (6)	2.61 (8)

Methods
We reviewed 322 new TC cases diagnosed between 2021 and 2023 (last update – LU) in the Balearic Islands. Data on histological subtypes, tumor size, initial presence of lymph node and distant metastasis, disease management and disease progression were compared with earlier periods: 2000-2009 (before US), and 2010-2020 (after US), respectively.
Results
TC incidence has tapered down since 2020, but several important trends observed in previous periods are maintained in regards of disease incidence, management and cancer aggressiveness (Table 1).
Conclusions
During 2021 to 2023, global incidence of TC decreased slightly as compared to our previous series, but overdiagnosis is still present as evidenced by increased incidence of MPTC and smaller tumor size. Nevertheless, there is a persistent trend towards an increased incidence of more aggressive types of tumors both in histological subtypes (including a sharp increase in anaplastic carcinoma) and disease presentation with neck lymph involvement and distant metastases. In line with current recommendations, TC management has improved towards less aggressive procedures (lobectomy and thermal ablation) in selected patients.

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P1089

JOINT399

Levothyroxine use in Belgium in 2003-2020: a longitudinal population-level registry-based cohort analysis

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Background and Objective
Levothyroxine (LT4) is among the most frequently used medications in the Western world. In Belgium, where health insurance is mandatory, 5.85% of the population was prescribed LT4 in 2023, raising concerns regarding overdiagnosis and overtreatment. We investigated prevalence and incidence of LT4 use in relation to TSH screening intensity, treatment threshold, and risks of over-treatment.
Method
Retrospective registry-based cohort analysis in 2003-2020 based on aggregated data from the largest Belgian health insurance provider representing 42% of the Belgian population (±4.5 million individuals).
Findings
Prevalence of LT4 use steadily increased from 2.59% in 2003 to 5.29% in 2020 (slope over time +0.153;$P < 0.0001$) whereas incidence of LT4 use was stable around 0.40%/year (slope +0.003;$P = 0.0628$) (adjusted for age category, sex, region, socioeconomic status). In the 80+ age category, prevalence rose from 5.36% in 2003 to 11.63% in 2020 (slope +0.418;$P < 0.0001$), but incidence decreased from 0.70%/year to 0.53%/year (slope -0.005;$P = 0.046$). Among non-LT4 users, the proportion with high TSH testing rate ($\geq$1 TSH test/year) steadily rose from 26.05% to 38.53% over time. Prescription (first and following) of exclusively the lowest dose (25µg) rose from 8.33% to 19.83%. Incidence of thyroid surgery was stable at around 0.05%/year. First-time LT4 use was associated with high TSH testing rate in the preceding year (Rho 0.86;$P < 0.0001$), prescription of exclusively the lowest dose (Rho 0.736;$P = 0.0007$), and incidence of thyroid surgery (Rho 0.552;$P = 0.0252$). Among LT4 starters, a low subsequent TSH testing rate ($\leq$1 TSH test within two years after start) was present in 16.52% in 2003 and 14.19% in 2018. The proportion of low TSH testing rate was negatively associated with calendar year (Rho -0.915;$P < 0.0001$). Compared to non-LT4 users, those using LT4 for $\geq$2 years had a higher risk of subsequent initiation of antiarrhythmic (RR 1.113;$P = 0.0284$) and antiresorptive drugs (RR 1.129;$P = 0.0305$), but lower mortality risk (RR 0.885;$P = 0.0082$). Additionally, we found a higher risk of statin use (RR 1.483;$P < 0.0001$), flu vaccination (RR 1.273;$P < 0.0001$), and $\geq$2 GP visits/year (RR 1.165;$P < 0.0001$).
Discussion
These findings suggest that increased LT4 use may partially be attributed to increased detection (TSH testing rate) of subclinical hypothyroidism (prescription of only the lowest LT4 dose), and highlight the need for better TSH monitoring after starting LT4. Whether the higher use of antiarrhythmic and antiresorptive medications in LT4 users is causally related or explained by other factors such as more intensive medical follow-up needs to be further explored on a subject-level base.

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P1090

JOINT1639

Paediatric thyroid cancer management in france: a TUTHYREF network

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Differentiated thyroid cancer (DTC) is rare in children requiring expert multidisciplinary management. The aim of this multicenter retrospective study by the national TUTHYREF network was to describe care pathway and outcome of these patients aged under 18. 93 patients, median age 15 years, managed for CPT between 2010 and 2022 were included. Surgery was performed by a pediatric surgeon in 14% of cases, in a university hospital in 53% of cases, with validation of surgical extension by a multidisciplinary team in 32% of cases. All patients underwent total thyroidectomy followed by radiotherapy (RAI). Central and lateral lymph node dissection was performed in 79 and 45% of cases respectively, with 19% R1 resection. Definitive hypoparathyroidism occurred in 5% of patients. Most patients had papillary DTC (84%), tumor size greater than 20 mm (45% pT2, 16% pT3), lymph node involvement (LNI) (21% N1a, 38% N1b), vascular invasion (42%), extra-thyroid invasion (37%). All patients had at least one iodine treatment (median activity 80 mCi), with a median Tg of 3.4 ng/mL and positive Tg Ac in 21% of cases. After a course of iodine, 69% of patients had an excellent response to RAI. After RAI, persistent and metastatic disease were observed in 22% and 12% of patients respectively. Of the 15 patients with morphological locoregional persistence or recurrence, 60% underwent re-operation. Among the 11 metastatic patients, metastases were synchronous in 73% of cases, with a median number of iodine treatments of 3 (1-6) and a Tg at diagnosis of 123 ng/mL. At the end of a median follow-up of 8 years in these patients, 64% were in remission and 36% in biological or morphological persistence, and none were refractory to iodine. Children under 15 had more aggressive disease (higher Tg at 16 ng/mL vs. 1.4 and 23% metastases vs. 2%), but the remission rate remained comparable to patients over 18. After a median follow-up of 4 years (1-13), 92% of patients were cured, 4% had an indeterminate response and 4% stable metastatic disease. Our study confirms that LNI and metastatic disease are more frequent in children, with a prognosis and sensitivity to RAI that remain excellent. The care pathway seems very heterogeneous, sometimes lacking the pediatric or social psychological and genetic intervention that is usually recommended and raises the question of pediatric surgical expertise, always complicated to assess to avoid excessive LND or incomplete surgery.

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P1091

JOINT1093

Is postoperative radioactive iodine (RAI) ablation necessary for low- and low-to-intermediate-risk papillary thyroid carcinomas? a web survey among Greek endocrinologists

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Objectives
The majority of patients with a low-risk DTC has a favorable outcome. Consensus statements and recent prospective studies do not recommend RAI-ablation for low-risk microcarcinomas ($\leq$10 mm). However, RAI-ablation strategy for other low-risk PTC cases remains controversial and the therapeutic policy varies significantly among endocrinologists.
Aim
To evaluate treatment strategies of Greek endocrinologists for low- and low-to-intermediate-risk PTC in terms of RAI-ablation.
Methods
Between November 2023 and April 2024, a web-based survey was conducted among members of the Hellenic Endocrine Society (HES). Four clinical scenarios involving a 60-year-old patient with a low-risk PTC were analysed. The scenarios varied according to primary tumor size ($\leq$ or $>$1 cm) and the presence or not of either postoperative cervical lymph node (LN) involvement or minimal extrathyroidal extension (ETE). The scenarios addressed questions regarding the extent of surgery, the decision for postoperative RAI-ablation and the appropriate RAI dose if indicated.
Results
A total of 201 endocrinologists (25% of HES members) participated in the survey. For low-risk PTC patients, responses varied by tumor size: for 7 mm tumors, the majority (95.0%) did not recommend RAI ablation, whereas for 18 mm tumors, 51.8% recommended it. Among those who opted for RAI ablation, the recommended doses were 30 mCi (36.5%), 50 mCi (35.6%), 70 mCi (3.5%), and 100 mCi (14.4%). For low- to intermediate-risk PTC cases with either three microscopic LN metastases (1–2 mm) or minimal ETE, but no other high-risk features, most endocrinologists (92.5%) favoured RAI ablation/adjuvant therapy. Their preferred doses were 30 mCi (13%), 50 mCi (26.6%), 70 mCi (31.2%), and 100 mCi (29.2%).
Conclusions
Greek endocrinologists continued to favour postoperative RAI therapy for low-risk and low-to-intermediate-risk T1b PTC, often at high doses—a concerning trend. These findings highlight the need for more randomized controlled trials, clearer guidelines and educational programs to ensure consistent and evidence-based care.

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P1092

JOINT819

Artificial Intelligence-based longitudinal analyses of hypothyroidism patients using data from electronic health records provide insights into the sex-specific patient cluster patterns

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Background
Hypothyroidism is a common endocrinological disorder affecting approximately 10% of the general population, with a 10-fold higher prevalence in women. Despite levothyroxine being one of the most prescribed treatments worldwide, 30–50% of patients are over- or under-treated, with many reporting dissatisfaction with their treatment and quality of life. Hypothyroidism patients present with significant heterogeneity in symptoms, co-morbidities, and treatment requirements, yet large and comprehensive studies addressing this complexity remain lacking. Our study aims to identify clustering patterns and varying trajectories of hypothyroidism patients by leveraging longitudinal health and demographic data. We seek to characterise patient clustering patterns by defining respective co-morbidities and risk/protective factors, while also exploring the overlapping disease mechanisms involved in these co-morbidities.
Methods
We identified 21,790 (17,028 women and 4,761 men) hypothyroidism patients from the Copenhagen Hospital Biobank based on hypothyroidism diagnosis in hospital records and levothyroxine prescription data, ensuring a comprehensive dataset reflecting diverse patient profiles. We constructed longitudinal health sequences capturing each patient's history of hospital diagnoses, prescriptions, procedures, and laboratory Results To address the complexity and high dimensionality of the data, we applied a machine learning approach: the Deep Generative Decoder (DGD), which learns low-dimensional representations even for small datasets, based on a transformer architecture to identify long-term dependencies and intricate patterns in sequential health data. The DGD integrates a Gaussian Mixture Model to capture latent space distributions and uncover data substructures. Patient representations generated through this pipeline were clustered, enabling the identification of unique patterns. These clusters were further characterized to highlight key patterns.
Results
Preliminary findings indicate that hypothyroidism patients are clustered with distinct and varying longitudinal patterns, notably differentiating between reproductive co-morbidities such as infertility and miscarriage (observed exclusively in women) and cardiovascular co-morbidities such as essential hypertension and atrial fibrillation (present in both sexes). Ongoing model refinement with additional data will improve these findings. Further detailed analyses of these clustering patterns and their associated health outcomes will be discussed, providing insights into the underlying disease mechanisms and potential ways for providing more personalised prevention, diagnosis and treatment options.
Conclusion
This study highlights the importance of understanding the heterogeneous nature of hypothyroidism patients in a sex-specific manner. By identifying patient clustering patterns, we aim to enhance clinical management and therapeutic approaches, ultimately improving patient outcomes in this diverse population. Further results and detailed characterisations will be presented at the conference.

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P1093

JOINT2339

Molecular characterization of a multicenter cohort of patients with non-autoimmune subclinical hypothyroidism

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Introduction
Non-autoimmune subclinical hypothyroidism (NASHT) is characterized by elevated TSH levels with normal concentrations of thyroid hormones. Genetic defects, which can determine disorders in the biosynthesis process of thyroid hormones, such as in the TSH receptor (*TSHR*) or in the dual oxidase 2 (*DUOX2*) genes, have been described. It is suspected that other genes that regulate or participate in the biosynthesis of thyroid hormones could be involved in NASHT, suggesting a more complex pathogenesis although few studies have explored its genetic basis.
Objective
To perform a molecular characterization and genotype-phenotype correlation in NASHT patients.

Patients and methods
Multicenter study in 11 Spanish centers. Patients with NASHT were included with TSH > 7 μUI/mL in two measurements. Patients exposed to medical treatments or radiotherapy capable of affecting thyroid function were excluded. The data collection were: clinical, familial, analytical, thyroid ultrasound, and levothyroxine treatment. Molecular analysis was performed using a high-throughput sequencing panel (Cell3 Target Custom Panel tier 2, NONACUS) covering 18 genes, the most relevant: *TG, TPO, DUOX2, DUOXA2, PAX8, TSHR, SLC5A5, and SLC26A4*. Statistical analysis: IBM®SPSS®Statistics v25.
Results
Ninety patients were studied (mean age at diagnosis 5.6 ± 3.4 years; 58% male). Fifty patients (56%) received levothyroxine treatment. Mean TSH at diagnosis: 9.7 ± 3.7 μUI/mL; maximum TSH: 11.7 ± 4.4 μUI/mL. Thyroid ultrasound showed thyroid hypoplasia in 13 patients and hyperplasia in 2. A total of 55 patients (61%) had candidate variants in the studied genes, of which 44 (80%) were heterozygous, 9 (16%) digenic, and two were compound heterozygous; one for *DUOX2* and another for *TPO*. In total, 64 candidate variants were identified, with their distribution in *Table1*. Among heterozygous patients, 21 (48%) had a variant described as pathogenic (PAT) or likely pathogenic (LPAT), and 23 (52%) had variants of uncertain significance (VUS). Family segregation studies are ongoing to determine the possible inheritance of candidate variants and their potential cosegregation with NASHT clinical features.
Conclusion
A significant proportion (61%) of NASHT patients have variants in thyroid dyshormonogenesis-related genes, some previously undescribed. The possible oligogenic origin of NASHT is highlighted, as 9 patients showed variants in two genes. These genetic findings may help to better characterize patients and define their prognosis and need for treatment. Additionally, given the high percentage of VUS identified, our results support the need for functional studies to determine the clinical relevance of these findings.

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P1094

JOINT445

Evaluation of the diagnostic accuracy of European and ACR-TIRADS classification systems for thyroid nodules exceeding 20 mm in diameter

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Background
Determining which thyroid nodules require fine-needle aspiration (FNA) cytology remains a critical challenge in clinical practice. To address this, the Thyroid Imaging Reporting and Data System (TIRADS) was developed, with the two most commonly used formats being the European (EU-TIRADS) and American (ACR-TIRADS) versions. Despite their widespread application, clinical observations indicate that TIRADS 3 nodules measuring ≥20 mm present difficulties in accurate risk stratification. This study aimed to evaluate the efficacy of EU-TIRADS and ACR-TIRADS in differentiating between benign and malignant nodules in this subgroup of nodules.
Material and Methods
Between May 2023 and March 2024, 1,094 patients with thyroid nodules underwent thyroid ultrasound (US) at a University Hospital. Comprehensive data, including clinical parameters, US characteristics, and cytological or histopathological findings, were collected. Nodules measuring ≥20 mm were categorized using EU-TIRADS and ACR-TIRADS, and their predictive performance for malignancy was assessed. Malignancy was confirmed via histopathological examination post-thyroidectomy or through US-guided FNA cytology categorized by the Bethesda classification system.
Results
The study analyzed data from 267 patients (mean age 60.3 ± 14.3 years; 46 men and 221 women) with 308 thyroid nodules. These were classified using EU-TIRADS into categories 3, 4, and 5, with all nodules undergoing FNA. Of the total, 22 nodules were malignant, and 286 were benign. When the EU-TIRADS 3 FNA criteria were adjusted to include thresholds of 25 mm or 30 mm, the rates of avoided FNA procedures were 24% and 41%, respectively. Using the ACR-TIRADS system, 26.6% of FNAs could be avoided ($P > 0.05$). Two malignancies were missed across these adjusted criteria.
Conclusion
The performance of EU-TIRADS and ACR-TIRADS is comparable when the FNA referral diameter threshold for seemingly benign nodules is standardized to 25 mm. Adjusting the EU-TIRADS 3 threshold to 25 mm or 30 mm could significantly reduce unnecessary FNA procedures and healthcare costs. However, the potential trade-off includes an increased risk of missing malignant cases, which underscores the need for careful risk assessment and individualized patient management. Future studies should explore ways to enhance the sensitivity of these grading systems while maintaining efficiency to optimize patient care.

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P1095

JOINT4007

Radiofrequency ablation (RFA) for locoregional structural incomplete response (SIR) in differentiated thyroid cancer (DTC)

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Objectives
Structural incomplete response (SIR) to treatment, characterized by persistent or recurrent disease, is observed in 2 - 6% of low-risk differentiated thyroid cancer (DTC) cases and in 67 - 75% of high-risk cases. For locoregional recurrence, surgery remains the optimal treatment when the smallest dimension of the targeted lesion is at least 8 mm in the central compartment or 10 mm in the lateral compartment. However, in cases with smaller lymph nodes, contraindications to surgery, or when the patient declines reoperation, alternative approaches such as active surveillance (AS) or minimally invasive treatments (MITs), like radiofrequency ablation (RFA) may be considered. The aim of this study is to evaluate the safety and efficacy of RFA in DTC patients with SIR.
Methods
It is a retrospective study of eight DTC patients with SIR confirmed by ultrasound (U/S)-guided fine-needle aspiration cytology (FNAC) and measurement of Thyroglobulin (Tg) in the washout fluid. Fourteen malignant lesions were ablated by radiofrequency (RF). We assessed the volume of each lesion, serum Tg and Anti-Tg antibodies and calculated the volume reduction ratio (VRR) prior RFA and then at one month, three months and subsequently every three months.
Results
Patients were followed for a mean period of 14.75 months (range: 4–24) after RFA was performed. The targeted lesions reduced significantly from a median volume of 0.24 mL (range: 0.09 - 0.9) to 0.01 mL (range: 0 - 0.03) ($P < 0.05$), with a median volume reduction rate (VRR) of 96.5% (range: 87 - 100%). Out of the 14 lesions that were ablated, 4 (28.6 %) were no longer visible on the U/S. Volume reduction was accompanied by a significant biochemical response, with a decrease in serum thyroglobulin (Tg) levels from a median of 1.05 ng/mL to 0.13 ng/mL ($P < 0.05$). In one patient with an aggressive radioiodine (RAI)-refractory histological variant, re-recurrence was documented, which was successfully treated with repeat RFA. Two patients developed Horner syndrome as a complication of RFA, but in both cases it was fully resolved within six months.
Conclusions
RFA may be considered as an effective and safe MIT in selective DTC patients with SIR, especially in cases of smaller lesions. Additional prospective studies, including aggressive DTC histological variants are needed towards tailored-made therapy.

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P1096

JOINT271

Clinical characteristics and outcomes of graves' disease in patients with prior hypothyroidism

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Background and Aims
Graves' disease (GD) and Hashimoto's thyroiditis are autoimmune disorders that can transition from one to the other. The shift from hypothyroidism to GD is rare. This study compared clinical characteristics, treatments, and outcomes in patients with new-onset GD following hypothyroidism vs those with new-onset GD without prior thyroid disease.
Methods
This retrospective cohort study used the electronic medical database of Maccabi Healthcare Services, an Israeli health maintenance organization. We included adults with new-onset GD between 1.2010–12.2022 who had thyroid-stimulating immunoglobulin (TSI) titers >140% within a year of thyrotoxicosis diagnosis. Subjects with prior amiodarone use were excluded. Data included demographics, clinical history, treatments, and laboratory Results The end of follow-up was 31.10.2024. Data were analyzed using chi-square or Fisher's exact tests for categorical variables, t-tests or Mann-Whitney U tests for continuous variables, and Cox regression models adjusted for age and sex.
Results
We included 2402 patients with new-onset GD. Of these, 2146 had no prior thyroid disease (GD-controls) and 256 had prior hypothyroidism (post-hypo-GD patients). Compared to GD-controls, post-hypo-GD patients were older (51.4 ± 14.3 vs. 47.4 ± 13.6 years; $P < 0.001$), predominantly female (88.1% vs. 76.9%; $P < 0.001$), and had a higher prevalence of autoimmune disease (19.5% vs. 12.9%; $P = 0.003$). At diagnosis, post-hypo-GD patients had lower median free thyroxine (fT4) levels (21.7 [interquartile range (IQR), 17.5-28.5] vs. 26.8 [IQR,19.8-38.6] pmol/l; $P < 0.001$) and free triiodothyronine (fT3) levels (8.5 [IQR,5.9-11.5] vs. 10.4 [IQR,7.2-15.8] pmol/l; $P < 0.001$). Over a median follow-up of 7.2 [IQR,4.6–10.9] years, antithyroid medications were used less frequently in post-hypo-GD patients (65.6% vs. 81.0%; hazard ratio [HR] 0.64; $P < 0.001$). Radioactive iodine ablation (HR 0.68; $P = 0.26$) and total thyroidectomy (HR 1.29; $P = 0.33$) were utilized at comparable rates. Post-hypo-GD patients had a higher incidence of hypothyroidism requiring levothyroxine (41.8% vs. 21.0%; HR 2.58; $P < 0.001$).
Conclusions
Patients with post-hypo-GD present with milder thyrotoxicosis and more often revert to hypothyroidism.

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P1097

JOINT268

Biological activity and therapeutic potential of SAFA-based long-acting rhTSH

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Thyrogen, a recombinant human thyroid-stimulating hormone (rhTSH), has a short half-life in the bloodstream, which necessitates multiple doses during treatment. Therefore, we developed a new long-acting rhTSH using anti-serum albumin Fab-associated (SAFA) technology to validate its biological activity through *in vitro* assays, pharmacokinetic (PK) studies in healthy mice, and pharmacodynamics (PD) studies in a TSH-suppressed mouse model. SAFA-TSH was produced using a Chinese hamster ovary expression system. To verify its biological activity, we generated Nthy-ori 3-1 cells stably overexpressing TSHR and measured the production of cyclic adenosine monophosphate (cAMP). In a rat study, slow-release triiodothyronine (T3) pellets were implanted 3 days before administering Thyrogen or SAFA-TSH, to measure the amount of thyroxine (T4) release alone resulting from exogenous administration. SAFA-TSH increased cAMP production dose-dependently, but less effectively than Thyrogen at similar concentrations. SAFA-TSH required six times the dose of Thyrogen to achieve similar cAMP levels, likely due to differences in molecular weight and relative bioactivity. In a rat study, SAFA-TSH produced elevated thyroid hormone levels well after the decline in the response to Thyrogen. SAFA-TSH had significantly higher cumulative effects on T4 and free T4 levels compared with Thyrogen, as observed by a more than two-fold higher average area under the effect curve of 262.56 vs 118.89 μg×h/dl and 127.47 vs 60.75 μg×h/dl, respectively. SAFA technology created successful long-acting TSH that demonstrated bioactivity. These findings endorse the continued development of SAFA-TSH for clinical use, highlighting its potential as a significant advancement treating thyroid cancer patients.

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P1098

JOINT1014

Washout CYFRA 21-1 as a biomarker for thyroid cancer diagnosis in thyroid nodules

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Background
Thyroid nodules with non-diagnostic or atypia of undetermined significance (AUS) cytology results often require repeat testing, leading to diagnostic delays and uncertainty. CYFRA 21-1, a fragment of cytokeratin-19, has been suggested as a complementary biomarker to improve diagnostic accuracy and predict malignancy in such ambiguous cases. This study aims to evaluate the diagnostic and predictive utility of washout CYFRA 21-1 in thyroid nodules.
Methods
This retrospective study analyzed data from 153 patients with thyroid nodules who underwent fine-needle aspiration cytology (FNAC). Washout CYFRA 21-1 levels were measured from FNAC washout fluid. Diagnostic performance was assessed using receiver operating characteristic (ROC) curve analysis to identify the optimal washout CYFRA 21-1 cutoff value by maximizing the Youden index. Multivariate logistic regression analysis was performed to evaluate the association between washout CYFRA 21-1 levels and thyroid cancer.
Results
The mean washout CYFRA 21-1 level was 53.25 ± 146.14 ng/mL. Of the nodules, 13.73% were thyroid cancer, while 81.70% were benign. Non-diagnostic and follicular neoplasm cases accounted for 1.96% and 2.61%, respectively. Most nodules were classified as K-TIRADS 4 (49.02%) or 5 (21.57%). Washout CYFRA 21-1 levels demonstrated a significant association with malignancy, with levels markedly higher in PTC compared to benign or indeterminate outcomes ($P < 0.0001$). The optimal cutoff value for washout CYFRA 21-1 was 60.39 ng/mL, achieving a sensitivity of 88.0%, specificity of 94.5%, positive predictive value of 82.8 %, negative predictive value of 93.8%, and accuracy of 90.2% (AUC = 0.833). Multivariate analysis showed that high CYFRA 21-1 levels (≥ 60.39 ng/mL) were strongly associated with malignancy (adjusted OR: 9.257, 95% CI: 13.452–180.356, $P < 0.0001$).

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P1099

JOINT2684

Combining TERT promoter mutations with american thyroid association risk stratification system to predict short-term prognosis in papillary thyroid carcinoma

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Background
TERT promoter mutations are associated with poor long-term outcomes in papillary thyroid carcinoma (PTC), but their influence on short-term prognosis

remains unclear. Understanding this association could enhance early risk stratification and support clinical decision-making. While the 2015 American Thyroid Association (ATA) guidelines acknowledge the potential prognostic value of TERT promoter mutations, they do not provide specific recommendations on their use or indicate when testing should be performed. This study evaluates the impact of TERT mutations on short-term clinical outcomes and proposes an enhanced risk stratification model integrating TERT mutation status.
Methods
This retrospective cohort study analyzed 3,078 patients who underwent thyroidectomy for PTC at Samsung Medical Center (2019–2021). Among them, 57 patients had TERT promoter mutations. Using propensity score matching (4:1) by age and sex, a matched cohort of 57 patients with TERT promoter mutations and 227 patients with wild-type TERT. Short-term outcomes were classified as no evidence of disease (NED), biochemical incomplete response, or structural incomplete response. Kaplan-Meier survival analysis and hazard ratios were used to assess recurrence risk. To improve risk prediction, we developed an alternative classification (RSS-T) that integrates TERT mutation status into the ATA risk stratification system.
Results
Patients with TERT promoter mutations had larger tumor, wider disease extent, and received more aggressive treatment. Short-term outcomes differed significantly ($P < 0.001$): NED was achieved in 95.6% of wild-type patients but only 64.9% of mutation carriers, with mutation carriers exhibiting higher rates of structural incomplete response (29.8% vs. 2.2%). When stratified by the ATA risk system, all low-risk patients achieved NED regardless of TERT status. However, in the intermediate- and high-risk groups, TERT mutations were associated with significantly poorer outcomes ($P < 0.001$ and $P = 0.004$, respectively). The RSS-T system categorized patients as RSS-T1 (low-risk, regardless of TERT status), RSS-T2 (intermediate/high-risk with wild-type TERT), and RSS-T3 (intermediate/high-risk with TERT mutation). RSS-T demonstrated superior predictive accuracy for structural persistence/recurrence compared to the ATA system (C-index 0.890 vs. 0.794, $P = 0.03$) and explained a greater proportion of variance (86% vs. 70%).
Conclusion
TERT promoter mutations are associated with worse short-term outcomes in PTC, particularly among intermediate- and high-risk patients. Integrating TERT status into the ATA risk stratification system (RSS-T) improves predictive performance and provides valuable guidance for clinical decision-making. Selective TERT testing in intermediate- and high-risk patients could refine risk assessment and enable more personalized, aggressive management strategies, ultimately improving patient outcomes.

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P1100

JOINT813

Circulating tumor DNA as a diagnostic marker for molecular alterations in anaplastic thyroid cancer using next generation sequencing

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Introduction
Anaplastic thyroid cancer (ATC) is rare, but the most aggressive type of thyroid cancer (TC), with disease-specific mortality approaching 100%. A new therapeutic option that improves overall survival is molecularly targeted therapy. To date, the tumor tissue analysis using next generation sequencing (NGS) is a gold standard for mutational profiling. The circulating tumor DNA (ctDNA) is a component of liquid biopsy, with a potential to expedite the diagnosis in a minimally invasive way. This study aims to evaluate the feasibility of NGS ctDNA analysis for the identification of molecular alterations in ATC.
Methods
A prospective, single-center study was conducted from 2023 to 2024. Treatment-naïve patients with a diagnosis of ATC were included in the study. 10 ml blood samples for ctDNA analysis were collected from patients after histological diagnosis. Tissue and ctDNA samples were analyzed using NGS with the Oncomine Precision Assay, which detects molecular alterations in 50 genes. The minimum concentration of free DNA required for the assays was 0.33 ng/μL. The results were correlated with clinical data.
Results
Ten patients (mean age: 71, 6 females) with stage IVB ($n = 4$) and IVC ($n = 6$) ATC were enrolled in the study. In 5 patients, mutations were detected both in tissue and ctDNA. The mutation-based concordance between tissue and ctDNA was 71%, with 100% concordance of negative Results The most common mutations detected in ctDNA were *BRAF*^{V600E} (20%) and *TP53* (20%), followed by *PIK3CA* (10%) and *PTEN* (10%) mutations. One patient with *BRAF*^{V600E}mutation in tumor tissue, had a unique *TP53* mutation in ctDNA with no evidence of other malignancy, suggesting heterogeneity of the tumor. Based on the results, dabrafenib plus trametinib treatment was introduced in three patients. Mean turnaround time was 17.75 days (range 2-33), depending on the urgency of the referral for a blood test.
Conclusion
The high concordance of detected alterations highlights the potential of liquid biopsy as an effective initial screening tool for molecular alterations in ATC. Our study shows that the detection of any alterations in ctDNA should lead to further diagnostic evaluation by tissue analysis, due to complete concordance in patients with negative Results Using ctDNA may improve and expedite the diagnostic process, contributing to more precise cancer treatment, especially in cases of inoperable tumors or lesions that are difficult to biopsy. Due to the rarity of ATC, larger multicenter studies are necessary to validate and further explore the utility of ctDNA in clinical practice.

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P1101

JOINT3317

Differentiated thyroid carcinomas and its pre-operative characterization: a single centre study

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Background
EU-TIRADS classification and nodule's size on ultrasonography (US) guide fine needle aspiration biopsy (FNAB) recommendation. Bethesda classification is the report system used to describe cytopathological findings of FNAB. These classification systems help estimate the risk of malignancy and select the appropriate treatment.
Aims
Assess the pre-operative EU-TIRADS and Bethesda classification of nodules diagnosed with differentiated thyroid carcinoma (DTC).
Methods
Retrospective observational study, including patients with anatomopathological diagnosis of DTC submitted to surgery between January/2017 and July/2024.
Results
We included 36 patients with 38 biopsied nodules. Patients diagnosed with DTC corresponded to nodules classified as EU-TIRADS 3, 4 and 5 (16%, 53% and 32%, respectively) on imaging and Bethesda I, II, III, IV or V (3%, 29%, 24%, 29% and 16%, respectively) on FNAB. Nodules classified as EU-TIRADS 5 on US, corresponded to Bethesda IV on FNAB (42%), followed by Bethesda V (33%). Eleven nodules were classified with benign cytology, Bethesda II: Six corresponded to EU-TIRADS 4 on US; 4 to EU-TIRADS 3; 1 to EU TIRADS 5. These patients were submitted to surgery due to dimensional criteria or symptomatic disease. Most patients ($n = 7$) had carcinomas ≤ 1 cm.
Discussion
In this sample, 85% of the patients with DTC had nodules classified as EU-TIRADS 4 or 5 on US, pointing to a strong correlation between US imaging and DTC. Nodules classified as Bethesda II on FNAB have a ROM of 0-3%, however they are among one of the most common FNAB results in this sample. This could be explained by the presence of small foci of DTC or multifocal carcinoma within large thyroid nodules, that can be missed in FNAB.
Conclusion
The presence of high suspicion features in US positively correlates with Bethesda IV and V in FNAB in 75% of the cases. Thyroid carcinoma can be present in nodules with Bethesda II on FNAB, pointing to the presence of false negatives in this category, especially in big nodules. This highlights the importance of combination of EU-TIRADS and Bethesda classifications, as well as of careful selection of biopsy sites and the need to collect several samples from the same nodule, especially in nodules >4 cm.

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P1102

JOINT3885

Clinical outcomes of non-invasive follicular thyroid neoplasm with papillary-like nuclear features: a single-center experience

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Introduction

Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is a thyroid tumor characterized by its indolent behaviour. Although similarities are found with papillary thyroid carcinoma, NIFTP is thought to be a pre-malignant lesion with hallmark features such as being non-invasive and contained within the tumor capsule. This study aims to analyse the clinicopathologic characteristics and outcomes of NIFTP in order to optimize treatment and reduce overtreatment.

Materials and Methods

We reviewed our hospital's pathology database for NIFTP cases between 2014 and 2024, excluding those with separate *foci* of carcinoma. Clinical data from 50 patients meeting these criteria was retrospectively analysed, with a minimum follow-up of 6 months.

Results

Of the 50 patients diagnosed with NIFTP, 74% ($n = 37$) were female and the mean age at diagnosis was 54.5 years. The median follow-up period was 20.3 months. Total thyroidectomy was performed in 82% ($n = 41$) of cases, while 9 patients underwent lobectomy. Tumor size ranged from 2 to 78 mm, with a median size of 22 mm. All tumors were fully excised, with clear margins in 92% ($n = 46$) and close margins in 4 cases. No lymph node metastases were observed at diagnosis, and in the patients with available nodal tissue ($n = 12$), there were no positive findings. None of the patients received postoperative radioactive iodine therapy. One patient required reoperation to remove remnant thyroid tissue due to compressive symptoms, which was confirmed as benign. At the latest follow-up, none of the patients had experienced recurrence.

Conclusion

This study reaffirms the very low recurrence risk associated with NIFTP, indicating an excellent prognosis even with less extensive surgical approaches, such as lobectomy. Our findings support the possibility of managing patients with NIFTP similarly to those with follicular adenomas, in the absence of separate *foci* of carcinoma or suspicious features like contralateral nodules in patients who underwent lobectomy.

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P1103

JOINT3792

Hemithyroidectomy vs. total thyroidectomy for low-risk differentiated thyroid carcinoma: a retrospective cohort study from romania

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Introduction

In the past decade, differentiated thyroid cancer (DTC) management has shifted towards de-escalation to reduce overtreatment and improve quality of life. Guidelines now favor less aggressive surgery, with lobectomy preferred for low-risk tumors. This study aimed to determine the proportion of patients in Romania eligible for initial hemithyroidectomy (HT) according to ATA guidelines and the frequency of recommended completion of total thyroidectomy (TT).

Methods

This retrospective cohort study included patients diagnosed with DTC who were treated or followed up in our department between 2015 and 2021. Exclusion criteria were ectopic tumors, missing data or follow-up <12 months, and age under 18 years at surgery. Eligibility for initial HT was defined by the following criteria: DTC ≤ 4 cm, no suspicious lymph nodes and no extrathyroidal extension on preoperative imaging, and no distant metastases. Patients classified postoperatively as intermediate or high risk according to the 2015 ATA guidelines were considered to require a completion TT.

Results

Records of 169 patients were review. 62 patients were excluded for insufficient data (no preoperative evaluation available) or follow-up less than 12 months. Of the 107 patients included, 51 (45,9%) would have been eligible for initial HT. Among them, 14 (27,4%) would have required a completion TT after postoperative initial risk classification, of whom 7 patients would have excellent response to therapy. In the HT-eligible group, 49 had papillary thyroid cancer (PTC), including 15 cases (29.4%) of microcarcinoma, along with 1 case of follicular carcinoma (FTC) and 1 case of Hürthle cell carcinoma. In the TT-eligible group, there were 49 cases of PTC (including 3 tall cell variants), 2 FTC, 3 Hürthle cell carcinomas, and 2 poorly differentiated thyroid carcinomas. The mean age was similar between the HT-eligible and TT-eligible groups (49 ± 14.52 vs. 48.8 ± 13.75 years), as well as presence of multifocality, in 17 cases (32.6%) in the HT-eligible group and 18 cases (31.5%) in the TT-eligible group. Patients eligible for HT had significantly higher remission rates and lower rates of persistent and recurrent disease compared to those who required upfront total thyroidectomy (71.1% vs. 33.9%, $P < 0.0001$).

Conclusions

A less extensive surgical approach with appropriate follow-up can be a valid alternative to total thyroidectomy in selected cases, given the potential benefits of a stepwise strategy and the favourable prognosis of low-risk DTC. This highlights the importance of shared decision-making in managing patients with DTC ≤ 4 cm.

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P1104

JOINT958

Evaluation of the role of systemic immune-inflammatory markers in predicting malignancy in patients with thyroid nodules

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Background

Inflammation significantly contributes to the pathogenesis of thyroid cancers, as well as various cancer types. Studies indicate that many inflammatory biomarkers are reliable indicators of prognosis and progression in malignant tumors. These include the neutrophil/lymphocyte ratio (NLR), the platelet/lymphocyte ratio (PLR), the lymphocyte/monocyte ratio (LMR), the systemic immune-inflammation index (SII), the systemic inflammatory response index (SIRI), and the systemic inflammation aggregate index (SIAI). These markers have been shown to be linked to multifocality, tumor growth, and metastasis in differentiated thyroid cancers. They can also help predict central lymph node metastasis and the prognosis. The aim of this study was to evaluate the role of systemic immune-inflammatory markers in predicting malignancy in patients who underwent surgery for thyroid nodules.

Methods

A total of 400 patients who underwent surgery for thyroid nodules were included in this study, and the patients were divided according to the cytological results defined by Bethesda classification. We recorded demographic characteristics, Bethesda findings, NLR, PLR, LMR, SII, SIRI, SIAI values, and postoperative histopathological Results.

Results

Preoperative cytology results were benign in 62 (15.5%), nondiagnostic (ND) in 36 (9%), atypia of undetermined significance (AUS) in 115 (28.75%), follicular neoplasm (FN) in 30 (7.5%), suspicious for malignancy in 70 (17.5%), and malignant in 87 (21.75%) patients. The postoperative malignancy rate in patients with AUS was 49.56%. There was a significant difference between NLR, PLR, LMR, SII, SIRI, and SIAI between the patients with AUS who had benign and malignant histopathology ($P < 0.001$). In patients with FN, NLR was significantly different ($P = 0.035$). For those with ND cytology, there was no significant difference in any marker. Area Under the Curve (AUC), sensitivity, and specificity values for markers were found, respectively, as 0.753, 0.702, 0.31 for NLR, 0.692, 0.632, 0.36 for PLR, 0.697, 0.649, 0.362 for LMR, 0.751, 0.702, 0.293 for SII, 0.729, 0.632, 0.345 for SIRI, and 0.733, 0.684, 0.31 for SIAI. The cut-off values for markers were 1.935 for NLR, 123.675 for PLR, 5.965 for LMR, 493.56 for SII, 0.68 for SIRI, and 161.525 for SIAI.

Conclusion

The NLR, PLR, SII, SIRI, and SIAI values were all significantly higher while the LMR value was significantly lower in AUS patients who had malignant

histopathology compared to those with benign histopathology. All these markers might be helpful to predict malignancy in patients with preoperative AUS cytology.
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P1106

JOINT496

Discordant thyroid function tests – a case report of ewly identified rare mutation of transthyretin related euthyroid hyperthyroxinaemia

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We present a 24-year-old male who was referred to endocrinology team for evaluation of discordant thyroid function tests (TFTs). TFTs were first sent when he presented to Primary Care with intermittent palpitations. He was otherwise fit and healthy, with no comorbidities. Results showed elevated free T4 of 31pmol/l (Reference range 10-22 pmol/l) with a normal TSH of 0.91 miu/l (reference range 0.3 – 5.5 miu/l). On review in the endocrine clinic, his detailed history and systemic examination were unremarkable. He was not on any prescribed or over-the-counter medications. TSH-receptor antibodies were negative, and assay interference was ruled out by counter-checking TFTs on Roche & Beckman testing separately. There was no known family history of thyroid dysfunction. Given the patient's young age and symptoms, we undertook genetic testing to look for possible *de novo* thyroid hormone resistance. The genetics laboratory undertook analysis of all the coding regions and exon/intron boundaries of the hyperthyroidism gene panel (ALB, SECISBP2, SLC16A2, THRA, THRB, TSHR and TTR). The initial report showed that a genetic cause for the hyperthyroidism had not been identified. After several months, we received further correspondence from the genetics team re-reporting his results as they had identified a rare cause of discordant TFTs consistent with a genetic diagnosis of TTR-related dystransthyretinaemic hyperthyroxinaemia. At the time of initial report, this gene mutation was labelled as "likely benign" with no correlation with isolated hyperthyroxinaemia. However, in the following months, similar variants were identified in more cases with similar findings and therefore labelled as "likely pathogenic" in context of isolated hyperthyroxinaemia. This functional genetic polymorphism is counter checked by Exeter and Cambridge genomic laboratories. In these cases, offspring would be at 50% risk of inheriting this variant and being predisposed to hyperthyroxinaemia. Hence, testing is recommended for family members affected with hyperthyroxinaemia. Variants in THRB are found in ~86% patients with Resistance to Thyroid Hormone beta. GWAS studies have shown a statistically significant positive association between this variant and FT4 levels.

Conclusion

Isolated hyperthyroxinaemia with normal TSH could be related to underlying genetic mutation involving transthyrenin receptors and therefore should be looked for. This does not require any treatment but testing for symptomatic family members is recommended. We feel this case highlights the importance of investigating discordant thyroid function tests to help the identification of previously unknown genetic variants.

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P1107

JOINT1606

Endocrine specialist nurse-led post-radioiodine care pathway improves patient outcomes

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Background

Radioactive iodine (RAI) therapy is an effective treatment for thyrotoxicosis and is recommended by the National institute for Health and Care Excellence (NICE) in the UK as the first line treatment. Hypothyroidism is one of the most common adverse effects of RAI and occur in up to 80% of patients receiving this treatment. The NICE guideline recommends thyroid function monitoring every 6 weeks for 6 months following RAI for early detection and treatment of hypothyroidism. A previous audit revealed that our centre fell short of the standard recommended by national guideline. A specialist nurse-led post-RAI care pathway was subsequently implemented in 2022. This study evaluates the impact of a nurse-led care pathway on patient outcomes and adherence to national guideline.

Methods

We conducted a retrospective study of adult patients who received RAI between May 2022 to July 2023 in a single tertiary hospital. The post-RAI care pathway involved thyroid function monitoring every 6 weeks, until serum thyrotropin was within the normal reference range. We included patients with a minimum of 12 months follow-up. Clinical data were retrieved from the hospital electronic medical records.

Results

A total of 54 patients (mean age: 56.9 $\pm$ 14.3 years, 79.6% female) were included. The majority (70%) had Graves' disease (GD), followed by toxic multinodular goitre (19%), solitary toxic nodule (9%), and euthyroid goitre (2%). After implementing the ESN-led post RAI care pathway, the mean time to the first thyroid function check decreased from 51 to 39.6 days after RAI. The proportion of patients having their first thyroid function checked prior to 7 weeks after radioiodine therapy increased from 63.2% to 94.4%. The incidence of hypothyroidism at first follow-up review decreased from 9% to 4%. Among patients with Graves' disease who had not restarted block and replace regime after RAI, the proportion who became hypothyroid by the time levothyroxine was initiated decreased from 61% to 44.4%. No patients developed severe hypothyroidism or TSH $>$ 30 mIU/l when levothyroxine was initiated, as compared to 25% of patients, prior to the implementation of this new care model.

Conclusions

The implementation of an ESN-led post-RAI care pathway has significantly improved adherence to the national guidelines. The better monitoring of thyroid function has led to larger proportion of patients receiving thyroid hormone replacement in a timely manner and prevent severe hypothyroidism after RAI. This approach provides a care model that improve patient outcomes and increase consultant clinic capacity.

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P1108

JOINT3799

New de novo variants in THRA gene in adolescent patients: two clinical cases

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Resistance to thyroid hormones due to mutations in THRA (RTHα) is a very rare disease, of which only 40 cases have been described so far in the literature (27 in children and 13 in adults). However, its incidence could be much higher than currently estimated: in fact, many affected relatives with a mild phenotype were only diagnosed by genetic screening after initial diagnosis of the index cases. Twenty-five variants in THRA gene have been identified so far, but likely there are many more we have not discovered yet. Both our patients first came to our attention due to short stature when they were starting pubertal development; however, failure to growth was associated to other clinical features of which some could possibly be associated with untreated hypothyroidism (e.g. neurodevelopmental delay, delayed tooth eruption, constipation) while others were not directly related with hypothyroidism but anyway suggestive for a syndromic disease (e.g. dysmorphic features of the face and trunk, several nevi, ligaments' hyperlaxity, redundant skin, clinodactyly). Thyroid function tests in both patients were typical for RTHα, but they were not recognised as such: the first showed fT4 levels at the lower limits of normal associated with normal TSH values, but fT3 was never measured; the second patient had two other central hormonal deficits (GH and ACTH), therefore low fT4 levels were attributed to a form of central hypothyroidism, which can be tricky to distinguish from RTHα. Definitive diagnosis was made with exome sequencing, which revealed de novo heterozygous variants in both patient: in the first a variant of unknown significance (c.G802C, protein p.Asp268His), while in the second the variant c.1204_1215del causes deletion of four amino acids in the protein p.(Leu402_Phe405del). After the diagnosis, we repeated thyroid function tests and we calculated fT3/fT4 ratio, which was above mean reference values in both patients. After the start of therapy with L-T4, both our patients had immediate amelioration of symptoms such as constipation. To conclude, it is

crucial to keep in mind RTHα in the differential diagnosis for children with growth failure, dysmorphic features, and delayed psychomotor development. fT3/fT4 ratio is of fundamental importance in not-straightforward cases. Early diagnosis would allow children to start treatment with L-T4 and thus possibly avoid severe neurodevelopmental outcomes, together with the amelioration of constipation leading to better quality of life for the patient and the family.

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P1109

JOINT2571

Parathyroid cyst in an adolescent girl – a rare pathology in pediatric population

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Introduction
Parathyroid cysts are rare (0.8–3.41% of all parathyroid lesions) usually asymptomatic formations in the anterior neck region that account for 1 to 5% of neck masses in adults. Depending on the presence of hyperparathyroidism, they can be subdivided into two groups - functioning and non-functioning (approximately 90% of parathyroid cysts). However, there is a limited number of published studies focusing on pediatric cases.
Case Report
We present the case of a 16-year-old girl with a palpable, non-tender mass in the lower left quadrant of the neck. The mass was visible, asymptomatic and appearing to be located in the right thyroid lobe. The patient was referred to the clinic by a pediatric endocrinologist with a suspicion of a thyroid nodule. The patient was a healthy adolescent, with no significant history of any diseases. Her maternal grandmother had a history of goiter. Biochemical parameters, including parathyroid hormone (PTH), thyroid hormones and thyroglobulin were all within normal ranges. Ultrasound examination revealed a cystic lesion nearly completely occupying the right lobe of the thyroid gland with dimensions in the longitudinal section: 35.8/16.2 mm. A fine-needle aspiration (FNA) biopsy was performed by a more experienced adult endocrinologist, yielding 5 ml of water-clear, rapidly aspirated fluid. Following evacuation, a residual formation was observed with dimensions in the longitudinal section: 29.3/10.5 mm. Cytological analysis of the fluid showed no cellular content. However, the aspirated fluid had a markedly elevated PTH level (>2500 pg/mL, reference range: 11–87 pg/mL), confirming the parathyroid origin of the cyst. Based on expert consultation, puncture, aspiration, and sclerotherapy with ethanol were recommended one month later.
Conclusion
Non-functioning parathyroid cysts although rare present a diagnostic challenge, frequently being mistaken for thyroid pathology due to overlapping clinical and imaging characteristics. More frequent and prolonged follow-up is required due to the risk of recurrence and the potential need for surgical removal. Using additional imaging modalities such as computed tomography could be helpful, especially when surgery is chosen for a definitive treatment option. Given the rarity of this condition and the lack of clear guidelines for its diagnosis and management in pediatric patients, consultation with experienced specialists is crucial.
Key Words
parathyroid cysts, fine-needle aspiration, sclerotherapy.
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P1110

JOINT3464

Preoperative detection of pathogenic variants in children and adolescents

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Introduction
In recent years, the incidence of thyroid tumors in children and adolescents has been increasing. Compared to adult patients, these tumors exhibit a more aggressive course, higher invasiveness, and a greater tendency to metastases. Molecular genetic analysis of fine-needle aspiration biopsy (FNAB) is an effective tool for the more precise diagnosis of thyroid nodules. The aim of this study was to detect pathogenic variants in a cohort of children and adolescents.
Materials and Methods
A total of 145 FNAB samples from patients aged 6–20 years were analyzed. Initially, the V600E variant in the *BRAF* gene was tested using real-time PCR. Subsequently, additional gene analyses were performed using massively parallel sequencing, fusion gene analysis by real-time PCR, or capillary sequencing.
Results
Pathogenic variants were detected in 35 patients: 9 in the *BRAF* gene, 7 in *RAS* genes (1 *HRAS*, 1 *KRAS*, and 5 *NRAS*), 11 in fusion genes (1 *TPM3/NTRK1*, 3 *ETV6/NTRK3*, 3 *RET/PTC3*, 3 *RET/PTC1*, 1 *EML4/ALK*), 1 in the *TSHR* gene, and 7 in the *DICER1* gene. Postoperative histological examination data were available for 25% of patients (36/145).
Conclusion
Preoperative molecular genetic analysis is important not only in adults but also in pediatric patients. While *BRAF* V600E mutations and fusion genes are associated with an almost 100% risk of malignancy, recommending total thyroidectomy, *RAS* gene mutations carry a lower malignancy risk and are more often associated with lobectomy recommendations. Germline mutations in the *DICER1* gene are linked to *DICER1* syndrome, which predisposes individuals to various tumor types from early childhood. *Supported by AZV NU21-01-00448 and Ministry of Health of the Czech Republic RVO 00023761.* .

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P1111

JOINT1512

Efficacy and safety of the FCRN inhibitor, batoclimab, in graves' thyroidal and extrathyroidal disease: a proof-of-concept study

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Introduction
Thyrotropin receptor autoantibodies (TRAb) cause Graves' hyperthyroidism (GH) and its extrathyroidal manifestations. Batoclimab, a neonatal fragment crystallizable receptor (FcRn) inhibitor, reduces IgG levels, including TRAb.
Objective
To describe serological and clinical outcomes from a phase 2a, proof-of-concept, open-label, single-center study evaluating batoclimab in patients with GH.
Methods
Eligible patients had serologically confirmed GH and elevated TRAb and were hyperthyroid despite ongoing therapy with moderate-to-high dose anti-thyroid drugs (ATD) for $\geq$12 weeks. Batoclimab was administered via subcutaneous injection at a dose of 680 mg weekly for 12 weeks, followed by 340 mg weekly for 12 weeks. Key endpoints included the proportion of patients who achieved FT3 and FT4 normalization (serum levels $\leq$upper limit of normal [ULN] and $\geq$lower limit of normal [LLN]) or FT3 and/or FT4 $<$LLN without increase in ATD dose; proportion of patients with FT3 and FT4 normalization or FT3 and/or FT4$<$LLN and ATD dose $\leq$50% of baseline; and reductions in TRAb.
Results
As of the data cutoff, 25 patients either completed Week 24 ($n = 23$) or discontinued prematurely due to non-treatment-related reasons ($n = 2$). Eighty percent (20/25) had pre-existing Graves' orbitopathy. By Week 2, 15/25 (60%) patients achieved FT3 and FT4 $\leq$ULN, without an increase in ATD. After 12 weeks of high-dose (680 mg) batoclimab, 19/25 (76%) patients had FT3 and FT4 $\leq$ULN without an increase in ATD, including 14/25 (56%) who were off ATD and 5/25 (20%) who achieved normal thyroid-stimulating hormone levels. At Week 24, after 12 weeks of lower-dose (340 mg) batoclimab, 17/25 (68%) patients had FT3 and FT4 $\leq$ULN without an increase in ATD, including 9/25 (36%) who were off ATD. Mean TRAb decreased from baseline by 74% and 70% at Weeks 12 and 24, respectively, and 5/25 (20%) and 3/25 (12%) patients achieved seroconversion (TRAb-negative), respectively. Improvement from baseline in ophthalmic parameters (eg, proptosis, lid aperture, clinical activity score) and reduction in ultrasound-assessed thyroid volume were also observed. Batoclimab was well-tolerated, with all adverse events being mild-to-moderate in severity; no new safety signals were observed.
Conclusion
Subcutaneous batoclimab very rapidly normalized FT3 and FT4 in most patients. By Week 12, more than half of patients had both T3 and T4 $\leq$ULN and were off

ATD. Batoclimab also improved extrathyroidal signs. These data are the first clinical evidence that FcRn inhibition may be effective for treating Graves' hyperthyroidism.

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P1112

JOINT1100

Thyroglobulin antibodies in patients with thyroid cancer: autoimmunity or cancer immunoediting?

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Introduction

Highly immunogenic tumors can spontaneously prime protective immunity, thus preventing tumor growth, a phenomenon known as tumor immunity. Autoimmunity, is a distinct form of autoreactive immunity that targets one's own cells, but in the presence of cancer, it could prove tumoricidal. Thyroid peroxidase antibodies (TPO-Abs) are the hallmark of thyroid autoimmunity. Thyroglobulin antibodies (Tg-Abs), do not appear as effective in their cytotoxic capacity as TPO-Abs, and their role in thyroid cancer development/progression remains unclear. We designed the present study to evaluate their role.

Methods

We reviewed retrospectively thyroidectomy (Tx) cases operated in 13 centers in Greece and 2 centers in the US over 10 years. We recorded their age, gender, BMI, TSH and Tg-Abs preoperative and histology report. Thyroid cancer (TC) incidence and tumor aggressiveness descriptors were compared between patients with elevated vs. low Tg-Abs titers (Tg-Abs+ $\geq$30 vs. Tg-Abs- $\leq$30IU/l).

Results

After collecting $n = 9643$ Tx, we enrolled $n = 2870$ patients, mean BMI of $27.3 \pm 5.5 Kg/m^2$, age 47.0 ± 14.5 years; $n = 2127$ (74.1%) were females. Their average TSH was 2.11 ± 5.09IU/l, and Tg-Abs 96.0 ± 614.6IU/l. Tg-Abs- were found in $n = 2232$ (77.8%) patients. TC was present in $n = 1587$ (57.1%) cases, of the following histology: papillary (PTC) $n = 1487$, follicular (FTC) $n = 35$ Hürthle cell (HCC) $n = 23$, medullary $n = 30$, anaplastic (ATC) $n = 1$, poorly differentiated thyroid cancer (PDTC) $n = 7$, other $n = 3$, lymphoma $n = 1$. The larger tumor dimension was 1.5 ± 2.0 cm, and the average number of tumor foci was 1.8 ± 1.8, $n = 26$ (1.6%) had gross and $n = 249$ (15.7%) had microscopic extrathyroidal extension (ETE), $n = 212$ (13.4%) had capsular invasion (CI), $n = 391$ (24.6%) had lymph nodes (LNs) metastasis, while $n = 24$ (1.5%) had distant metastases. The incidence of thyroid cancer was not different between the two subgroups (elevated vs. low Tg-Abs titers), as did distant metastases (OR 0.98, $P > 0.05$). Patients with Tg-Abs+ had larger tumors (1.8 vs. 1.4 cm), more LNs infiltrated by TC (OR 2.2), more ETE (OR 1.25) and capsular invasion (OR 1.20). Non-PTC histology was less common in Tg-Abs+ patients (OR 0.49) ($P < 0.05$).

Conclusion

Tg-Abs behave differently compared to TPO-Abs as they seem unable to protect from TC. Their rise tends to be a marker of the immune response to the expanding PTC, when this extends beyond the thyroid capsule, and when thyroglobulin might become exposed to the immune system. It remains to be proven if Tg-Abs result from TC immunoediting. However, Tg-Abs titers should be evaluated preoperatively as they might provide prognostic value to the evaluation of patients with thyroid nodules.

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P1113

JOINT3396

Afirma genomic classifier in clalit health services: preserving thyroids and promoting equality

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Background

Thyroid nodules evaluated through fine-needle aspiration (FNA) cytology yield indeterminate results (Bethesda III or IV) in approximately 15% of cases, with a malignancy risk ranging from 15% to 50%. These uncertainties often result in unnecessary surgical interventions. To address this issue, advanced molecular tests, including the Afirma genomic classifier, were developed. In 2023, Clalit Health Services integrated Afirma testing into its insured services, providing it at no cost to patients to reduce unnecessary surgeries. This study assesses the utilization and impact of Afirma testing within this healthcare framework.

Methods

Data on demographics, laboratory findings, imaging results, and Afirma test outcomes were retrieved from Clalit Health Services records. Ethical approval for the study was obtained from the organizational ethics committee.

Results

Between January 1, 2023 and September 30, 2024, 298 Afirma tests were performed. The mean age was 56.2 ± 16.6 years, and the mean TSH level prior to testing was 2.1 ± 1.5. During this period, patients underwent an average of 4 ± 3.5 neck ultrasounds and 2.9 ± 1.6 FNAs. Among the cohort, 26 patients (8.7%) were Arabs, 16 (5.4%) were Orthodox Jews, and 96 (33%) had a low socioeconomic score. Fifty-two percent of the tests (156 patients) yielded benign Results Among the suspicious findings, NRAS mutations were identified in 13 cases (10%), BRAF V600E in 8 cases (6%), and HRAS in 6 cases (5%). Within the study period, 38 patients underwent thyroidectomy following Afirma testing.

Conclusion

Afirma testing prevented surgery in 52% of patients. The inclusion of Afirma testing in Clalit Health Services facilitated access to advanced diagnostics for patients with lower socioeconomic status, who represented 33% of the cohort, thus reducing healthcare disparities in Israel.

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P1114

JOINT3789

The increased coexistence of autoimmune thyroid disease (AITD) in children and adolescents with differentiated thyroid carcinoma (DTC) in years 2015–2024 compared to 1996-2000; one center experience

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Introduction

37 thyroid carcinomas were diagnosed in our region in years 1996–2000, 30 in girls (81.1%) and 7 in boys (19.9%). The predominance of papillary thyroid

carcinoma (PTC - 26/37 - 70.3%) compared to follicular thyroid carcinoma (FTC - 10/37 - 27.0%) and medullary thyroid carcinoma (MTC -1 - 2.7%) was observed. AITD (autoimmune thyroiditis – AIT and Graves' disease - GD) coexisted in 1 PTC/GD among all DTCs (1/36 - 2.8% of all DTCs and 3.8% in PTC group) (Med Pediatr Oncol 2004;42:84–92).
Aim
The aim of retrospective study was to analyze the coexistence of AITD (AIT and GD) and DTC in years 2015-2024 (10-year-period) in relation to years 1996–2000 (5-year-period).
Material and Methods
Patients aged <18 years with the postoperative histopathological diagnosis of DTC were analyzed. All patients had prior ultrasound examination and US-guided fine needle biopsy of a suspicious nodule/area and thyroid aspirates were classified based on Bethesda system. AITD was confirmed/treated prior or at diagnosis of DTC by the presence of a classic clinical manifestation, hormonal profile and ultrasonographic imaging of both autoimmune thyroid disorders, AIT and GD, confirmed by specific antithyroid antibodies in serum (TPOAb/TgAb/TRAb).
Results
75 thyroid carcinomas were confirmed in 2015–2024 (71 PTC - 94.7%, 1 FTC - 1.3% and 3 MTC - 4.0%), 57 in girls (76%) and 18 in boys (24%). MTCs were not enrolled to this analysis however all three cases had negative antithyroid antibodies. AITD was diagnosed in 37/72 (51.4%) of patients with DTC, i.e. 18-fold more frequently than in 1996–2000. A single patient with FTC had no features of thyroid autoimmunity. 5 more patients had isolated and mildly elevated TgAb (up to 3-fold to an upper limit of normal range).
Conclusions
High coexistence of PTC and AIT in years 2001–2015 suggests that the careful follow-up of patients with AIT, particularly with ultrasound examination, is mandatory to detect the cancer at early stage in this group of patients.

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P1115

JOINT4038

Total thyroidectomy vs thyroid lobectomy for low-risk papillary thyroid cancer

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Introduction
Papillary thyroid carcinoma (PTC) has a rising incidence and a good prognosis in low-risk cases. The choice of surgery in low-risk papillary thyroid carcinoma (PTC) is important in order to balance recurrence rates and surgical complications.
Objective
To evaluate whether the extent of thyroidectomy influences survival and recurrence rates in patients with low-risk-PTC.
Methods
A retrospective analysis was conducted for all patients treated at our institution who had low-risk papillary thyroid carcinoma and underwent either lobectomy or total thyroidectomy(TT), between 2015-2021. Exclusion criteria included patients treated with radioactive iodine post-surgery and those without complete postoperative follow-up. Recurrence was defined as the presence of structural evidence of disease(confirmed by cytology or post-contralateral lobectomy histology), or biochemical recurrence, defined as a serum TG value >30 ng/mL with stable TSH in patients with lobectomy, or positive ATG($>$ 115) with an upward trend.
Results
Fifty patients who underwent thyroidectomy were included. The preoperative cytology was malignant in 27%. TT was performed in 25 patients, 80% female, with a mean age of 60 years and a mean follow-up time of 9 years. The lobectomy group included 25 patients, 92% female, with a mean age of 63 years and a mean follow-up time of 10 years. Tumor size was similar between both groups (0.7 cm for TT and 0.6 cm for lobectomy). Biochemical recurrence occurred in 4 patients from the lobectomy group: 2 with elevated TG and no suspicious lesions found on ultrasound, who are being managed with active surveillance; 1 with rising ATG and a 5 mm nodule with subcentimetric lymph nodes, also under active surveillance; and 1 with a suspicious nodule and a doubling of TG levels over 3 months, for whom TT will be performed. No recurrences were observed in the TT group. There was no significant difference in disease-free survival between groups. Hypothyroidism developed in all TT patients and 92% of lobectomy patients, with higher levothyroxine doses in the TT group (115.8 ± 27.3 mg vs 71.5 ± 49.4 mg). Surgical complications were more common in the TT group, including transient dysphonia(20% (5/25) vs 12%(3/25) and transient hypoparathyroidism(in 8% (2/25). Overall, 4 patients were discharged, 1 passed away unrelated to thyroid cancer, and the remaining 45 continued follow-up.
Conclusion
This study suggests that the extent of thyroidectomy does not influence survival in low-risk PTC, and lobectomy may be a suitable option due to lower rates of hypothyroidism and postoperative complications. However, these data need to be confirmed in multicenter studies.

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P1117

JOINT235

Rituximab in addition to methylprednisolone pulse therapy for graves' orbitopathy improves the remission of graves' hyperthyroidism

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Background
Graves' disease (GD) frequently recurs following the cessation of anti-thyroid drugs (ATDs), particularly in patients with concomitant Graves' orbitopathy (GO), which poses additional therapeutic challenges. This clinical epidemiological study aimed to evaluate the efficacy of intravenous methylprednisolone (IVMP) therapy alone or in combination with rituximab (RTX) in achieving long-term remission of GD in patients with moderate-to-severe and active GO.
Methods
This study involved a cohort of 52 patients with moderate-to-severe and active GO treated at the National Taiwan University Hospital from 2008 to 2023. Patients who received IVMP or RTX in addition to IVMP for the treatment of GO were enrolled. Demographic and clinical data, thyroid function tests, and thyroid autoantibodies were collected. The primary outcome measured was the time to remission from GD, defined as the maintenance of euthyroidism for more than 12 months after stopping the antithyroid drug.
Results
Among the 52 patients, 35 were treated with only IVMP and 17 with RTX after IVMP. The RTX group demonstrated a significantly higher remission rate compared to the IVMP group (58.8% vs. 17.1%, $P = 0.002$). The Kaplan-Meier curve revealed an evident likelihood of the RTX group on the rate of GD remission (log-rank test, $P=0.0086$). Multivariate analysis identified several predictors of remission, including RTX use with thyrotropin-binding inhibitory immunoglobulin (TBII) levels less than 88%, BMI within the range of 19.7 and 24.1, and the age of IVMP initiation, highlighting the potential benefits of RTX therapy in this context.
Conclusions
The addition of RTX to IVMP for patients with moderate-to-severe GO significantly increases the likelihood of achieving and sustaining remission of GD, particularly in those with TBII levels less than 88%. These findings suggested that incorporating RTX into the therapeutic protocol for patients with GO could be a valuable strategy to improve long-term disease control and achieve remission of GD.

Multivariate analyses of the Predictors of Time to Remission of GD Using Cox's Models in Patients with GO.

Covariate	Estimated Regression Coefficient	Estimated Standard Error	Wald's Chi-Square Test	*P* Value	Estimated Hazard Ratio	95% Confidence Interval
TBII $\leq$ 88% $\times$ Rituximab use	1.8726	0.5981	11.4117	0.0007	6.5049	2.1849–21.9584
TBII $>$ 88%	-1.7997	1.6140	2.1434	0.1432	0.1654	0.0012–1.6316
19.7 $<$ BMI $\leq$ 24.1	2.1137	0.6847	11.6861	0.0006	8.2786	2.3887–34.4155
Age of IVMP initiation (years)	2.2324	0.7533	9.5348	0.0020	9.3220	2.2577–43.7287
Male vs. Female	-1.5702	0.7887	4.6077	0.0318	0.2080	0.0407–0.8764

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P1118

JOINT1840

The role of blood cell derived parameters in the differential diagnosis of subacute thyroiditis and Graves' disease and long-term outcomes in subacute thyroiditis: a tertiary center experience

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Background
Subacute thyroiditis (SAT) and Graves' disease (GD) are characterized by thyrotoxicosis with different treatment approaches. It may not always be easy to distinguish these two diseases. We aimed to evaluate the utility of blood cell derived parameters in the differential diagnosis of SAT and GD. Additionally, we investigated the factors affecting the development of recurrence and permanent hypothyroidism in the patients with SAT.
Methods
The study involved 414 patients with SAT, 415 patients with GD, and 92 healthy controls. Pre-treatment hematological parameters were retrospectively compared, especially in cases where differentiation is challenging, including painless SAT, acute phase reactants negative SAT, and TSI, TRAB (Thyroid Stimulating Immunoglobulin, TSH-receptor-antibodies) negative GD. Factors influencing recurrence and permanent hypothyroidism were also analyzed in SAT group.
Results
When compared with the GD group, ratios of neutrophil/lymphocyte (NLR), platelet/lymphocyte (PLR), systemic inflammatory response index (SIRI), systemic immune inflammatory index (SII) and pan immune inflammation value (PIV) were significantly higher, while large unstained cells percentage (LUC%) and the ratios of eosinophil/monocyte (EMR), eosinophil/lymphocyte (ELR), eosinophil/neutrophil (ENR), eosinophil/platelet (EPR), MPV/neutrophil, MPV/monocyte and MPV/platelets were significantly lower in the SAT group. Among these markers, SII with an optimal cutoff of 652,784 showed the best diagnostic value [area under the curve (AUC) = 0.875; 95% confidence interval (CI): 0,85-0,90; $P < 0.001$; sensitivity, 81%; specificity, 80%]. No significant association was observed between these parameters and recurrence or permanent hypothyroidism. Recurrence occurred in 8% and permanent hypothyroidism developed in 26% of the patients with SAT. Recurrence was not observed in the group receiving NSAIDs or in those who remained untreated, whereas 15% of patients treated with methylprednisolone (MPS) experienced recurrence ($P < 0.001$). When comparing patients with and without recurrence in MPS group, pre-treatment TSH were significantly higher in the recurrence group, while fT3 and fT4 were significantly lower (p: 0.04, 0.048 and 0.03 respectively). In the univariate logistic regression analysis, we found that low fT4 levels in the MPS group increased the risk of recurrence (Hazard ratio: 0.46, 95% CI=0.23-0.93, $P = 0.032$).
Conclusion
Differentiation between SAT and GD can be reliably achieved using blood cell derived parameters, and that these markers are also applicable in groups where differentiation is challenging. To the best of our knowledge, this is the first study to investigate the LUC%, ELR, ENR, EPR, MPV/neutrophil, and MPV/monocyte ratios and revealed that they are significantly different between these two diseases.

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P1119

JOINT1845

The association between subcategorization, cytomorphological features, ultrasonographic characteristics, ACR and EU-TIRADS classifications with surgical outcomes of aus nodules

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Background
Nodules diagnosed in the atypia of undetermined significance (AUS) category represent a heterogeneous group with an indeterminate risk of malignancy. This study aimed to investigate malignancy rates in AUS subcategories and to examine the association of malignancy with cytomorphologic features in fine-needle aspiration (FNA) and ultrasonographic characteristics.
Methods
This study analyzed 196 thyroid nodules with AUS cytology that underwent surgical resection, Among these, 176 nodules were classified as AUS-Nuclear (AUS-N), while 20 were categorized as AUS-Other (AUS-O). Cytomorphological and ultrasonographic features, along with the American College of Radiology Thyroid Imaging Reporting and Data System (ACR-TIRADS) and the European Thyroid Imaging Reporting and Data System (EU-TIRADS) classifications, were analyzed to assess the association between malignancy and AUS subcategories.
Results
Risk of malignancy (ROM) for AUS nodules was determined to be 19,4% (21% for AUS-N and 5% for AUS-O, $P = 0,132$). We observed that malignancy was more frequently associated with nodules of smaller maximum diameter ($P = 0.003$). A significantly higher ROM was observed in nodules with an oval shape, solid composition, hypoechogenicity, irregular margin and microcalcification (Odds Ratio (OR): 5,83, 2,24, 2,31, 9,75 and 3,34 respectively). The presence of irregular margins was found to independently increase the risk of malignancy by 6,53-fold, regardless of other sonographic features. A statistically significant difference in ROM was observed across ACR and EU-TIRADS categories within the AUS nodules ($P = 0.005$ and 0.003, respectively) and the AUS-N group ($P = 0.001$ and $P = 0.002$, respectively). In the AUS-O group, no significant results were observed for either system ($P = 0.3$ for both). A marked increase in ROM was observed with nuclear enlargement, overlapping, hyperchromasia, and pseudoinclusions (OR: 3.33, 2.17, 3.31, and 4.55, respectively), while oncocytic atypia was associated with a reduced risk (OR: 0.44). The presence of pseudoinclusion and nuclear overlapping were found to significantly increase malignancy risk independently of other factors (OR:7,99 and 5,50 respectively). Repeat AUS FNAs ($P = 0.07$), were found to significantly increase the ROM.
Conclusion
We found that the ROM in AUS nodules, particularly in the AUS-N category, were higher than those reported in the literature. We established an association between cytomorphologic features and malignancy. To the best of our knowledge, we are the first to report an increased malignancy risk linked to nuclear hyperchromasia in AUS nodules and the association between ACR-TIRADS and the AUS-N subcategory.

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P1120

JOINT1852

Fear of recurrence in thyroid papillary cancer: a risk based comparison

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Background
Papillary thyroid cancer (PTC) exhibits a high long-term survival rate in contrast to other types of cancer. Despite its favorable prognosis, fear of cancer recurrence (FCR) is common among thyroid cancer survivors. The prognosis of ATA (American Thyroid Association) low-risk disease is more favorable than for intermediate and high-risk diseases. However, FCR has also been observed in patients with low-risk PTC. The aim of the study was to compare the FCR in low-risk PTC patients to that of patients in the intermediate and high-risk groups and to examine the factors influencing FCR.
Material&Methods
The present study was conducted on a total of 240 patients diagnosed with PTC between September 2023 and November 2024. The patients were categorized into low risk, intermediate risk, and high risk, according to the ATA risk-stratification system. Each patient completed two questionnaires with the assistance of the same physician. The first was the Fear of Recurrence Inventory (FCRI), which evaluates the fear or anxiety of cancer recurrence; higher scores indicate a greater level of fear. The second was the Beck Anxiety Inventory (BAI), which measures the intensity of anxiety. A multiple linear regression model was utilized to identify the independent determinants of the FCRI score.
Results
132 patients were classified as low risk, 86 as intermediate risk, and 22 as high risk based on the ATA risk stratification. FCRI scores were found to be similar between low risk (56.50, 24.25-80.50), intermediate risk (50.50, 27.25-73), and high risk (47.50, 35.75-73.25) patients ($P = 0.895$). There were no significant differences in FCRI scores in terms of gender, marital status, education level, and radioactive iodine (RAI) status ($P = 0.085$, $P = 0.724$, $P = 0.857$, and $P = 0.148$, respectively). Patients with a disease duration of one to five years had a higher FCRI score (61, 43.50-84.50) in comparison to those with a disease duration of less than one year (50.50, 23.75-71.75) or more than five years (43, 21-70) ($P = 0.03$). A moderate level of correlation was identified between FCRI and BAI scores ($r = 0.441$, $P < 0.001$). FCRI scores of the three ATA risk groups exhibited no significant differences across the four BAI categories (minimal, mild, moderate, and severe) ($P = 0.932$, $P = 0.968$, $P = 0.562$, and $P = 0.100$, respectively).

Conclusion
FCR was found to be similar between ATA low risk, intermediate risk, and high risk groups, despite the good prognosis. Therefore, appropriate psychosocial care for these patients should be provided at the time of diagnosis and during follow-ups.

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P1121

JOINT3361

A case of pendred syndrome presenting due to thyroid nodule

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Introduction
Pendred Syndrome is an autosomal recessive syndrome characterized by congenital sensorineural hearing loss and goiter. It is seen as a result of mutation in the SLC26A4 gene, which encodes the chloride/iodine/bicarbonate transporter known as pendrin, which causes organification disorder of iodine in the thyroid gland. The transmembrane protein pendrin is secreted from the inner ear, kidney and bronchial epithelial cells in addition to the thyroid gland. Mutations in the SLC26A4 gene have also been reported in cases of enlarged vestibular aqueduct (EVA) accompanied by deafness.
Case Presentation
An 11.5-year-old girl patient was referred to the pediatric endocrinology clinic due to a thyroid nodule detected incidentally. It was learned that the patient's 3.5-year-old brother was receiving L-thyroxine treatment due to congenital hypothyroidism, her mother had a total thyroidectomy due to a thyroid nodüle (3 cm size), and her mother's aunt had a history of multinodular goiter. It was also learned that the patient had a cochlear implant at the age of three due to congenital sensorineural hearing loss, had attention deficit hyperactivity disorder, and wore glasses due to myopia. The patient, who was not related to her parents, had no other known history of hearing loss in her family. In her physical examination, her weight and height are within the normal range for her age, thyroid stage 2 goiter, puberty stage 3. Thyroid function tests were euthyroid, anti thyroglobulin: 1484 IU/mL (0-115) anti TPO: normal thyroglobulin: 76 ng/mL (0.73-84) there was no iodine deficiency. Thyroid ultrasonography reported increased thyroid gland size, slightly heterogeneous parenchyma and several bilateral cystic nodules, the largest of which was 5 mm in size in the lower pole of the right lobe. In light of these findings, the patient underwent a full gene sequence analysis with a preliminary diagnosis of Pendred Syndrome. A homozygous pathogenic variant c.919-2A>G (IVS7-2A>G) located in the splice region of the SLC26A4 gene was detected.
Conclusion
Pendred Syndrome, the most common syndromic form of deafness, is an autosomal recessive disease associated with developmental abnormalities of the cochlea and diffuse goiter (with/without hypothyroidism). The development of goiter and hypothyroidism is closely related to iodine intake. In addition to presentation with solitary thyroid nodule, cases of thyroid carcinoma have also been reported. Treatment is based on clinical findings. Patients with Pendred Syndrome should be followed up by a multidisciplinary team including otolaryngology, endocrinology, genetics and surgery.

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P1122

JOINT3922

Predictors of initial remission in patients treated with antithyroid drugs for graves' disease

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Introduction
Graves' disease (GD) is the most common cause of hyperthyroidism. Patients with GD are typically treated with one of three medical interventions: antithyroid drugs (ATDs), radioactive iodine (RAI) therapy, or thyroidectomy. The majority of patients begin treatment with ATDs, with current clinical guidelines recommending a treatment duration of 12 to 18 months. This study aims to compare the clinical characteristics of patients with Graves' disease who achieved remission after optimal medical treatment with those who were resistant to therapy, and to identify factors that predict remission.
Methods
This retrospective cohort study reviewed medical charts from 2020 to 2024. Patients who achieved euthyroidism with medical treatment within 18–24 months and remained relapse-free for at least one year after therapy cessation were classified as having achieved remission. Patients who failed to attain euthyroidism despite 18–24 months of medical treatment, could not discontinue therapy, or required definitive treatment for these reasons, were classified as non-remission. Of the 565 Graves' patients, 108 met the inclusion criteria for the study. After completing antithyroid drug therapy, patients were divided into remission ($n = 64$) and non-remission ($n = 44$) groups. Predictive factors analyzed included age, gender, smoking history, presence of orbitopathy, thyroid volume, thyroid function tests (TSH, free T3, and free T4), TSH receptor antibody (TRAB) levels, and systemic inflammatory parameters (systemic immune inflammation index [SII], pan-immune-inflammation value [PIV]) at the time of initiation.
Results
There were no significant differences in age or gender between the remission and non-remission groups ($P = 0.918$ and $P = 0.727$). However, in the non-remission group, FT4, FT3 levels, TRAB levels, and thyroid volume were significantly higher compared to the remission group [(3.7 ± 2.1 vs. 2.5 ± 1 ng/dl; $P < 0.001$), (13.8 ± 5.8 vs. 9.3 ± 4.8 ng/l; $P < 0.001$), (13.1 ± 9 vs. 4.6 ± 3.5 IU/l; $P < 0.001$), (26.6 ± 15.4 vs. 12.2 ± 4.4 mL; $P < 0.001$)]. Smokers and patients with Graves' orbitopathy were more prevalent in the non-remission group ($P = 0.03$ and $P = 0.004$). There were no significant differences in SII and PIV values between the groups. In multivariate regression analysis, lower thyroid volume and lower TRAB titers were identified as independent predictors of remission (OR [95% CI]: 1.620 [1.213–2.164]; $P = 0.001$, OR [95% CI]: 1.287 [1.081–1.532]; $P = 0.005$).
Conclusion
This study suggests that ultrasonographic thyroid volume measurements and TRAB titers at the time of diagnosis in Graves' disease could serve as valuable prognostic indicators for predicting disease remission.

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P1123

JOINT1696

Extracellular vesicles as a novel immunotherapeutic strategy in hashimoto's thyroiditis: advances in targeted delivery technologies

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Hashimoto's thyroiditis (HT), the leading cause of hypothyroidism, is characterized by a dysfunction of regulatory T cells (Tregs), resulting in a breakdown of self-tolerance and a chronic immune-inflammatory response driven by intra-thyroidal lymphocytic infiltration. The persistence of pro-inflammatory cytokines (e.g., IFN-γ, IL-17) and chemokines (e.g., MCP-1) fuels the autoimmune attack on the thyroid, highlighting the inflammatory cascade as a promising therapeutic target, particularly in the early stages of the disease. In recent years, extracellular vesicles (EVs) derived from mesenchymal stem cells (MSCs) have garnered increasing attention in regenerative medicine due to their ability to transfer the immunomodulatory properties of their cells of origin. Harnessing these properties, our study investigates the impact of Th1 priming on the cargo of small EVs (sEVs) derived from human fibroblast-like limbal mesenchymal stem cells (f-LSCs) and their capacity to modulate the activation state of peripheral blood mononuclear cells (PBMCs) in HT patients. To this end, f-LSC-derived sEVs were isolated using tangential flow filtration (TFF) and extensively characterized through dynamic light scattering, flow cytometry, and western blot analysis. Furthermore, an optimized single-step freeze-drying protocol was developed to enable stable EVs storage, facilitating future clinical applications. PBMCs from HT patients and healthy controls were exposed to sEVs under pro-inflammatory conditions to assess their effects on T cell proliferation and immune modulation. The ex vivo model developed in this study demonstrated that TFF isolation combined with lyophilization enhances EVs stability and preserves their bioactivity while reducing financial and instrumental constraints. Notably, Th1 priming enriched the bioactive protein cargo of sEVs, leading to a dose-dependent modulation of key inflammatory mediators (e.g.,

MCP-1, IL-2) and an increased presence of immunomodulatory proteins such as COX-2 and Hsp70. These molecular changes promoted Treg activity, suggesting that sEVs may serve as carriers of proteins capable of restoring a functional Treg population. In conclusion, our findings position EVs as a promising immunotherapeutic tool for HT, leveraging cutting-edge delivery technologies to optimize their therapeutic potential. The ability to tailor EVs cargo through Th1 priming opens new avenues for precision medicine, offering innovative strategies to modulate immune dysregulation in autoimmune thyroid diseases.

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P1124

JOINT1461

CD74+ thyrocytes in hashimoto's thyroiditis: a potential therapeutic approach

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Introduction

Hashimotós thyroiditis (HT) is an autoimmune thyroid disorder (AITD) that result from the dysregulation of the immune system tolerance, leading to an immune response against self-thyroid antigens. Thyroid follicular cells (TFCs) display a key role in antigen presentation due to the acquisition of the major histocompatibility complex II (MHC-II) in a proinflammatory environment. CD74 is the invariant chain of MHC-II and collaborates in the endosomal trafficking and the assembly of this complex. The antigen presentation process requires costimulatory signals to reinforce the contact between the antigen presenting cells and the receptor immune cell. Hereby, CD80 and CD86 display a key role as correceptors of MHC-II. Regarding the contribution of TFCs to HT pathogenesis, we evaluated the role of CD74 in TFCs from HT patients.

Methodology

We analyzed CD74 and CD80 expression in thyroid tissue from controls and HT patients by spatial transcriptomics and immunofluorescences (IF). We measured the expression of these markers in a human thyroid cell line *in vitro* model with the stimulation of proinflammatory cytokines (IFN-γ and TNF-α) by western blot (WB), IF and flow citometry. Furthermore, we established coculture assays of thyrocytes with a T lymphocyte cell line (Jurkat E6.1) in combination with a CD74 inhibitor (milatuzumab) and we evaluated the levels of CD69 and CD25 as T cell activation markers.

Results

We observed a significant increase of CD74 expression in tissue from HT patients compared to controls. Interestingly, CD74 staining was associated to CD80 only in TFCs from HT patients. In the *in vitro* model, IFN-γ and TNF-α increased the expression of CD74, CD80 and MHC-II. The use of milatuzumab could partially revert the increase of antigen presentation markers in thyroid cells and reduced the activation of T cells, suggesting a role of CD74 in antigen presentation and T cell activation.

Conclusions

Our data suggests a role of CD74 in HT pathogenesis. The use of milatuzumab as a CD74 inhibitor may represent a potential therapy to ameliorate immune cell reactivity.

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P1125

JOINT2855

Method related differences in fT4 immunoassays are marked in the hyperthyroid range and support the need for assay standardisation

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Introduction

Measurement of free thyroxine (fT4) is challenging because of its picomolar concentrations, intricate equilibrium with binding proteins, and the minute fraction of "free" relative to total hormone. Method related differences in fT4 measurement may be under-appreciated by clinicians and laboratories alike, which has implications for the clinical management of patients with thyroid disease. To capture these differences, we undertook a multi-method study comparing fT4 immunoassays on the platforms most widely used in Australia: Roche Cobas, Abbott Architect, Siemens Atellica, Beckman DxI and Ortho Vitros.

Methods

fT4 was measured in 94 serum samples spanning the clinical dynamic range, from severe hypothyroidism to euthyroid status and severe hyperthyroidism. For completeness, TSH and fT3 were also measured in parallel. Passing & Bablok linear regression was performed relative to the Roche assay which was chosen as an arbitrary gold standard.

Results

Passing & Bablok regression generated the following equations: Abbott fT4 = 0.5503*Roche fT4 + 3.944; Siemens fT4 = 0.945*Roche fT4 + 1.549; Beckman fT4 = 0.800*Roche fT4 -0.331 and Vitros fT4 = 1.204*Roche fT4-1.685. Method related differences in fT4 results were subtle in the hypothyroid range, became more pronounced with increasing fT4, and were marked in the hyperthyroid range. There were also notable differences in the analytical range of each assay, with some (eg Siemens) capturing a more than two-fold wider linear range than others (eg Abbott). In comparison, method-related differences in TSH were minor and differences in fT3, though more conspicuous than TSH, were smaller than fT4 method-related differences.

Discussion

Method related differences in fT4 lead to conspicuous differences in the apparent biochemical severity of hyperthyroidism. In patients with severe hyperthyroidism, measured fT4 concentrations on the Siemens, Roche and Ortho platforms were between 2-3 times higher than the Abbott platform, which showed only modest fT4 levels and was conspicuously flat in the hyperthyroid range. Interestingly, the one-step fT4 immunoassays (Roche, Siemens and Ortho) were much more closely aligned and read significantly higher than the two-step assays (Abbott and Beckman). Our study points to the clinical value of standardising fT4 methods and highlights the risks of monitoring hyperthyroid patients across laboratories using different methods. Method related differences may masquerade as biochemical worsening or improvement of disease, even in the absence of true change, and may confound dosing of anti-thyroid medication and other clinical decision making.

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P1126

JOINT3620

Thyroid nudules in girls with mccune-albright syndrome(MAS) and gnrh independent precocious puberty concurrently

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Background and Objectives

Thyoid abnormalities were regarded common in McCune-Albright syndrome(-MAS), however, thyroid nudular may be more than abnormalites of thyroid function. The aim of this study is to detect the prevalence of thyroid nudular in girls who was diagnosed MAS and had GnRH independent precocious puberty as the initiation manifestation.

Methods

From 2019 to 2024, 65 girls who had the precocious puberty as the first manifestation and were diagnosed MAS, as well as had thyroid ultrasoud inspection were enrolled in our study, the prevalence of thyroid nudules was analysed and was compared with 89 normal girls.

Results

The age of onset of precocious puberty was 3.44 ± 2.03 years old, and the age at thyroid ultrasound detction was 10.91 ± 5.66 years. In this 65 girls, 29 (44.6%) were found thyroid nudular, while in normal girls, only 15 (16.9%) were detected thyroid nudular, and the difference was significant($P < 0.001$). In MAS grils with thyroid nudules, 17 were nodular goiter (58.6%), the others were follicular cyst (37.9%) and diffuse goiter (3.4%).18 cases (62.0%) were bilateral, while 11 (37.9%)were unilateral. In whom, only 2 had hyperthyroidism, and the other 2 had hypothyroidism. Anti-thyroid antibodies were negtive in all girls. 21 girls Ti-RADS grade were less than 3, 7 were grade 3 and only 1 was grade 4. Duration of follow-up was 0.5-6 years, and fine-needle aspiration biopsy was performed in 2 patients, however, no malignancy were found.

Conclusion

In girls with MAS and has precocious puberty concurrently, abnormalities of thyroid ultrasound dection were more prevalent than prevalence of hyperthyroidism or hypothyroidism. In addition to evaluatiion of thyroid function, thyroid ultrasound examination should also be considered and the follow-up of thyroid nudular is recommended.

Key words
thyroid, McCune Albright syndrome, GNAS gene, precocious puberty,.
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P1127

JOINT2267

Re-emergence of iodine deficiency-induced thyroid disorders in children: a comprehensive review and meta-analysis

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Background
Iodine, a micronutrient, plays a vital role in thyroid hormone production. Despite worldwide efforts to combat iodine deficiency through salt iodization programs, a primordial prevention, recent findings indicate a resurgence of thyroid disorders caused by iodine deficiency, such as hypothyroidism and endemic goitre among children. This comprehensive review and meta-analysis aim to evaluate the prevalence, contributing factors, diagnostic indicators, and the effects of iodine supplementation on thyroid health among children.
Methods
A comprehensive literature search was conducted in databases like PubMed, Scopus, and Web of Science, following PRISMA guidelines. The analysis included studies that examined iodine deficiency, urinary iodine concentration (UIC), thyroid function markers (TSH, Free T4), and the efficacy of iodine supplementation in children. During last decade, data from five selected studies were synthesized using a random-effects model to estimate both the prevalence of iodine deficiency disorders (IDD) and the impact of iodine supplementation on thyroid function. The I^2 statistic was used to quantify the degree of variability among experiments.
Results
The meta-analysis estimated that 7.8% (95% CI: 5.4% -10.2%) of children experience iodine deficiency-related thyroid disorders, highlighting a persistent issue despite ongoing iodization programs. The average urinary iodine concentration reported across studies was 126 µg/l (95% CI: 110-142 µg/l), with mild iodine deficiency identified in certain populations. Key risk factors included increased consumption of non-iodized salt, restrictive diets (such as veganism or allergy-based exclusions), and modifications in food processing that reduce iodine levels. The analysis further demonstrated that iodine supplementation significantly lowered TSH levels by 3.2 mIU/l (95% CI: 1.8 - 4.5 mIU/l, $P < 0.01$) and increased free T4 levels by 0.6 ng/dl (95% CI: 0.3-0.9 ng/dl, $P < 0.05$), confirming its effectiveness in reversing thyroid dysfunction. The heterogeneity analysis indicated moderate variation among studies ($I^2 = 45\%$), underscoring the need for further extensive research.
Conclusion
Findings suggest a concerning resurgence of iodine deficiency-related thyroid disorders in children, particularly in populations with dietary restrictions or decreased intake of iodized salt. Iodine supplementation has proven beneficial in restoring thyroid function, yet public health measures must be strengthened to ensure sufficient iodine consumption through continuous food fortification, dietary assessment, and educational initiatives. Future large-scale epidemiological studies and controlled trials are required to refine iodine supplementation approaches and prevent a further rise in IDD cases.

Keywords
Iodine Deficiency Disorders (IDD), Endemic Goitre in Children, Thyroid Function and Nutrition, Iodine Supplementation.
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P1128

JOINT870

Genetic characterization of congenital hypothyroidism with gland *in situ*: findings from a cohort of italian pediatric patients

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Over the past few decades, the diagnosis of congenital hypothyroidism with a thyroid gland *in situ* (CH-GIS) has significantly increased, partially due to the widespread implementation of newborn screening programs. Although recent advancements in genetic research have enabled the identification of a genetic etiology in approximately 40-60% of CH-GIS cases, the etiology of this condition remains not completely understood.
Methods
In this study, we performed Targeted Next Generation Sequencing (NGS) of 18 thyroid-related genes in 78 pediatric patients with CH-GIS identified through newborn screening in Emilia-Romagna, Italy, from 2003 to 2021. All patients were diagnosed with permanent CH after diagnostic reevaluation. The goal was to genetically characterize this cohort, identify pathogenic variants, and explore the correlation between genotype and clinical phenotype.
Results
NGS analysis revealed 72 potentially pathogenic allelic variants (AVs) in 44 out of 78 patients, distributed across 10 genes: DUOX2, DUOXA2, GLIS3, IYD, NKX2-5, SLC26A4, TG, TPO, THRB, and TSHR. Of these, 78% were in genes involved in thyroid hormone synthesis, with DUOX2 being the most frequently affected gene (34.7%). We identified 25 AVs not previously reported, mostly missense mutations (18/25). A monogenic inheritance pattern was suggested for 22 patients: 8 with a single variant in a dominant gene and 14 with two variants in the same gene. Nine patients exhibited two or more variants in different genes, suggesting oligogenic inheritance. Additionally, 13 patients had a single variant in genes with autosomal recessive inheritance. Regarding the genotype-phenotype relation, the 14 patients with two AVs on the same gene presented a more severe phenotype, with median blood TSH levels of 200 µU/mL at diagnosis (significantly higher than other groups, $P = 0.006$), lower fT4 levels ($P = 0.002$) and an increased need for levothyroxine at 36 months of age.
Conclusion
NGS is a valuable diagnostic tool for the etiological characterization of CH-GIS. The confirmation of a relationship between genotype and clinical phenotype found in our population allows us to state that the early application of NGS can help define the etiologic diagnosis and plan appropriate follow-up. Despite this, in line with what has already been reported in the literature, abou half of the cases in our sample remain partially or completely genetically unsolved, highlighting the need for further investigation into alternative etiopathogenetic mechanisms.

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P1129

JOINT3871

Improving hormonal balance in the treatment of pediatric congenital hypothyroidism: the role of combined LT4-LT3 therapy

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Introduction
Congenital hypothyroidism (CH) is managed with levothyroxine (LT4) to normalize TSH levels. However, LT4 monotherapy does not always ensure adequate tissue euthyroidism due to variability in peripheral conversion of thyroxine (T4) to triiodothyronine (T3). The FT3/FT4 ratio has emerged as a sensitive marker of thyroid hormone balance, with a persistently low ratio suggesting suboptimal T3 availability, as T3 is the biologically active hormone primarily generated from peripheral T4 conversion. This study investigates whether the addition of liothyronine (LT3) to standard LT4 therapy can restore a physiological FT3/FT4 ratio in pediatric CH patients.
Methods
15 pediatric CH patients with an altered FT3/FT4 ratio, despite normal or high-normal TSH and FT4 levels, were enrolled. Notably, 53% of patients had TSH and FT4 within range but with FT4 value at the upper limit and TSH at the high-normal threshold, making LT4 dose adjustments challenging. LT3 was introduced gradually, targeting an LT4:LT3 dose ratio between 10:1 and 20:1 to approximate physiological hormone production. Thyroid function tests (TSH, FT4, FT3, FT3/FT4 ratio) were evaluated according to age-specific reference ranges and measured at baseline, within six months of LT3 initiation, upon FT3/FT4 ratio normalization, and at a subsequent stability evaluation.
Results
At baseline, all patients exhibited an altered FT3/FT4 ratio, suggesting inadequate conversion of T4 to T3. Following LT3 introduction, FT4 levels decreased significantly ($p=0.0005$), while FT3 increased modestly, leading to progressive normalization of the FT3/FT4 ratio. The 92% of patients who achieved a normalized FT3/FT4 ratio, remained stable at the final follow-up ($p<0.0096$). Correlation analysis suggested that even small LT3 doses contributed significantly to optimizing thyroid balance.

Parameters	Pre-therapy w/LT3	1° evaluation	2° evaluation	3° evaluation	p-value
TSH (mcU/mL)	5.49(1.27-7.58)	2.53(0.70-8.13)	2.64(0.78-5.48)	2.16(2.16-3.6)	*0.349*
FT4 (pmo/l)	25.67(±6.32)	21.40(±3.00)	19.31(±2.7)	19.11(±2.33)	**0.0005**
FT3 (pmol/l)	6.69(±0.63)	9.96(±0.70)	6.92(±0.70)	7.04(±0.72)	*0.230*
FT3/FT4	0.29(±0.04)	0.36(±0.03)	0.38(±0.02)	0.39(±0.05)	**0.0037**

Conclusion
Our results suggest that the addition of LT3 to standard LT4 therapy can help restore a physiological FT3/FT4 ratio in pediatric CH patients with altered peripheral conversion. This approach may provide a more physiologic thyroid hormone balance, where LT4 monotherapy fails to optimize tissue hormone availability. While these results highlight the potential benefits of combination therapy, careful titration dose and monitoring therapy remain crucial. Future studies with larger cohorts and long-term follow-up are needed to refine treatment strategies and personalize the management of CH.

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P1131

JOINT19

Metabolic dysfunction-associated steatotic liver disease and the risk of thyroid cancer: a complication of systemic metabolic disorder

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Background
Metabolic dysfunction–associated steatotic liver disease (MASLD) represents a hepatic manifestation of metabolic syndrome. This study investigated the association between MASLD and the risk of thyroid cancer in a Korean population.
Methods
After excluding individuals with a history of liver disease or malignancy, we analyzed a cohort of 214,502 Korean adults aged 40 and above who participated in the National Health Screening Program from 2009 to 2010. Participants were categorized into four groups; no SLD without a cardiometabolic risk factor (CMRF), no SLD with at least one CMRF, MASLD, and metabolic and alcohol related/associated liver disease (MetALD). SLD was diagnosed using a fatty liver index threshold of $\geq$30. The primary outcome was the diagnosis of new thyroid cancer during the follow-up period. We examined the relationship between CMRF/SLD and thyroid cancer incidence using the Cox proportional-hazards model with adjustments for multiple variables.
Results
A total of 2,761 participants (1.3%) were newly diagnosed with thyroid cancer over an average follow-up of 9.61 years. Compared with participants without CMRF and SLD, those with CMRF (hazard ratio [HR] 1.33, 95% CI 1.16-1.52), those with MASLD (HR 1.36, 95% CI 1.17-1.58), and the MetALD group (HR 1.40, 95% CI 1.04-1.88) exhibited a significantly higher risk of thyroid cancer. In addition, MetALD significantly associated with thyroid cancer incidence solely in men.
Conclusion
In addition to CMRF, MASLD and MetALD was associated with an increased risk of thyroid cancer in the Korean population. This study is the first to demonstrate the association between thyroid cancer and the CMRF-MASLD-MetALD continuum.

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P1132

JOINT3526

Grave's orbitopathy: an atypical presentation

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Introduction
Grave's orbitopathy (GO) is an autoimmune disorder most commonly associated with Graves' disease (GD). It is typically manifested by exophthalmos, chemosis, and palpebral retraction. We report the case of a patient with GO presenting without exophthalmos and with normal MRI findings.
Observation
A 25-year-old female patient was referred for further management of GO. Hyperthyroidism was diagnosed in the presence of diplopia. The initial ophthalmological examination revealed partial paralysis of the medial branch of cranial nerve III, ptosis, and paralysis of the right superior rectus muscle, without exophthalmos. Initial cerebro-orbital MRI was unremarkable, showing intact oculomotor muscles and normal appearance of the optic nerves and chiasm. The initial thyroid function tests revealed FT4 at 68 pmol/l (reference range: 13-24 pmol/l) and TSH $<$0.01 mU/l (reference range: 0.5-5 mU/l). The patient was started on methimazole and oral corticosteroids. However, there was no improvement in the ophthalmological examination. A second cerebro-orbital MRI showed hypertrophy and inflammation of the inferior right oculomotor muscle, with T2 hyperintensity, T1 isointensity, and strong enhancement following gadolinium administration. The patient received three doses of methylprednisolone (1 g daily for three consecutive days), with a marked improvement in her diplopia at the two-week follow-up.
Conclusion
This case highlights the diagnostic challenges of GO, which may mimic other conditions and present in atypical forms. It should be considered in any patient with an oculomotor abnormality, particularly in young women. Repeated imaging is recommended even when initial imaging results are normal.

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P1133

JOINT1069

Management of low-risk differentiated thyroid carcinomas in nuclear medicine: a retrospective study of 280 cases

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Introduction
The risk stratification for recurrence of differentiated thyroid carcinomas, as outlined by the 2015 American Thyroid Association (ATA) guidelines, has enabled a therapeutic de-escalation, particularly for patients classified as low-risk for recurrence.
Materials and Methods
This monocentric retrospective study held within the Nuclear Medicine Unit of the Central Military Hospital of Algiers, follows a total of 280 patients, initially classified as low-risk according to the 2015 ATA criteria (pT1bN0/NxMx, pT2N0/NxMx), who after total thyroidectomy, received 1.1 GBq (30 mCi) of iodine-131 after thyrotropin stimulation (with either of the follwoing processes: rhTSH or thyroid hormone withdrawal) for ablation purposes. Thyroglobulin (Tg) and anti-thyroglobulin antibodies (ATg) levels were measured after thyrotropin stimulation, along with a cervical ultrasound, conducted 9 to 12 months post-treatment for all patients.
Results
Out of the 280 patients, 265 showed a complete biological response and a normal cervical ultrasound, resulting in a success rate of 94.6%.
- A cranial metastasis was identified in one patient.
- Four patients presented loco-regional metastasis (metastatic cervical adeonpathies).
- Ten patients presented an incomplete biochemical response with a negative cervical ultrasound and responded well to a second course of iodine-131 treatment.
Discussion
The results of our study are consistent with those of the ESTIMABL 1 study (98% remission), which allowed us to avoid overtreatment in more than 97% of patients. Additionally, dose reduction minimizes treatment-related side effects and has a considerable economic and organizational impact.
Conclusion
The use of low-dose iodine 131 (1.1Gbq), demonstrate excellent outcomes, yielding comparable results to higher dose treatment in low-risk differentiated thyroid carcinoma, ensuring optimal patient care, all the while reducing the economic and the organizational burden associated with former protocols.

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P1134

JOINT1555

A study on the correlation between hyperthyroidism and bone metabolism & bone mass in children

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Objective
To explore the alterations in bone metabolism and bone mass in children with hyperthyroidism, both before and during puberty.
Methods
Children newly diagnosed with hyperthyroidism from January to December 2024 were recruited and categorized into two groups: pre-pubertal and pubertal. A control group of healthy children from the same period was also included. Bone metabolism markers, including bone glaprotein (BGP), type I procollagen amino-terminal propeptide (PINP), type I collagen carboxy-terminal (β-CTX), alkaline phosphatase (ALP), 25-hydroxyvitamin D (25(OH)D), and bone mineral density (BMD), were measured in both untreated hyperthyroid children and healthy controls.
Results
Pre-pubertal hyperthyroid children: Significant differences were observed in BGP (167.33±79.21), PINP (1062.96±151.36), ALP (298.28±74.19), β-CTX (1.10±0.35), and 25(OH)D (79.67±19.11) compared to the control group ($P < 0.05$). However, no significant difference was found in BMD ($P > 0.05$). Pubertal hyperthyroid children: Significant differences were observed in BGP (151.81±81.23), ALP (252.71±87.90), β-CTX (1.14±0.56), and 25(OH)D (66.12±19.27) compared to the control group($P < 0.05$). No significant difference was found in PINP ($P > 0.05$). However, a significant difference was observed in BMD (-1.19±1.47) compared to the control group ($P < 0.05$).
Conclusion
Pre-pubertal children with hyperthyroidism exhibit increased bone metabolism. Pubertal children with hyperthyroidism experience bone loss.
Key Words
Hyperthyroidism, bone metabolism, bone mass, pre-pubertal children, puberty.
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P1135

JOINT1818

Levothyroxine absorption test with daily levothyroxine dose: preliminary results in patients with refractory hypothyroidism

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Introduction
Levothyroxine is the mainstay treatment of hypothyroidism. However, more than 15% of levothyroxine-treated patients failed to achieve the recommended serum TSH, due to either malabsorption, increased metabolism of thyroxine (T4) or non-adherence to treatment. A levothyroxine absorption test can differentiate true malabsorption from non-adherence or pseudo-malabsorption. Multiple protocols of levothyroxine absorption test have been published with differences in test doses, formulations, test duration, frequency of blood collection, absolute or relative peak or increments of total or free T4, and thresholds for normal absorption.
Patients and Methods
143 patients (109 women), mean (±SE) age 42±1 years, body mass index 25.5±0.5 kg/m^2, were treated after total thyroidectomy for benign ($n = 71$) or malignant ($n = 41$) diseases, autoimmune thyroiditis ($n = 29$), congenital ($n = 5$), central ($n = 4$) and post-radioiodine ($n = 3$) hypothyroidism, with levothyroxine alone ($n = 137$) or in association with liothyronine ($n = 6$). The mean daily dose of levothyroxine was 3.27±0.9 μg/kg. After an overnight fast, the first blood sample (baseline) was taken; then patients absorbed the daily levothyroxine dose and blood samples were drawn every 2 hours during 24 hours. Serum TT4 and FT4 concentrations were evaluated in all samples, TSH concentrations were measured before and 24-hour after levothyroxine absorption.
Results
Prior intake of levothyroxine, baseline TT4, FT4 and TSH concentrations were 7.6 ± 0.2 μg/dl, 12.5 ± 0.4 pg/ml and 25.1 ± 3.3 mU/l respectively, demonstrating refractory primary hypothyroidism ($n = 139$). After orally levothyroxine intake, TT4 and FT4 concentrations increased at 9.4 ± 0.2 μg/dl and 15.8 ± 0.5 pg/ml ($P < 10^{-3}$), respectively. TT4 and FT4 levels peaked after 4.2 ± 0.2 and 4.3 ± 0.3 hours, respectively. TT4 increments were diminished in chronic gastritis ($n = 19$, 1.20 ± 0.23 μg/dl, $P < 0.01$), Helicobacter pylori infection ($n = 15$, 1.58 ± 0.2 μg/dl, $P = 0.02$) and proton pump inhibitor treatment ($n = 9$, 1.74 ± 0.2 μg/dl, ns) attesting decreased levothyroxine absorption in such patients. There were no adverse events reported by the patients during the levothyroxine absorption test.
Conclusion
Levothyroxine absorption test can be achieved via the absorption of daily dosage of levothyroxine with the evaluation of TT4/FT4 levels over 4 – 6 hours follow-up. The test is clinically well tolerated. In clinical practice, more studies are necessary in patients with refractory hypothyroidism due to either factors interfering with levothyroxine absorption or T4 metabolism or to pseudo-malabsorption.
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P1136

JOINT2692

Familial thyroid hormone resistance: a case series of two sisters with THRß mutation

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Introduction
Resistance to thyroid hormone beta (RTHβ) is a rare, typically autosomal dominant genetic disorder, caused by mutations in the *THRB gene*, encoding thyroid hormone receptor beta (TRβ*)*, leading to impaired responsiveness to thyroid hormone in tissues expressing TRβ. While affected individuals often present with elevated circulating free thyroxine (FT4) and free triiodothyronine (FT3) alongside non-suppressed thyroid-stimulating hormone (TSH), clinical manifestations, ranging from overt symptoms to asymptomatic presentations, complicate diagnosis. This case series highlights phenotypic variability and management of RTHβ in two sisters.
Case Report
The older sister, a 24-year-old woman, was referred to an endocrinologist during her first pregnancy at 26 weeks of gestation for elevated FT3: 4.19 pmol/mL (N 1.58–3.91) with other thyroid function tests normal. Thyroid ultrasound suggested possible autoimmune thyroiditis. She was started on L-thyroxine (50 mg daily), but follow-up two months later showed elevated FT4: 26.05 pmol/l (N 7.87–20.3) and FT3: 6.56 pmol/l (N 3.34–5.14) and non-suppressed TSH: 3.9 mU/l (N 0.4–3.6). Thyroid antibodies were negative. After delivering a healthy baby, L-thyroxine was discontinued. During her second pregnancy, she again had elevated FT4: 30.54 pmol/l and FT3: 6.65 pmol/l with a non-suppressed TSH: 3.52 mU/l. No treatment was initiated, thyroid hormone levels were monitored throughout pregnancy. Genetic testing confirmed a pathogenic heterozygous mutation in the *THRB* gene (c.1291A>T, p.Ile431Leu). She delivered another healthy, lower-birth-weight non-carrier baby. The younger sister, a 17-year-old female, underwent genetic testing after her sibling's diagnosis. Asymptomatic with no thyroid dysfunction on examination, she showed elevated FT4: 30.19 pmol/l and FT3: 7.13 pmol/l, with a non-suppressed TSH: 2.80 mU/l and negative thyroid antibodies (antiTPO, antiTg, antiTSH). Genetic testing confirmed the same *THRB* (c.1291A>T, p.Ile431Leu) mutation. Clinical management focused on monitoring thyroid function without initiating thyroid hormone suppression or beta-blocker therapy due to the absence of symptoms. Functional testing using a luciferase reporter assay in Jeg-3 cells showed reduced affinity of TRβ2-I341L (EC0 I341L vs WT: 9.1 [7.8-10.6] vs 0.71 [0.69-0.74] nM, $p<0.001$). The T3-affinity of the mutant was significantly reduced, as evident from a ~13-fold higher EC50 for T3 compared to wild-type in the reporter assay.
Conclusion
This family case demonstrates the phenotypic variability of RTHβ, ranging from pregnancy-associated thyroid dysfunction to an asymptomatic carrier state. It underscores the importance of familial genetic screening in diagnosing RTHβ and highlights the need for individualized, symptom-based management strategies to avoid overtreatment while ensuring appropriate monitoring for potential complications.
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P1137

JOINT1230

Differentiated thyroid cancer in acromegaly: increased risk, unaltered outcomes

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Introduction
Acromegaly is associated with an increased risk of cancer compared to the general population. Differentiated thyroid cancer (DTC) has been reported to be the most common type of malignancy in acromegaly. Whether DTC in patients with acromegaly are more aggressive is controversial.
Methods
The data of 14 acromegaly patients diagnosed with DTC and 42 non-acromegaly patients with DTC matched for age and sex (1:3) were retrospectively analyzed.
Results
In a cohort of 184 patients diagnosed with acromegaly, DTC was diagnosed in 14 (7.6%) patients. The mean age at DTC diagnosis was 49 ± 6.12 years. The

Table 1: Comparison of pathological and clinical features of acromegaly patients with DTC and non-acromegaly patients.

Parameter	DTC with acromegaly ($n = 14$)	Control group ($n = 42$)	*P* value
Tumor diameter (mm)	12.5 (IQR: 4.50 – 27.25)	7.0 (IQR: 4.75 – 11.25)	0.122
Multifocality (n, %)	5 (%35)	18 (%43)	0.638
Extracapsular invasion (n, %)	6 (%42)	7 (%17)	0.054
Lymph node metastasis (n, %)	2 (%14)	13 (%31)	0.223
Stage (n, %) -Stage 1 -Stage 2	13 (%93) 1 (%7)	40 (%95) 2 (%5)	0.732
RAI (n, %)	7 (%50)	18 (%43)	0.642
Total RAI dose (mCİ)	100 (IQR: 100 – 100)	100 (IQR: 75 – 131.25)	0.986
Response (n, %)			0.588
-Excellent response	13 (93%)	36 (%86)	
-Biochemical incomplete response	1 (7%)	3 (%7)	
-Structural incomplete response	0 (%)	3 (%7)	

median time from diagnosis of acromegaly to DTC was 36 months (IQR: 8.25 - 71.75). Two patients were diagnosed with PTC 12 months and 44 months before diagnosis of acromegaly, respectively. Five (37%) of the patients with acromegaly have active disease at the time of DTC diagnosis, 7 (50%) of them was in remission. Regarding the histological subtypes, 7 (50%) of them were classical subtypes, 6 (43%) of them were follicular subtypes and one (7%) of them was an oncocytic subtype Comparison of pathological and clinical features of acromegaly patients with DTC and non-acromegaly patients with DTC is summarized in table 1.

Conclusion

The incidence of thyroid cancer is increased in patients with acromegaly when compared to the general population. This phenomenon may be attributed to enhanced awareness, screening, and early detection bias. Our study concluded that patients with acromegaly did not demonstrate a more aggressive course. A longer follow-up period and the inclusion of a higher number of DTC patients may support the long-term validity of the present data.

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P1138

JOINT2084

Association of extra-thyroidal abnormalities and genetic variants in congenital hypothyroidism: a single-centre study

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Introduction

Extra-thyroidal abnormalities are common in congenital hypothyroidism (CH). This study aimed to investigate the frequency of extra-thyroidal abnormalities in CH cases and the relationship between extra-thyroidal disease and the genetic causes of CH.

Methods

Patients with CH were screened for non-thyroid congenital anomalies, and a thyroid genetic panel was analyzed using next-generation sequencing. The panel included the following genes: *NKX2-5, PAX8, PHEX, POR, SERPINA7, SLC16A2, SLC26A4, SLC26A7, SLC5A5, ALB, DIO1, DIO2, DIO3, DUOX1, DUOX2, DUOXA2, FOXE1, GLIS3, GNAS, IGSF1, SLC6A4, TG, THRA, TPO, TRH, TRHR, TSHB, TSHR, TTR, ZNF607, THRB*. Patients' data were obtained retrospectively from hospital records.

Results

The study included 77 patients (29 females and 48 males) diagnosed with CH. Among CH patients, 5 had central and 72 had primary hypothyroidism. The most common etiology was dyshormonogenesis (89.6%). Fifty-one variants were detected in 43 of the 77 patients who requested a genetic panel for CH etiology. *TG* variants were found in 10 patients, *ALB* in 8 patients, *TSHR* in 8 patients, *TSHB* in 5 patients, *TPO* in 4 patients, *THRA* in 4 patients, *POR* in 3 patients, *SLC26A4* in 2 patients, *PAX8* in 2 patients, *DUOX2, GNAS, PHEX, SLC16A2, THRB* variants in 1 patient each. The genetic panel detected pathogenic variants in 10 patients (13%), likely pathogenic variants in 14 patients (18.2%), variants of uncertain significance in 19 patients (24.7%), and no variants in 34 patients (44.2%). L-thyroxine treatment was discontinued in 14% (6 patients) of patients in whom a genetic variant was detected. In contrast, the withdrawal rate was 47.1% (16 patients) in cases without variants ($P = 0.002$). In the screening for anomalies accompanying CH, 26 patients (33%) had congenital anomalies. Cardiac anomalies were found in 8 patients, genitourinary anomalies in 7, central anomalies in 7, dysmorphic features in 5, musculoskeletal anomalies in 3, gastrointestinal anomalies in 1, and ocular anomalies in 2. Multiple system anomalies were observed in four patients. Genetic variants were reported in 16 of 26 patients with congenital anomalies, whereas 10 patients with extra-thyroidal anomalies had no genetic variants.

Conclusion

This study has showed that about one third of CH patients had non-thyroidal abnormalities, most commonly cardiac abnormalities. Identifying genetic mutations that cause CH may help elucidate the phenotype-genotype relationship of extra-thyroidal disorders and contribute to early diagnosis and feasible and appropriate treatment for these patients.

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P1139

JOINT746

Chronotype and daytime sleepiness in patients with hashimoto's thyroiditis

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Introduction

The hypothalamic–pituitary–thyroid axis controls the circadian clock via the suprachiasmatic nucleus. Chronotype refers to a person's natural preference for sleep-wake cycles and twenty-four-hour activity patterns. Daytime sleepiness, constant fatigue, and increased daytime sleepiness are common in many diseases, including Hashimoto's thyroiditis (HT). The evening chronotype may be associated with higher thyrotropin (TSH) levels and a higher risk of hypothyroidism. Concurrently, sleep disorders have become a serious public health problem as they impair endocrine function. The aim of the study was to estimate the association between thyroid status, chronotype, and daytime sleepiness among HT patients.

Material and Methods

The study included 115 patients, 106 women and nine men (43 ± 12 years of age) with clinical, ultrasound, and laboratory-confirmed HT. We used the short Morningness-Eveningness Questionnaire (rMEQ) to assess chronotype and the Epworth Sleepiness Scale (ESS) to evaluate daytime sleepiness. Based on chronotype, patients were categorized into intermediate + morning chronotype ($rMEQ > 11$) and evening chronotype ($rMEQ \leq 11$) groups. Patients were, based on the ESS, further categorized into those with normal daytime sleepiness ($ESS \leq 10$) and those with increased daytime sleepiness ($ESS \geq 11$).

Results

Most patients had normal daytime sleepiness (71.3%), and most of them had an intermediate chronotype (60.9%), while only one patient had a morning chronotype (0.9%). Age was significantly associated with chronotype ($\chi2 = 499.278$; $P = 0.012$), with younger patients tending to have an evening chronotype. A significant association was observed between chronotype and thyroglobulin antibodies (TgAb) ($\chi2 = 898.614$; $P = 0.008$) and TSH levels ($\chi2 = 833.323$; $P = 0.033$). Daytime sleepiness was also significantly associated with TgAb ($\chi2 = 1667.721$; $P = 0.050$), TSH ($\chi2 = 1531.095$; $P = 0.050$) and fT3 ($\chi2 = 618.605$; $P = 0.024$). Free triiodothyronine (fT3) levels were significantly higher in patients with intermediate + morning chronotype than in the evening ones ($Z = -2.160$; $P = 0.031$), while no significant differences in thyroid parameters were found between normal and increased daytime sleepiness.

Conclusion

Only 38.3% of patients had an evening chronotype, and only 28.7% had increased daytime sleepiness. The evening chronotype is associated with a higher rate of HT. Sleep affects the secretion of thyroid hormones and leads to a decrease in the amplitude of the circadian rhythm for TSH. The underlying mechanisms are not fully understood and require further investigation. Grant No. IP-FDMZ-2024.2025-09.

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P1140

JOINT3402

miRNA expression profiles in thyroid tumors with nras q61r variant

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Objective
The *NRAS* Q61R variant is frequently observed in a range of thyroid tumors, including benign nodules, low-risk neoplasms, and malignant tumors such as follicular thyroid carcinoma (FTC) and papillary thyroid carcinoma (PTC). The presence of the Q61R variant alone makes it challenging to distinguish between benign and malignant lesions.
Methods
This study investigated miRNA expression profiles in 12 PTC, four FTCs, five low-risk carcinomas, 11 benign nodules, and 12 healthy thyroid tissues free of genetic alterations. The miRNA libraries for NGS sequencing were prepared from RNA isolated from fresh-frozen thyroid tissues using the QIAseq miRNA Library Kit (Qiagen). To compare miRNA expression between *NRAS* benign and malignant tissues, as well as between *NRAS*-positive and healthy tissues the miRge3.0 tool and DESeq2 package in R were used.
Results
NRAS-positive samples displayed significant miRNA expression changes compared to healthy tissues, with 125 miRNAs altered (50 upregulated, 75 downregulated). Noteworthy upregulated miRNAs included hsa-miR-221-3p, hsa-miR-221-5p, hsa-miR-222-3p. When comparing *NRAS*-positive benign nodules to malignant tumors, we identified significant changes in the expression of 33 miRNAs. Malignant samples showed marked increases in miRNAs such as hsa-miR-520a-5p and hsa-miR-519d-3p, while hsa-miR-9-5p significantly decreased.
Conclusion
These data suggest distinct miRNA expression profiles that may help differentiate benign from malignant thyroid tumors with the *NRAS* Q61R variant. *Supported by AZV NU21-01-00448 and MH CZ RVO 00023761..*

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P1141

JOINT438

Unraveling clinical clues for deciphering thyroid nodule malignancy

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Background
While most nodules are benign and asymptomatic, certain characteristics may indicate malignancy, prompting fine needle aspiration biopsy. Factors like age and gender affect cancer risk, complicating ultrasound-based risk systems. We aimed to determine whether the cytological malignancy rate of thyroid nodules could be adjusted for several clinical parameters.
Methods
Data from patients aged 18 and above with thyroid nodules assessed via Fine Needle Aspiration (FNA) were retrospectively reviewed. Malignancy classification was based on cytopathology and histopathology Results The study examined how various clinical parameters, adjusted for the ACR TI-RADS category, affected thyroid nodule malignancy rates, including age, sex, Body Mass Index (BMI), nodule size, presence of autoimmunity, and thyroxine therapy. Additionally, we analyzed the performance of ACR TI-RADS in predicting malignant cytology across different age subgroups of thyroid nodules.
Results
The study included 1128 thyroid nodules from 1001 adult patients, with a median age of 48 years and predominantly female (76.68%). Univariate analysis revealed age, sex, and nodule size as risk factors for malignant cytology. For each year of age, there was a 2.33% reduction in the OR for malignant cytology (95% CI: 1.1%-3.1%; P = <0.001). Male sex and nodule size were risk factors for malignant cytology with OR of 1.47(95% CI: 1.10 – 1.95; $P = 0.009$) and 0.94 (0.93 - 0.96; $P < 0.00$), respectively. The multivariate logistic regression analysis involving 1128 thyroid nodules, adjusted for ACR TI-RADS categories, sex, and nodule size, showed a 2.5% reduction in the OR for malignant cytology for each year of age. cIntragroup analysis was performed in each group of ACR TI-RADS (TR3, TR4, and TR5) nodules ($n = 705$) where FNA was indicated. In ACR TI-RADS 3 category nodules, only age strongly predicted malignancy. ROC analyses revealed a diameter of >34 mm as the cut-off value with the best sensitivity and specificity (Youden index 0.564, Sensitivity 83.3 %, and Specificity 73.1%). There was a 4.3% decrease in the odds of malignancy for each year of age increase in patients in the ACR TI-RADS 4 category. For every one-year increase in age, there was a 2.1% decrease in the odds of malignancy for patients in the ACR-TIRADS 5 category.
Conclusion
Raising the size threshold for recommending FNA of TR3-3 nodules and incorporating patients' age and gender into the evaluation process could enhance the system's accuracy in assessing thyroid nodules and guiding clinical management decisions.

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P1142

JOINT3163

Differences between pediatric and adult treatment protocols in differentiated thyroid carcinoma: need for transitional guidelines for adolescents

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Introduction
The presentation and outcome of differentiated thyroid carcinoma (DTC) differ significantly between pediatric and adult patients, leading to distinct guidelines for each group. Adolescents may receive different treatment on either pediatric or adult protocols, raising the question whether this distinction is justified or if a dedicated guideline for adolescents is needed. A critical first step in addressing this issue is a systematic comparison of pediatric and adult DTC guidelines to identify key differences.
Methods
A national review of Dutch pediatric (2020)[1] and adult (2024)[2] DTC guidelines was conducted, categorizing differences as concordant, discordant or partially concordant.
Results
Of the recommendations in both guidelines, 32% are concordant, 47% are discordant, and 21% are partially concordant. The main difference is a more de-escalating approach to managing adult DTC patients, guided by a validated risk classification system. In contrast, no such validated risk classification system exists for pediatric DTC patients. For pediatric cases, total thyroidectomy followed by radioactive iodine treatment is recommended for all patients with tumors >1 cm. In adults, this approach is clearly indicated only for high-risk DTC patients.
Conclusions
The management of DTC differs significantly between pediatric and adult patients, which can result in adolescents receiving vastly different treatment strategies depending on whether they are classified under pediatric or adult protocol at diagnosis. Relying solely on age may not be appropriate, as other factors beyond age are increasingly recognized to play a critical role in determining the most appropriate treatment strategy. The next step is to collaborate with a multidisciplinary team to develop evidence-based guidelines for adolescents (15-25 years), identify research gaps, and plan further studies to develop tailored recommendations for more personalized treatment strategies.

Table 1. Overview of the management of DTC in a 17-year old- vs 18-year old patient.

2 cm tumor and no signs of lymph node or distant metastasis		
Age:	17 years old	18 years old
Surgery:	Total thyroidectomy *Thyroid hormone replacement therapy*	Hemithyroidectomy *Categorized as low risk*
RAI therapy:	Yes	No
TSH level:	0.5-1.0 mU/l	0.5-2.0 mU/l
Re-stratification	No	Yes, one year after initial treatment Excellent response: TSH level normal reference

Abbreviations: RAI: Radioactive iodine; TSH: Thyroid stimulating hormone.

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P1143

JOINT3557

A novel biallelic intronic variant in the TG gene associated with thyroid dyshormonogenesis and fetal goiter

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Background
Biallelic pathogenic variants in the *Thyroglobulin*(*TG*) gene have a well-established correlation with congenital hypothyroidism (CH) due to thyroid dyshormonogenesis (TDH), frequently associated with congenital goiter. The phenotypic spectrum is highly variable. Here, we describe a novel homozygous intronic *TG* variant in a family with recurrent congenital goiter and demonstrate its pathogenic impact through its transcript analysis.
Case Report
The proband, a 15.5-year-old male, was referred for a thyroid nodule. He had a prenatal diagnosis of goiter and was started on L- thyroxine postnatally due to CH. Born at term (3100 g) via spontaneous delivery, he required intensive care due to respiratory distress. He has been on L-thyroxine since infancy, with age-appropriate neurodevelopment. His parents were first-degree cousins, and his mother had a previous pregnancy complicated by fetal goiter. At presentation, his height and weight were 164.5 cm(-1.1SDS), and 73.5kg(0.8SDS), respectively. The thyroid gland was enlarged, and systemic examination was unremarkable. Thyroid ultrasound showed diffuse heterogeneity with fine septations and a 9 mm solid nodule. During follow-up, the iso-hypoechoic nodule increased to 14×9.5 mm. Fine needle aspiration biopsy (FNAB) initially indicated atypia of undetermined significance (Bethesda 3), later raising suspicion for follicular/-Hurthle cell neoplasm (Bethesda 4). Right lobectomy and isthmectomy revealed adenomatoid hyperplasia with oncocytic changes and reduced colloid. The presence of congenital goiter in both the proband and sibling with fetal goiter raised suspicion of TDH. Serum TG levels were markedly low (0.2 ng/mL;range: 3.5–77 ng/mL). Targeted next-generation sequencing identified a *novel* homozygous *TG* variant (NM_003235): c.5686+3A>C/p.(?) Parents were heterozygous. This variant was classified as a variant of uncertain significance (VUS) (PP3, Pm^2) according to ACMG criteria. *In silico* prediction tools defined a splice-altering effect, with strong pathogenicity scores. The variant was absent from gnomAD. A prenatal ultrasound in the mother's new pregnancy detected fetal goiter, prompting in-utero L-thyroxine. Segregation analysis confirmed the homozygous variant. To assess its splicing impact, RNA from peripheral blood (proband and affected sibling) was reverse-transcribed into cDNA, amplified by PCR, and sequenced. The splicing analysis confirmed aberrant exon skipping, specifically predicted in-frame skipping of exon 30 leading to c.5549_5686del/-p.(Leu1851Cys (;)1852_1896del) with loss of 45 residues from type IIIA and type IIIB repeat regions (UniProt).
Conclusion
This study identifies a novel *TG* splice-site variant, expanding the genetic landscape of CH. Functional RNA analysis confirmed its pathogenicity by demonstrating aberrant splicing. Our findings underscore the importance of early genetic diagnosis in dyshormonogenesis, enabling timely genetic counseling.

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P1144

JOINT1575

Antithyroid drug therapy for pediatric graves' disease: a dose-effect relationship study of initial dose and short-term efficacy

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Purpose
To investigate the optimal initial dose of methimazole (MMI) in the treatment of pediatric Graves' disease (GD).
Methods
A retrospective analysis was conducted on clinical data from GD patients treated at our hospital between December 2015 and August 2023. Patients were further divided into low-dose (< 0.5 mg/kg/d) and high-dose (≥ 0.5 mg/kg/d) groups. A restricted cubic spline logistic regression analysis was used to assess the nonlinear relationship between the initial dose and the probability of normalizing free thyroxine (FT_4) within 30 days.
Results
The 324 GD patients ranged in age from 2.1 to 16.1 years. The mean initial doses for the mild, moderate, and severe groups in the low-dose and high-dose groups were 0.32±0.09 *vs.* 0.73±0.19, 0.39±0.08 *vs.* 0.71±0.18, and 0.35±0.09 *vs.* 0.73±0.17 mg/kg/d, respectively. There was no significant difference in the time to normalize FT_4 between the low-dose and high-dose groups for different severity categories ($P > 0.05$); however, the results of linear analysis showed that thyroid volume, initial dose and disease severity affected the days for FT_4 to return to normal. After adjusting for these factors, there was a nonlinear relationship between the initial MMI dose and the probability of normalizing FT_4 within 30 days, with the probability increasing until reaching a plateau at a dose of 0.58 mg/kg/d.
Conclusion
For patients with mild disease, an initial dose of 0.3 mg/kg/d is recommended. For those with moderate to severe disease, an initial dose of 0.5 to 0.6 mg/kg/d is recommended.

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P1145

JOINT3550

miRNA expression profiles in braf v600e positive thyroid tumors

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Objective
Thyroid tumours are more often diagnosed and prognosticated using molecular testing. Accounting for approximately 85-88% of cases, papillary thyroid

carcinoma (PTC) is the most common subtype of thyroid cancer. The *BRAF* p.(Val600Glu) variant is the most prevalent genetic alteration in PTC or papillary thyroid microcarcinoma (PTmC) and is associated with aggressive clinicopathological features and an increased risk of disease-related mortality. However, many of these aggressive features can only be identified postoperatively on histological specimens. The miRNA expression profile is an additional tool that is being explored in the diagnosis of thyroid cancer to help fill this gap in our knowledge.
Methods
In this study, we examined the expression profiles of miRNAs in PTC samples harbouring the *BRAF* p.(Val600Glu) variant, focusing on comparing the group of *BRAF*-positive PTC cases with indolent tumour behaviour (patients with T1/T2N0M0 without angioinvasion, persistence or recurrence) with more aggressive PTC cases (e.g. patients with lymphatic or distant metastases, angioinvasion, extrathyroidal invasion or radioiodine-refractory PTC). The QIAseq miRNA Library Kit (Qiagen) was used to generate miRNA libraries from fresh frozen thyroid tissue samples and for the bioinformatic comparison of the expression profiles, the miRge3.0 tool and the DESeq2 package in R were used.
Results
In *BRAF*-positive samples, a total of 80 miRNAs showed significantly altered expression (44 upregulated, 36 downregulated) compared to healthy thyroid tissue. The expression of 10 miRNAs exhibited significantly altered expression in more aggressive PTC cases - 7 miRNAs were significantly upregulated and 3 miRNAs were significantly downregulated. The most significant findings were upregulated expression of hsa-miR-642a-5p, hsa-miR-205-5p, hsa-miR-150-5p and downregulated expression of hsa-miR-520a-5p, hsa-miR-181d-5p and hsa-miR-3065-5p.
Conclusion
In conclusion, knowledge of the expression of miRNAs could be a useful tool for better prognosis. Our data suggest that the indolent and aggressive behaviour of PTC cases can be differentiated using miRNA expression profiles. Verification using a different method and the analysis of a larger set of samples are to follow.
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P1146

JOINT3555
miRNA expression profiles in medullary thyroid carcinoma with HRAS Q61R variant
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Objective
The Q61R variant is the most frequent genetic alteration in the *HRAS* gene. It is observed in benign nodules, low-risk neoplasms and even malignant tumors including medullary thyroid carcinoma (MTC). Pathogenic variants in the *HRAS* gene are the ones most frequently detected in *RET*-negative MTC, but their prognostic significance is still unclear due to their occurrence across both benign and malignant thyroid tissue. Also, the presence of the Q61R variant alone makes it difficult to distinguish MTC from thyroid tumors derived from follicular cells in fine needle aspiration biopsy (FNAB) samples.
Methods
This study investigated miRNA expression profiles in 12 MTC, 12 papillary thyroid carcinoma (PTC) and 6 benign nodules with *HRAS* Q61R variant. The miRNA libraries for NGS sequencing were prepared from RNA isolated from fresh-frozen thyroid tissues using the QIAseq miRNA Library Kit (Qiagen). To compare miRNA expression of *HRAS*-positive MTC with *HRAS*-positive benign tissues and *HRAS*-positive PTC the miRge3.0 tool and DESeq2 package in R were used.
Results
In *HRAS*-positive MTC, a significant change in expression was found for 238 miRNAs compared to *HRAS* positive benign thyroid nodules and for 232 miRNAs compared to *HRAS*-positive PTC. Some miRNAs with significant expression changes in MTC were the same compared to *HRAS*-positive benign thyroid nodules and *HRAS*-positive PTCs (e.g., increased expression of hsa-miR-224-5p, hsa miR-132-3p, hsa-miR-132-5p, hsa-miR-769-5p, hsa-miR 10a 3p and decreased expression of hsa-miR-181a-2-3p and hsa-miR-126-5p), others were unique and were only changed compared to *HRAS*-positive benign thyroid nodules (e.g., increased expression of hsa-miR-137-3p, hsa-miR-10a 5p and decreased expression of hsa-miR-190a-5p, hsa-miR-130b-5p) or *HRAS*-positive PTCs (e.g., increased expression of hsa-miR-212-3p, hsa-miR-330-3p and decreased expression of hsa miR 130a-3p, hsa-miR-551b-3p, hsa-miR-30a-5p).
Conclusion
These data indicate the presence of distinct epigenetic alterations, manifesting in the form of altered miRNA expression profiles that may distinguish MTC from thyroid nodules derived from follicular cells in FNAB with the *HRAS* Q61R variant. Subsequent to the present study, verification will be undertaken using an alternative method, and an analysis of a larger set of samples will be conducted.
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P1147

JOINT1058
The impact of dry eye disease on magnetic resonance imaging findings and quality of life in patients with graves' orbitopathy
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Introduction
Graves' orbitopathy (GO) is an autoimmune manifestation of Graves' disease (GD) affecting the orbit and the periorbital tissues. Among its other manifestations, an important percentage of patients experience symptoms of Dry eye disease (DED). The aim of this study was to investigate a possible association between DED and clinical, demographic, and imaging parameters of GO.
Material and Methods
This is a single-center observational study in an outpatient clinic of autoimmune endocrinopathies at a Tertiary, General, University Hospital between 09.2022-12.2024. Sixty-seven patients with GO were included in the study. We evaluated GO activity and severity parameters, functional and psychological well-being scores as assessed by the EUGOGO- GO Quality of Life Questionnaire, TSI levels. All patients underwent orbital MRI. Tear secretion was measured in all patients by applying a Schirmer test strip. Depending on the measured value, patients were divided into 4 subgroups: normal tear secretion (>15 mm), mild dry eye (10- 15 mm), moderate dry eye (5- 10 mm) and severe dry eye (<5 mm). Statistical analysis was performed using IBM SPSS Statistics version 26 and statistical significance was set at $P < 0.05$.
Results
Mean age was 52.34 $\pm$ 12.04 years (range 30–85 years) and 79.1% were females. We found that tear dysfunction severity was significantly associated with eye muscle involvement in MRI ($P = 0.005$), which was evident in all patients in the severe dry eye subgroup. IV contrast enhancement in MRI, indicative of active inflammation, was also positively correlated with dry eye severity ($P = 0.037$). Moreover, dysthyroid optic neuropathy (DON) was significantly associated with Schirmer categories ($P = 0.029$), with DON present in 25% of severe cases and 16.7% of moderate cases. Patients with moderate DED were older (mean $= 59.37$ $\pm$ 11.51 years) compared to those with normal tear function (mean $= 46.38$ $\pm$ 9.71 years, $P = 0.003$). Functional well-being scores were lower in severe dry eye cases (mean $= 13.08$ $\pm$ 3.25) compared to moderate cases (mean $= 17.78$ $\pm$ 4.78, $P = 0.039$).
Conclusion
In our study, we showed that there is a significant association between DED severity and older age, evident orbital MRI findings, DON and lower quality of life scores among patients with GO. Further prospective studies are needed to

confirm a possible correlation between DED severity and GO parameters, such as disease activity and TSI levels.

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P1148

JOINT1421

Risk of psychiatric disorders in patients with graves' disease: a nationwide population-based analysis

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Background

Graves' disease (GD) is an autoimmune hyperthyroidism and is associated with various psychiatric symptoms, such as irritability, mood changes, and insomnia. However, the epidemiological risk of psychiatric disorders among individuals with GD remains unclear. This study aimed to investigate whether a diagnosis of GD is associated with an increased incidence of various psychiatric disorders at a nationwide level.

Methods

This study was a retrospective cohort study using data from the Korean National Health Insurance Claims database. We identified 20,851 patients with newly diagnosed GD and 46,008 age- and sex-matched controls. Cox proportional hazards models were used to estimate the risk of incident psychiatric disorders in patients with GD compared to controls. We further analyzed the hazard ratios (HRs) by follow-up period (<2 years, ≥ 2 years) since the diagnosis of GD.

Results

Patients with GD exhibited a higher risk of developing psychiatric disorders compared to controls. The risk for incident depression (HR: 1.34, 95% CI: 1.24-1.44), bipolar disorder (HR: 1.57, 95% CI: 1.31-1.89), anxiety disorder (HR: 1.52, 95% CI: 1.43-1.63), and sleep disorder (HR: 1.44, 95% CI: 1.32-1.58) was significantly elevated. This increased risk for various psychiatric disorders, except schizophrenia, persisted even two years after the GD diagnosis. The association between GD and schizophrenia was not statistically significant.

Conclusions

This large-scale, population-based study demonstrates a significant association between GD and an increased risk of developing depression, bipolar disorder, anxiety disorder, and sleep disorder. The findings underscore the importance of long-term monitoring for psychiatric disorders in patients with GD.

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P1149

JOINT1525

Simultaneous occurrence of subacute thyroiditis and graves' disease

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background

Subacute thyroiditis (SAT) is a transient, post-viral inflammatory disorder of the thyroid gland characterized by transient thyrotoxicosis, neck pain, and eventual recovery of thyroid function. In some cases, hypothyroidism may develop due to glandular damage. The coexistence of SAT and Graves' disease (GD) is extremely rare, with only a few cases reported in the literature.

Patient findings

We report a case of the simultaneous occurrence of SAT and GD with active orbitopathy in a 46-year-old woman. The patient presented with malaise, generalized weakness, nausea, vomiting, neck pain, and orbitopathy symptoms persisting for approximately one month. Physical examination revealed a heart rate of 100 beats per minute, a diffusely enlarged and tender thyroid gland, conjunctival redness, eyelid swelling, and mild exophthalmos. Laboratory findings included: Thyrotropin (TSH) <0.01 mIU/l, Free thyroxine (FT4) $>$ 64.4 pmol/l, Free triiodothyronine (FT3) >30.7 pmol//l, Thyroglobulin 1038.52 ng/mL, Thyiroglobulin antibody 1.1 IU/mL, Thyroperoxidase antibody 19.1 IU/mL, Thyroid-stimulating hormone receptor antibody 19.1 IU/mL, Thyroid-stimulating hormone receptor antibody >40 IU/l, Erythrocyte sedimentation rate 85 mm/h, C-reactive protein 11.9 mg/dl and Interleukin-6 82 pg/mL. Thyroid ultrasound showed an enlarged, heterogeneous gland with hypervascularity. Ophthalmological examination confirmed active Graves' orbitopathy with a Clinical Activity Score (CAS) of 4–5/7 based on EUGOGO criteria. The patient was treated symptomatically with thyrosuppressive therapy and pulse corticosteroids for 12 weeks.

Conclusion

The simultaneous occurrence of SAT and GD, especially with active Graves' orbitopathy, is exceedingly rare. In this case, SAT-induced autoimmune alterations may have triggered the development of GD in a predisposed individual. This case highlights the importance of considering overlapping thyroid pathologies in complex clinical presentations.

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P1150

JOINT2986

Angioinvasion and multifocality in papillary thyroid cancer: identifying prognostic biomarkers

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Papillary thyroid carcinoma (PTC) represents the most prevalent malignancy of the thyroid gland and is generally associated with a favorable clinical trajectory. Nevertheless, a subset of cases exhibits a markedly more aggressive phenotype, often distinguished by angioinvasion and multifocality, both of which are significant prognosticators of increased locoregional invasion, heightened recurrence rates, and a greater propensity for distant metastases. These pathological features are strongly correlated with adverse clinical outcomes. Consequently, the identification of reliable molecular markers associated with angioinvasion and multifocality is paramount for refining risk stratification models and optimizing therapeutic decision-making, particularly in guiding the implementation of more extensive surgical interventions and early adjuvant radioiodine (RAI) therapy. Among the emerging molecular determinants implicated in tumor progression and neovascularization, thioredoxin (Thx) and tetraspanin 30 (CD63) have garnered significant attention. Thx, a critical modulator of redox homeostasis, has been linked to tumor proliferation, immune evasion, and metastatic dissemination, whereas CD63, a member of the tetraspanin superfamily, plays a pivotal role in tumor-endothelial interactions and vascular invasion. Given the established relationship between oxidative stress and poor prognosis in aggressive PTC variants, Thx and CD63 have emerged as promising biomarkers with potential mechanistic relevance to both angioinvasion and multifocality. This study included 20 patients diagnosed with PTC who exhibited both multifocality and angioinvasion. The reference cohort consisted of 45 patients without evidence of angioinvasion or multifocality, representing a very low-risk group following thyroidectomy. Serum levels of Thx and CD63 were quantified and analyzed for their association with aggressive histopathological features, followed by an assessment of their diagnostic performance using area under the curve (AUC) analysis. Both biomarkers were significantly elevated in patients with angioinvasive and multifocal PTC (Thx: $P < 0.001$, CD63: $P = 0.025$). Logistic regression analysis demonstrated a strong correlation between these biomarkers and aggressive tumor characteristics, supporting their potential role in vascular invasion and multifocality. Furthermore, multivariate regression confirmed their independent predictive value. Notably, a combined biomarker panel incorporating Thx and CD63 further improved the accuracy of risk stratification (AUC $= 0.87$), highlighting its potential clinical applicability in prognostication and personalized therapeutic decision-making for high-risk PTC cases.

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P1151

JOINT1764

C cell hyperplasia and multifocal papillary thyroid microcarcinoma in a patient with remarkably elevated basal and stimulated calcitonin levels

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Introduction
Medullary thyroid carcinoma (MTC) is calcitonin (CT) secreting tumor, originating from parafollicular thyroid cells. Serum basal and stimulated CT levels are helpful for early detection of MTC, while it is still a matter of debate whether it can differentiate between MTC, reactive and neoplastic C cell hyperplasia (CCH). According to the growth pattern CCH is subclassified into focal, diffuse and nodular. Neoplastic CCH -which is mostly nodular- precedes familial MTC, and often accompanies sporadic MTC with uncertain preneoplastic significance. Physiological CCH is associated with various conditions. It is not always possible to distinguish between these two based on C cell morphology. CCH is often found near differentiated thyroid lesions, and hypercalcitoninemia is not shown to be indicative of PTC.
Case Presentation
A 56 years old man was admitted to our hospital due to raised basal CT of 58.6 pg/mL, associated with incidentally discovered hypoechoic thyroid nodule measuring 9 mm by ultrasound. He had history of hypertension and hypokalemia, coxarthrosis, basal cell carcinoma and suspicion of polycythemia vera (PV). He was not obese, denied alcohol consumption and taking PPI. Basal CT in our institution was 34 pg/mL, CEA was normal. Calcium stimulation test was performed and the peak CT value of 893 pg/mL was highly suggestive of MTC. Laboratory analysis were consistent with the diagnosis of PV and hypokalemia with no other abnormalities. Thyroid-specific antibodies were negative and he was euthyroid. Thoracal CT scan, done for 6 mm pulmonary nodule on prior X ray scan, showed voluminous body of left adrenal gland. Autonomous cortisol secretion and catecholamine excess were excluded. Testing for primary aldosteronism was postponed and patient underwent total thyroidectomy. Histopathological examination revealed two bilateral microfoci of papillary thyroid carcinoma (1.5 and 0.5 mm), modest nodular hyperplasia, as well as focal, diffuse and nodular C cell hyperplasia (Calcitonin +) in both lobes of the thyroid. Testing for RET germline mutation is ongoing.
Conclusion
There are still no appropriate cut offs for discriminating MTC and neoplastic CCH from reactive forms, while it is sometimes hard to distinguish between reactive, neoplastic CCH and micro-MTC on histological evaluation. Thorough pathological search of whole specimen in cases with high CT levels is of great importance.

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P1152

JOINT1257

Re-considering wolff chaikoff effect in paediatrics

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The Wolff-Chaikoff effect refers to the temporary inhibition of thyroid peroxidase synthesis of thyroid hormone following excessive iodine exposure. Primary hypothyroidism has been reported in neonates, particularly very low birth-weight, following the use of iodine-based antiseptics and contrast agents. Thyroid function tests (TFTs) are not routinely monitored in this population. This case series describes 3 paediatric patients where severe hypothyroidism was (incidentally) detected following iodine exposure. Although typically transient, hypothyroidism can persist and evidence-based management protocols are lacking.
Cases
Three paediatric patients were referred to the Paediatric Endocrinology service for primary hypothyroidism following iodine exposure (cases summarised in table 1). All had prior TFTs, which were repeated post procedure for unrelated reasons. Cases 1 & 2 had iodine antiseptic exposure during laparotomy and bowel resection, while case 3 was exposed to an iodine-containing contrast agent (Omnipaque 240). Cases 1 & 3, with pre-exposure TSH elevation, were treated with thyroid hormone replacement due to persistent hypothyroidism.

Table 1

	Case 1	Case 2	Case 3
Gestation at birth	32+4	34	23+6
Iodine exposure procedure	Iodine antiseptic	Iodine antiseptic	Iodine contrast
Age at procedure in weeks (CGA)	14 (47/40)	154	13 (36/40)
TPO antibodies	ND	Negative	Negative
NBST for congenital hypothyroidism	NS	NS	NS
TFTs pre-exposure		Autoimmune encepha-	
Rationale for test	Pituitary screen	litis	Pituitary screen
Days prior to exposure	2	114	2
TSH mU/l (0.27-4.2)	10	0.1	15.4
fT4 pmol/l (11-21.2)	16.7	16.9	13.5
TFTs post exposure results (days)		Pituitary screen for	
Rationale for test	Prior TFTs abnormal	hypotension	Prior TFTs abnormal
First abnormal	2	2	3
Peak abnormal	5	5	10
First normal TSH	15	11	26
TFTs post-exposure (peak abnormal)			
TSH mU/l (0.27-4.2)	58.2	37	70.6
fT4 pmol/l (11-21.2)	5.2	5.5	9.7
Management			
Type Day commenced	L3/l4	-	L3/l4
post exposure	7	-	12
Treatment duration (months)	3 +	-	37 +
Current dose (mg/kg)	3	-	5

CGA Corrected gestational age; NBST New-born screening test; NS Not Suspected; ND No data; L3 liothyronine sodium; L4 levothyroxine; + Ongoing.

Conclusion
Wolff-Chaikoff effect should be considered in paediatric cases following high-dose iodine exposure. Although congenital hypothyroidism's neurodevelopmental impact is well-known, the effect of transient hypothyroidism is less understood, raising uncertainty about management. This series highlights two neonatal cases with pre-existing TFT derangements where hypothyroidism persisted beyond the typical period following iodine exposure. This underscores the need for careful iodine use and peri-exposure monitoring particularly in patients where thyroid abnormalities are already detected.

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P1153

JOINT1716

Variable phenotype of resistance to thyroid hormone due to a pathogenic THRA gene variant in a mother and her two daughers

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Background
Resistance to thyroid hormone (RTH) alpha is caused by pathogenic variants in the thyroid hormone receptor alpha (*THRA*) gene. Diagnosis is frequently delayed due to its rarity, association with near-normal thyroid function tests and variable nature of its clinical presentation. This report describes three family members exhibiting variable clinical and hormonal manifestations of RTH due to a heterozygous missense variant in the *THRA* gene.
Case Presentation
Two sisters, aged 5 and 2.5 years, presented with short stature and developmental delay. The oldest sister was born at 40 weeks of gestation with an average birth weight, length, and head circumference (HC). Between 6 and 20 months, she experienced faltering growth, although weight gain remained normal. She had chronic constipation and delayed language development with dysarthric speech. The younger sister was born at 38 5/7 weeks gestation, with a birth weight of -1.4 SDS, birth length of -1.2 SDS, and HC of -0.7 SDS. Postnatally, she exhibited limited catch-up growth, but a significant BMI increase after the age of 6 months. She had delayed tooth eruption, general hypotonia, and a delayed motor and language development. The mother had a history of learning problems, dysarthric speech, heart rhythm disorder, insulin resistance with hepatic steatosis. Her height was 159 cm and weight 105 kg. Her serum TSH (0.72 U/l) and fT4 (14.8 pmol/l) were normal. Clinical examination revealed in both sisters short stature (-3.8 SDS and -2.5 SDS), relative macrocephaly (HC +0.2 SDS and +0.9 SDS), and increased BMI (+1.5 SDS and +1.3 SDS), global hypotonia and hypermobility and additionally a facial dysmorphism (round face, full

cheeks, and an upturned nose) in the oldest girl. Biochemical testing showed low fT4, elevated fT3, normocytic anemia, and elevated serum copper in the youngest and normocytic anemia, normal serum FT4 but an elevated FT3/FT4 ratio and a normal serum copper in the oldest girl. Whole-exome sequencing revealed a maternally inherited, pathogenic missense variant (c.1207G > A, p.(Glu403Lys)) in the *THRA* gene in both sisters and the mother.

Conclusion

Missense variants in the *THRA* gene can result in a mild RTH phenotype with normal serum FT4 concentrations and remain undiagnosed during childhood. A familial history of delayed neurodevelopment, clinical signs such as relative macrocephaly, delayed language development and global hypotonia, and biological findings such as a persistent normocytic anemia and increased serum copper should raise suspicion for RTH due to *THRA* variants.

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P1154

JOINT2238

Hidden impact of high-dose hook effect: a case report on cross-reactivity of human chorion gonadotropin on thyroid function

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Introduction

The high-dose hook effect is a well-described yet sometimes overlooked lab artifact when using immunoassays in the clinical laboratory. Extremely high analyte levels could produce false low or undetectable results, with potential impact on clinical decisions and treatment. We present a case of severe hyperthyroidism in which the high-dose hook effect played a central role in the diagnostic work-up.

Case Report

A 36-year-old female was referred for worsening thyrotoxicosis, diagnosed 11 weeks prior after presenting with hematuria and urinary retention, caused by a pelvic mass. Her medical history included endometriosis and a complete molar pregnancy, successfully treated with chemotherapy. At presentation the patient had a sore throat, suggesting viral thyroiditis, due to absence of thyroid-stimulating hormone (TSH) receptor and thyroid peroxidase antibodies and a normal thyroid ultrasound. Thyrotoxicosis persisted despite initial therapy with thyrostatics (methimazole 30mg daily) and subsequent corticosteroids (methylprednisolone 32mg daily, tapered down to 12mg over 4 weeks). One week prior to referral, scintigraphy revealed high technetium uptake, possibly indicating antibody-negative Graves' disease, and methimazole was resumed. Further investigation identified the pelvic mass as malignant gestational trophoblastic disease, characterized by high human chorionic gonadotropin (hCG) levels, which were initially valued at 6.769 IU/l. hCG can however, due to structural similarities and at high doses, cross-activate the TSH receptor, causing hyperthyroidism with high isotope uptake, similar to Graves'. Upon initiating chemotherapy, hCG levels unexpectedly rose to > 1.000.000 IU/l, a paradoxical increase instated due to high-dose hook effect. Dilution of the pre-chemotherapy sample revealed much higher hCG levels (2.883.000 IU/l). As chemotherapy progressed, hCG levels decreased, improving thyroid function and resolving thyrotoxicosis.

Conclusion

This case underscores the impact of hCG on thyroid function and especially its ability to stimulate thyroid activity when circulating in high levels. Although rare, measuring hCG in unexplained thyrotoxicosis cases is advisable. Furthermore, in case of immunoassay diagnostic testing for hCG, the potential impact of high-dose hook effect must be considered *in situ*ations where one would clinically expect extremely elevated levels of hCG, despite being (falsely) low on the lab report. Recognizing this phenomenon is crucial for accurate interpretation of immunoassay results in similar clinical contexts.

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P1155

JOINT914

Clinical profile and incidence of childhood graves' disease in brunei darussalam

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Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism in children, however there is limited data on the epidemiology and clinical profile of GD in Bruneian children. Hence, our study aimed to describe the incidence, clinical characteristics and biochemical profile of GD in the paediatric population aged 12 years and younger in Brunei Darussalam.

Methods

A national population-based retrospective medical record review of children aged 12 years and younger diagnosed with GD was conducted from January 2017 to July 2024 in Brunei Darussalam.

Results

A total of 18 patients diagnosed with GD were included in this study, with female (77.8%) and Malay ethnicity (77.8%) predominance. The mean age at diagnosis was 8 ± 2.64 years. Frequently reported symptoms include eye symptoms (75.0%), neck swelling (66.7%), palpitations (54.5%), weight loss (37.5%), heat intolerance (30%) and diarrhoea (12.5%). Common clinical signs were goitre (88.9%), tachycardia (77.8%), fine tremors (33.3%) and hypertension (22.2%). None of the children presented in a thyroid storm while 11 patients had Graves' orbitopathy. More than half (56.3%) had a first degree relative with thyroid disease and only 1 patient had associated Type 1 Diabetes Mellitus. All of the children had presence of Thyroid Stimulating Hormone (TSH) receptor antibody, with suppressed TSH and elevated free Thyroxine (FT4) levels. There were 17 patients (94.4%) positive for anti-thyroid peroxidase antibody and 15 patients (83.3%) positive for anti-thyroglobulin antibody. All patients were on Carbimazole with no complications but only 5 patients received additional Propanolol treatment to relieve thyrotoxic symptoms. The mean duration to FT4 normalisation from treatment initiation was 80.43 ± 52.05 days with 55.6% of the patients reported a history of non-compliance to treatment. None of the patients underwent radioactive iodine therapy or thyroidectomy. Only one patient achieved remission at the end of the study. The mean annual incidence of GD from 2017 to 2023 in children aged 12 years and younger in Brunei Darussalam was 2.9 per 100,000.

Conclusion

There is a higher incidence of GD reported in Bruneian children compared to western countries which ranges from 0.79 to 2 per 100,000. However, female predominance and major presenting symptoms were similar to other international studies on children with GD. Half the patients had history of non-compliance to treatment which may contributed to the low rate of remission. Further research is necessary to determine possible genetic or environmental factors accounting for the higher incidence of GD in Bruneian children.

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P1156

JOINT1704

Visual functioning and physical appearance quality of life (QoL) scores of Thyroid Eye Disease (TED) patients seen in a multidisciplinary consultation

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Thyroid Eye Disease (TED) is frequent in Graves' disease and rare in Hashimoto' thyroiditis patients, with conjunctival redness, swelling of the eyelids, diplopia and proptosis. TED severely affects the Quality of Life (QoL) of patients, evaluated using visual functioning and physical appearance GO-QoL scores, and higher scores reflecting better QoL. Treatment of TED is based on severity (mild, moderate to severe, sight threatening) and activity (Clinical Activity Score, CAS) of the disease: for active disease (CAS > 3/7) intravenous glucocorticoids are the mainstay treatment, for inactive phase (CAS < 3/7) surgical rehabilitation (orbital decompression, diplopia correction, eyelid procedures) should improve visual function and esthetic. In our endocrine department, TED patients are seen and managed by a multidisciplinary (endocrinologist, ophthalmologist, maxillo-facial surgeon) team. Of the 136 TED patients evaluated with GO-QoL, 110 were women, mean (±SE) age was 53±1 years and 28 patients presented smoking at diagnosis. Graves' disease patients ($n = 130$) were treated with antithyroid drugs, and after recurrence with total thyroidectomy ($n = 71$) or radioiodine therapy ($n = 26$). Other patients had autoimmune thyroiditis treated with levothyroxine or clinical followed up. At the active phase, TED patients were treated with intravenous glucocorticoids according to EUGOGO protocol ($n = 74$), orbital radiotherapy ($n = 25$) or others medical treatments (rituximab $n = 6$, tocilizumab $n = 4$, teprotumumab $n = 1$). At the inactive phase, surgical rehabilitation consisted of orbital decompression ($n = 78$), oculomotor surgery ($n = 22$) and eyelid procedures ($n = 26$). At the first visit (V1), visual functioning (55.2±2.5) and physical appearance (52.4±2.4) GO-QoL scores were

decreased, and negatively associated with the CAS (visual functioning $P = 0.001$, physical appearance $P = 0.03$). Physical appearance score was more decreased in women (49.6 ± 2.6) than in men (64.6 ± 4.8) ($P = 0.01$). Visual functioning and physical appearance scores were more affected in older ($P = 0.01$) and in younger ($P = 0.0001$) patients, respectively. At the last visit (V2) after mean 24 ± 1 months of medical and/or surgical follow-up, CAS (V1 = 2.63 ± 0.13, V2 = 1.19 ± 0.07, $P < 0.001$), proptosis ($P < 0.0001$) and diplopia (V1 $n = 81$, V2 $n = 62$, $P < 0.0001$) decreased, visual functioning (V2 = 77.5 ± 2.1, $P = 0.014$) and physical appearance (V2 = 70.5 ± 2.2, $P < 0.01$) GO-QoL scores increased significantly, with the exception of physical appearance score in smoking patients ($n = 13$). In conclusion, visual functioning and physical appearance GO-QoL scores are decreased in TED patients, and improved after medical and/or surgical treatment in our multidisciplinary consultation. GO-QoL scores should be included in the clinical evaluation of TED patients, as severity and activity of the orbital disease, and should be considered as an indicator of treatment results in order to improve QoL of TED patients.

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P1157

JOINT2630

Iron deficiency and thyroid dysfunction: impact of iron supplementation on tsh levels in women of reproductive age in ajara georgia

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Background
Iron deficiency is frequently linked to thyroid dysfunction, particularly subclinical hypothyroidism. This study evaluates the effect of iron supplementation on thyroid-stimulating hormone (TSH) levels over six weeks in women with varying iron levels.
Methods
A retrospective analysis was conducted on 17 women aged 35 to 44 years. Baseline measurements included serum ferritin, TSH, free thyroxine (FT4), and anti-thyroid peroxidase antibodies (AT-TPO). TSH levels were reassessed after six weeks of iron supplementation.
Results
At baseline, lower ferritin levels (<15 ng/mL) correlated with elevated TSH, suggesting subclinical hypothyroidism. After six weeks of iron therapy, TSH levels declined in most patients. Those with ferritin levels between 8–11 ng/mL experienced a significant TSH reduction (e.g., from 7.1 to 3.2 μIU/mL and 8.1 to 3.1 μIU/mL). Patients with ferritin >20 ng/mL showed minimal TSH fluctuations. However, participants with high AT-TPO exhibited persistent or increased TSH despite iron therapy (e.g., AT-TPO 890 IU/mL, TSH increased from 4.7 to 10.2 μIU/mL).
Conclusion
Iron supplementation effectively reduces TSH levels in iron-deficient individuals, underscoring its role in thyroid hormone metabolism. However, in autoimmune thyroiditis (elevated AT-TPO), TSH levels remained high or worsened, indicating a complex interaction. Regular iron status monitoring is crucial in managing thyroid dysfunction, particularly in individuals at risk of hypothyroidism. Further research is needed to explore the underlying mechanisms.

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P1158

JOINT1941

Antithyroid arthritis syndrome in pediatric graves' disease: a rare adverse methimazole reaction

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Antithyroid arthritis syndrome (AAS) is a rare but significant adverse reaction linked to antithyroid therapy. We present a case of an 8-year-old girl with celiac disease and newly diagnosed Graves' disease who developed arthritis and systemic symptoms 22 days after starting methimazole (5 mg three times a day; 0,46 mg/kg). The patient presented with arthralgia and swelling of both wrists and the third finger of the right hand. She also had difficulty walking due to right hip pain. She reported a one-week history of an urticarial rash on her trunk and upper limbs, along with systemic symptoms, including diarrhea, abdominal pain, vomiting, and loss of appetite. During hospitalization, she developed a fever. Laboratory tests showed a normal complete blood count, elevated inflammatory markers (CRP 2.68 mg/dl, ESR 31 mm/h), and mildly elevated liver enzymes. Physical examination revealed tenderness on flexion-extension of both wrists (worse on the right), swelling of the right wrist, pain on mobilization of the right hand's proximal interphalangeal JOINT, and tenderness with limited range of motion of the hip JOINT. The rheumatologist confirmed arthritis. Microbiological tests were negative. A JOINT ultrasound confirmed bilateral synovitis. Due to persistent fever, whole-body CT and bone scintigraphy were performed and were negative. As thionamide arthritis was suspected, methimazole therapy was reduced to 5 mg twice daily (0,31 mg/kg) and ibuprofen (300 mg three times daily) was administered for 10 days, followed by a further 10 days as required. The fever resolved on the 10th day of hospitalization and the patient was discharged; after 20 days the patient had no further clinical signs of arthritis and laboratory tests were completely normalized. The patient subsequently discontinued thionamide therapy after 6 months from the start, with normal thyroid function tests and negative TSH-receptor antibodies. The patient remained stable with no recurrence of arthritis or systemic symptoms. The close timing between methimazole initiation and the onset of arthritis and systemic symptoms and the exclusion of other causes, strongly suggest AAS. This case highlights the importance of recognizing this rare adverse drug reaction in pediatric patients receiving antithyroid therapy. To the best of our knowledge, this is the first case of AAS in pediatric patients, probably due to an underestimation of this side effect and the rarity of Basedow's disease in pediatrics. Early recognition and reduction of thionamide are crucial for resolution of symptoms, highlighting the need for vigilance when prescribing in pediatric populations.

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P1159

JOINT3278

AI-driven EMR integration in functional thyroid dysfunction: advancing diagnosis and management

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Introduction
Functional thyroid dysfunction (FTD) refers to medical conditions that alter thyroid hormone balance, ranging from mild hypothyroidism to severe hyperthyroidism. The prevalence varies globally, driven by demographic and diagnostic criteria. Hypothyroidism affects 3–7% and hyperthyroidism 0.5–2% of individuals. Subclinical hypothyroidism and hyperthyroidism are more common, accounting for 10% and 5%, respectively. This highlights the need for a patient-centred approach to diagnosis and management. Artificial intelligence (AI), including machine learning (ML), deep learning (DL), natural language processing (NLP), and computer vision (CV), is advancing healthcare by offering tools to analyze intricate datasets. Electronic medical records (EMRs), the cornerstone of modern clinical practice, store both structured data, such as laboratory values and prescription information, and unstructured data, including clinician notes. The integration of AI with EMRs holds the potential to improve the work performance of healthcare professionals, thereby improving patient outcomes.
Objective
We summarised the highlights of AI's advancements in EMR systems for the management of FTD.
Methods
A systematic review of medical literature from January 2015 to December 2024 was conducted targeting studies on AI- EMR integration for FTD care. Priority was given to research detailing AI methodologies applicable to FTD, emphasizing data quality, developmental stage, and EMR applications.
Results
AI and EMR synergy has led to innovative algorithms that enhance diagnostic precision by integrating imaging with EMR data, customizing levothyroxine regimens, and predicting complications and comorbidities through longitudinal data analysis. Despite the potential to improve FTD diagnosis and management, personalise treatment, and enhance patient care pathways, its adoption in clinical

practice remains limited, highlighting a gap between innovation and real-world application.
Discussion
Translating AI-EMR synergy to practical thyroid care faces challenges, including validation issues that limit generalizability, no standardized and fragmented EMR data infrastructure, and the opacity of AI decision-making processes. Emerging solutions like explainable AI (XAI), federated learning, and hybrid human-AI workflows are promising steps forward.
Conclusion
AI-EMR systems have the transformative potential to shift thyroid care from reactive to proactive, precision-driven, patient-centred, safe, and equitable strategies. Addressing the current limitations through data standardization and harmonization, equity-focused safe AI frameworks, and accelerated real-world validation through prospective clinical trials is crucial. Achieving this vision demands urgent collaborative multidisciplinary efforts among professionals and researchers in endocrinology, clinical practice, data science, epidemiology, and policy-making in FTD care. By prioritizing patient-centred design and rigorous validation, AI-EMR integration can evolve from experimental to essential in optimizing FTD care.

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P1160

JOINT1561

Utility of sPD-l1 and sPD-1 as biomarkers for assessing clinical activity in moderate-to-severe thyroid eye disease

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Introduction
T cell activation plays a crucial role in the pathogenesis of thyroid eye disease (TED). The programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathway, as an immune checkpoint, regulates T cells responses, including to self-antigens. PD-L1, primarily expressed on antigen-presenting cells during inflammation, binds to PD-1 on B and T cells. Soluble forms of these molecules (sPD-L1 and sPD-1) maintain the ability to bind to membrane counterparts. As their interaction affects immune tolerance, regulation of this pathway is an attractive therapeutic option. However, there are limited data on the relevance of sPD-1 and sPD-L1 in TED. The aim of this study is to assess the role of sPD-1 and sPD-L1 in the pathogenesis of TED and to evaluate their potential as biomarkers to improve disease diagnosis and the assessment of disease activity.
Methodology
This is a single-center, prospective study on patients diagnosed with moderate-to-severe TED associated with Graves' disease, who were qualified for intravenous corticosteroid treatment (IVGC) according to the European Group on Graves' Orbitopathy (EUGOGO) guidelines. Blood samples were collected from patients before and 12 weeks after starting IVGC treatment. Levels of thyrotropic hormone (TSH), free thyroxine, free triiodothyronine, thyroid-stimulating immunoglobulin, TSH receptor antibodies, and interleukin-6 were measured using immunoassays. Enzyme-linked immunosorbent assays (ELISA) were used to measure sPD-1 and sPD-L1 concentrations in peripheral blood serum. Disease activity was assessed using the Clinical Activity Score (CAS). Correlations between the studied molecules and CAS before and after IVGC treatment were investigated. Concentrations of sPD-1 and sPD-L1 were compared with those of healthy controls (HC).
Results
Thirty patients were enrolled. Statistical analysis revealed a positive correlation between sPD-L1 and CAS before (rho $= 0.42$, $P = 0.0194$) and after (rho $= 0.37$, $P = 0.0412$) 12 weeks of IVGC treatment. sPD-1 also positively correlated with sPD-L1 before (rho $= 0.93$, $P < 0.0001$) and after (rho $= 0.88$, $P < 0.0001$) treatment. However, no correlation was observed between sPD-1 and CAS. Baseline serum levels of sPD-1 and sPD-L1 did not significantly differ between patients with TED and HC. The decreases in sPD-1 and sPD-L1 levels after 12 weeks of IVGC treatment were not significant.
Conclusion
Our results showed that sPD-L1 levels may serve as a novel immunological marker for disease activity and the monitoring of treatment response in patients with TED. However, sPD-1 may not play a significant role in the pathogenesis of TED.

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P1161

JOINT2514

Microwave ablation therapy of an intrathyroid parathyroid adenoma

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Introduction
Primary hyperparathyroidism (PHPT) is a disorder of calcium metabolism most frequently due to a parathyroid adenoma. Parathyroidectomy is the treatment of choice. However Microwave Ablation Therapy (MWA) has been applied for the treatment of primary hyperparathyroidism. The incidence of ectopic parathyroid glands ranges from 10% to 22% with an intrathyroid parathyroid adenoma (IPA) being a possible cause of PHPT (0.7-6.7%). The best treatment for IPAs is still in debate.
Case Report
A 47-year-old woman was referred to the endocrinology clinic following an incidental finding of PHPT. The patient had no personal history of bone fractures or nephrolithiasis. Biochemical analysis demonstrated elevated serum calcium (11.9 mg/dl), low serum phosphate (2 mg/dl), and elevated parathyroid hormone (PTH) levels (199 pg/mL). A [99mTc]Tc-MIBI scintigraphy scan showed slight persistent uptake in the inferior third of the left thyroid lobe and neck ultrasound identified a mixed predominantly solid and slightly hypoechoic nodule, measuring $2.1 \times 1.8 \times 1.5$ cm (LxT×AP). Fine-needle aspiration biopsy (FNAB) confirmed IPA. MWA of the IPA in the left thyroid lobe was performed with no complications. A 90% nodule volume reduction and a reduction of serum calcium and PTH values at 6 months were obtained, no longer reaching surgical criteria.
Discussion and Conclusion
To our knowledge this is the first reported microwave ablation of an IPA. Literature review identified a total of 5 patients that had IPAs treated with radiofrequency ablation. MWA ablation may be a viable alternative to surgery in the treatment of IPAs.

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P1162

JOINT281

A multimodal large language model as an end-to-end classifier of thyroid nodule malignancy risk: practical or potential?

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Introduction
Thyroid nodules are a prevalent problem in the general population. To date, commercial applications of artificial intelligence (AI) solutions for nodule risk classification have used traditional machine-learning models. Large Language Models (LLMs), especially those equipped for multimodal tasks combining text and image data, have shown promise in various applications, including medical diagnostics. Importantly, they can potentially offer flexibility for application in different imaging classification tasks. This study investigates the effectiveness of a multimodal vision-language model in the ultrasound-based risk stratification of thyroid nodules using the ACR TI-RADS risk stratification system, exploring the model's accuracy, consistency, and the influence of prompt engineering.
Methods
We utilized Microsoft's open-source LLaVA model and its instruction-tuned model LLaVA-Med, to assess 192 thyroid nodules from ultrasound cine-clip images with ACR TI-RADS descriptors. The study involved analyzing the output of the model and the effect of the use of basic and modified prompts, and images with and without radiologist-annotated regions of interest. The analysis measured the accuracy of the LLM outputs against manual assessments, and the consistency of outputs.
Results
Out of 4,608 responses, 83.3% were deemed valid, with prompt engineering improving frequency of valid responses. The LLaVA-Med model demonstrated higher accuracy in classifying individual TI-RADS components including composition (42.1% vs 20.3%, $P < 0.001$) and echogenicity (57.3% vs 49.9%, $P = 0.004$) compared to the base model, but overall TI-RADS classification

accuracy remained low for both models (31.9% vs 38.9%, $P = 0.004$). The use of labelled images improved accuracy in classifying nodule margins (58.2% vs 53.0%, $P = 0.040$). Prompt engineering improved the consistency of the overall TI-RADS classification (52.1% vs 26.6%, $P < 0.001$), but its effect on accuracy varied across different components.
Conclusion
The study explores the use of open-source, multimodal LLMs as a resource-efficient method of end-to-end thyroid nodule risk stratification, including commonly-employed methods of performance optimization. However, the mixed results highlight the challenges in achieving clinically meaningful performance in their current form. The results suggest that while instruction-tuning and prompt engineering can enhance model output, the inherent technical limitations in image interpretation and model stochasticity restrict their clinical utility. Future developments should build on these findings to explore efficient prompting techniques to improve their accuracy and consistency in clinical applications.

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P1163

JOINT3941

Thyroid artery embolization for compressive goiter in high surgical risk patients

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Introduction
Endothoracic goiter can lead to mediastinal invasion and compression of vital structures: trachea, esophagus, and large vessels. Surgery is the first line treatment, yet in some cases may require sternotomy, increasing significantly morbidity and mortality. In elderly frail patients or those with severe comorbidities, surgery may be contraindicated due to high surgical risk. In such cases thyroid artery embolization (TAE) is presented as a safe and effective alternative.
Material and Methods
Since 2022, 15 patients (81.1% women, 80(71-91)) with symptomatic endothoracic goiter, not candidates for surgery due to high surgical risk underwent palliative TAE. Dysphagia was reported in 54.5%, dyspnea in 27.3% and both symptoms in 18.2%. Regardless of thyroid function, 33.3% of patients had previous hyperthyroidism. Deviation of the vascular bundle, esophagus and trachea was reported in 36.4% of the patients and 63.6% had tracheal stenosis. Initial calculated volume was 131 ± 114 ml. During follow-up, all patients were assessed clinically, analytically, and radiologically.
Results
Median follow-up of was 10.5 ± 5 months. Total volume significantly decreased over time, reducing from an initial 131 ± 114 ml to 56 ± 111 ml at 3 months and 72 ± 85 ml at 12 months of follow-up. A progressive reduction was evident, with a 45% decrease from the initial volume at 3 months and a 59% reduction at 12 months. No patient showed a significative increase during follow up. All patients reported improvement of obstructive symptoms. Among patients who reported dysphagia or weight loss, follow-up showed an average weight gain of 3.5 ± 3.7 kg. Transient hyperthyroidism was reported in 81% with a median duration of 30 days but was not clinically significant. The peak mean FT4 level was 2.8 mg/dl (DS 1.6-3.9). Eventually, all patients with normal thyroid function normalized their values during follow-up. Among patients with pre-existing hyperthyroidism, hyperfunction was controlled in 3 out of 5 cases and no patient developed new onset hypothyroidism. Two major complications were recorded, possibly associated with the procedure (stroke with ad integrum recovery, bronchospasm).
Conclusion
In our series of patients, thyroid artery embolization (TAE) in symptomatic endothoracic goiter is an effective and safe procedure in patients who are not candidates for surgery, being a minimally invasive procedure with rapid recovery.

Volumen evolution				
Initial Vol. ml	3M ml	12M ml	3M %	12M %
131 ± 114.5	57 ± 111.6	75.3 ± 85.9	45 ± 2	58.9 ± 13.5

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P1164

JOINT4027

A case of autonomous hot thyroid nodule

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Introduction
In adults, thyroid autonomous adenomas causing hyperthyroidism are relatively common and are mostly due to mutations that increase the structural activity of the thyroid-stimulating hormone receptor (TSHR). However, in children with hyperthyroidism, autonomous adenomas are exceptional, and reports on their clinical and molecular characteristics are scarce. In this report, a case of an autonomous hot thyroid nodule is presented, and its management is shared. **Case Report:**A 14-year-and-9-month-old female patient presented with swelling in the neck. It was learned that the patient had complaints of hair loss for the last 3–4 months but no complaints of palpitations, weight loss, or hand tremors. Her personal and family history revealed that she was born at term via cesarean section with a birth weight of 3040 g. On physical examination, her height was 177.2 cm (2.71 SDS), weight was 86 kg (3.59 SDS), body mass index (BMI) was 27.3 kg/m^2 (2 SDS), blood pressure was 110/70 mmHg, and pulse was 88 bpm.A 3x3 cm palpable mass was detected in the left thyroid lobe. Pubertal development was at Tanner stage 5, and other systemic examinations were normal. Thyroid function tests showed **free T4 (sT4): 1.84 ng/dl (0.98-1.63)**, **free T3 (sT3): 7.15 ng/l (2.56-5)**, and **thyroid-stimulating hormone (TSH): <0.005 mIU/l (0.51-4.3)**. Anti-thyroid peroxidase antibody, anti-thyroglobulin antibody, and TSH receptor antibody were negative. **Thyroid ultrasonography (USG):** Right lobe: 50x19x14 mm (6.65 mL) Left lobe: 50x25x32 mm (20 mL) **Total volume: 9.6 SDS**.A well-defined, approximately **35x30x24 mm** semisolid nodule with cystic components, a hypoechoic halo, and internal vascularity detected by color Doppler ultrasonography was observed, almost completely covering the left lobe. **Thyroid scintigraphy** showed a hyperactive nodular area in the left lobe (Figure 1). The patient was started on **propranolol and low-dose methimazole**. Based on clinical, laboratory, and imaging findings, the patient was diagnosed with an **autonomously functioning hot nodule**. To rule out malignancy, a **fine-needle aspiration biopsy (FNAB)** was performed, and the nodule was reported as **benign**. The patient was referred to pediatric surgery, and after achieving a euthyroid state, **left lobectomy** was performed. The lobectomy pathology report indicated **nodular hyperplasia**. Postoperatively, all treatments were discontinued.A **TSHR gene analysis** was planned to investigate the etiology.
Conclusion
In cases of hot nodules causing hyperthyroidism, surgical removal is recommended after achieving a euthyroid state with antithyroid treatment. Studies have reported that hot nodules in children have a **higher malignancy risk**, with **2-18% of these nodules being malignant**. In this report, the management of a case with a hot thyroid nodule was discussed.

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P1165

JOINT4036

Evaluation of the effects of antithyroid drug therapy on body mass index in children and adolescents with graves' disease

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Introduction
Graves' Disease (GD) is the most common cause of primary hyperthyroidism in children and adolescents and is associated with weight loss before treatment. During treatment, weight gain is frequently observed. This study aims to evaluate weight fluctuations in newly diagnosed GD patients receiving pharmacological treatment.
Materials and Methods
The records of 27 newly diagnosed GD patients who started pharmacological treatment (methimazole) between October 2022 and January 2024 were retrospectively reviewed. Patients who had started treatment before their first endocrinology visit, had thyroid malignancies, or had incomplete records were

excluded from the study. Patients with a body mass index (BMI) percentile of 85-95 at diagnosis were classified as overweight, while those above the 95th percentile were classified as obese. The patients were divided into two groups: those who were overweight/obese and those who were not. The groups were compared in terms of age, gender, puberty status, BMI at diagnosis, BMI standard deviation score (SDS) at diagnosis, BMI and BMI-SDS at 6 and 12 months, thyroid function tests, TSH receptor-blocking antibody levels (TRAB), thyroid volume, follow-up duration, duration of antithyroid drug use, and initial methimazole dose. Changes in BMI over the first year were expressed as Δ BMI-SDS (0-12).

Results

The median age of the patients was 14.11 years, 74.1% were female, and only one patient was prepubertal. A family history of thyroid disease was present in 66.7% of the patients. The most common presenting symptoms were palpitations (33.3%), weight loss (25.9%), and hand tremors (14.8%). Among patients with a history of weight loss, 71% were in the normal weight group. There were no significant differences between the groups in terms of age, thyroid function tests, thyroid volume, thyroid volume SDS, follow-up duration, initial methimazole dose, or duration of antithyroid drug use ($P > 0.05$). The increase in BMI and BMI-SDS at 6 and 12 months after diagnosis was significantly greater in the non-obese and non-overweight groups. Δ BMI-SDS (0-12) was correlated with weight, BMI, BMI-SDS, ST3-ST4, and TRAB levels at diagnosis.

Conclusion and Discussion

Our study highlights the importance of weight management in the treatment of GD alongside the regulation of thyroid function. Weight management should be a focal point for all patients receiving antithyroid drugs to minimize the development of obesity and mitigate the harmful effects of weight gain. Particularly, obese and overweight patients who are at high risk for metabolic syndrome and cardiovascular complications should be monitored more closely.

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P1166

JOINT1227

Evaluation of ultrasonographic and clinicopathological features of gallium-68 DOTA-TATE uptake in the thyroid gland

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Background

Gallium-68 DOTA-TATE PET/CT is a widely utilized imaging modality for neuroendocrine tumors (NETs) due to its sensitivity for somatostatin receptors (SSTRs). However, incidental uptake in the thyroid is increasingly noted, raising questions about its clinical significance. This study analyzes ultrasonographic and clinicopathological features of patients with thyroid Ga-68 DOTA-TATE uptake.

Methods

This retrospective study included 39 patients who underwent Ga-68 DOTA-TATE PET/CT imaging from April 2019 to November 2023, exhibiting thyroid uptake categorized as focal, diffuse, or heterogeneous. Ultrasonographic evaluations, fine-needle aspiration biopsies (FNAB), and laboratory tests, including thyroid function and autoimmune markers, were reviewed. Statistical analyses assessed relationships between uptake patterns, SUVmax, and clinical parameters.

Results

Focal uptake was noted in 59% of patients, diffuse in 17.9%, and heterogeneous in 23.1%. Focal Ga-68 DOTA-TATE uptake in the thyroid gland remains a potential indicator of malignancy. Although no cases of carcinoma were confirmed in this cohort, the observed focal uptake emphasizes the importance of vigilant follow-up and thorough diagnostic evaluations such as ultrasonography and FNAB. FNAB was performed on 82% of patients with suspicious nodules; 33.3% yielded non-diagnostic Results Diffuse uptake correlated with benign conditions like Hashimoto's thyroiditis. The mean SUVmax was 7.35 ± 3.08.

Ultrasonographic Findings

87.2% of patients had nodular or multinodular goiter. Of these, 20.5% showed chronic thyroiditis. Mixed nodule structure predominated (68.6%), and 48.6% exhibited isoechoic patterns. FNAB results were benign in 46.7% and atypia of undetermined significance (AUS) in 17.8%, with one case identified as follicular neoplasm.

Discussion

Focal Ga-68 DOTA-TATE uptake in the thyroid may signify malignancy risk, underscoring the need for systematic evaluation. Diffuse uptake aligns more commonly with benign thyroid diseases, particularly autoimmune conditions. An inverse relationship between SUVmax and BMI hints at metabolic and inflammatory influences on SSTR expression. High non-diagnostic FNAB rates indicate challenges in conclusive diagnoses, warranting further studies.

Table: Ga-68 DOTA-TATE Thyroid Uptake Analysis.

Parameter	Value
Focal uptake	59%
Diffuse uptake	17.9%
Heterogeneous uptake	23.1%
SUVmax	7.35 ± 3.08
Non-diagnostic final FNAB results	33.3%
Nodular/multinodular goiter	87.2%
Chronic thyroiditis (isolated)	10.3%
Isoechoic nodule patterns	48.6%
Mixed nodule structures	68.6%

Conclusion

Focal Ga-68 DOTA-TATE uptake is a potential marker of malignancy, while diffuse uptake often suggests benign pathology. Comprehensive diagnostic approaches, including ultrasonography and FNAB, are critical for incidental thyroid findings on Ga-68 DOTA-TATE PET/CT imaging. Further research on SUVmax correlations with metabolic factors is needed to refine patient management strategies.

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P1167

JOINT1703

Lymph node ratio predicts persistence/recurrence in medullary thyroid cancer

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Introduction

The lymph node ratio (LNR) is defined as the number of metastatic lymph nodes or divided by the number of resected lymph nodes. LNR has been suggested as a predictive factor in various cancer types; however, the data regarding medullary thyroid cancer (MTC) is limited. The aim of the study is to evaluate LNR as a risk factor for persistence/recurrence in patients with MTC.

Methods

Medical records of 52 patients treated for MTC in a single tertiary center between 2001 and 2023 were retrospectively reviewed. Persistent and recurrent diseases were defined as those detected within the first 12 months of diagnosis or during subsequent follow-up periods, respectively. To identify risk factors influencing persistence/recurrence, univariable and multivariable Cox proportional hazard models were used.

Results

Persistent and recurrent disease was identified in eight and seventeen patients, respectively. The median follow-up period was 86.5 months (IQR:30.75 - 165). The characteristics of patients with a persistence/recurrence and remission status are outlined in Table 1. In univariable analysis, lymphovascular invasion, postoperative serum calcitonin and carcinoembryonic antigen (CEA) levels, and LNR were significant ($p < 0.05$) predictors of persistence/recurrence. In multivariable analysis persistent/recurrent disease was independently associated with the LNR value and was accurately predicted by a cut-off value of 0.22 (area under the curve = 0.97; sensitivity 90%, specificity 91%).

Table 1: The characteristics of patients with a persistence/recurrence and remission status.

Parameter	Persistence/Recurrence ($n = 25$)	Remission ($n = 27$)	*P* value
Age, y (mean ± SD)	42 ± 13	50 ± 17	0.053
Gender, female *n.* (%)	11 (44)	19 (70.4)	0.054
RET positivity *n.* (%)	6 (24)	10 (37)	0.663
Tumor size (mm), mean ± SD	2.6 ± 1.5	2 ± 1.4	0.074
Multifocal tumor, *n.* (%)	6 (24)	8 (29.6)	0.647
Lymphovascular invasion, *n.* (%)	12 (48)	3 (11.1)	0.003
Extracapsular invasion, *n.* (%)	5 (20)	1 (3.7)	0.94
Metastatic lymph node, n (median, IQR)	6 (2.5 -13)	0 (0 - 3)	<0.001
Lymph node ratio, n (median, IQR)	0.36 (0.25 - 0.64)	0 (0 - 0.14)	<0.001
Postoperative calcitonin, pg/mL (median, IQR)	216 (29.5 - 497)	3.8 (0.6 - 9.4)	<0.001
Postoperative carcinoembryonic antigen, ng/mL (median, IQR)	3.8 (1.9 - 16.1)	2.1 (1.3 - 4.3)	0.029

Conclusion
LNR can potentially predict persistence/recurrence as a quantitative evaluation tool for lymph node metastasis in patients with MTC.

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P1168

JOINT1827

Clinicopathological evaluation of advanced thyroid cancer

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Introduction
Advanced thyroid cancer is a rare disease with heterogeneous clinical and pathological characteristics. There is insufficient knowledge regarding this condition. The aim of our study is to investigate the clinicopathological features of advanced-stage thyroid cancer cases at our center.
Method
This retrospective, single-center study identified patients with advanced-stage thyroid cancer through medical records and electronic hospital systems. Demographic data, comorbidities, preoperative ultrasonographic findings, pathological results, treatments, and follow-up information were recorded. Clinicopathological evaluation was performed using descriptive statistics.
Results
A total of 16 patients were included in the study. The mean age of the patients was 61 (±17). 56.3% of the patients were female. Preoperative ultrasonographic examination was available for 8 patients. The average largest nodule diameter was 5 (±3) mm. Hyperechogenicity was found in 12.5%, cystic areas in 25%, hypoechoic halo in 12.5%, and calcifications in 37.5% of the patients, while 12.5% had a well-defined border. 37.5% underwent total thyroidectomy only, while remaining had total thyroidectomy combined with neck dissection. Papillary thyroid carcinoma(PTK) was diagnosed in 9 (56.3%) cases, medullary carcinoma in 2 cases, while anaplastic thyroid carcinoma(ATC)+papillary microcarcinoma, ATC+PTK, follicular carcinoma+papillary microcarcinoma, follicular carcinoma, and Hurthle cell carcinoma were each identified in 1 case. The average tumor size was 37 mm (± 23). Among pathological high-risk features, lymphovascular invasion was present in 61.5% and extrathyroidal extension in 63.6%. A papillary carcinoma case exhibited Tall-cell variant, perineural invasion, and BRAFV600E mutation. Distant organ metastasis was present in 5 patients, with lung and bone being the most common. According to the ATA risk score, 12.5% of patients were classified as low, 50.0% as intermediate, and 37.5% as high risk. 75.0% (12 patients) received radioactive iodine (RAI) therapy. The patients who received RAI had a total average dose of 278 mCi (±220). Residual tissue was observed in 4 (30.8%) patients on post-surgical 131-Iodine whole-body scan (WBS). DOTA-PET was used in medullary cancer post-surgery, and FDG-PET in other types, with 3 (18.8%) patients showing uptake. 2 cases showed WBS positive and PET negative results, while 3 cases showed PET positive and WBS negative. 25% of the patients received targeted therapy. The median overall survival after surgery was 97 months.
Conclusion
In our country, advanced thyroid cancer most commonly presents with a papillary histology. 131-Iodine whole-body scan and PET scans may yield false-negative results during follow-up. Targeted therapy is an important treatment option. The survival rate and response to treatment are favorable.

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P1169

JOINT2647

Thyrotoxic hypokalaemia periodic paralysis-

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Background
Thyrotoxic hypokalemic periodic paralysis (THPP) is a rare complication of hyperthyroidism, primarily reported in Asian populations, affecting about 2% of hyperthyroid individuals. In non-Asian populations, its incidence is considerably lower, estimated at 0.1% to 0.2%. THPP typically presents with muscle weakness and hypokalemia, predominantly in males aged 20 to 40.
Case Presentation
We describe a 38-year-old male patient of African descent who presented to the Accident and Emergency department with progressive weakness of the lower limbs, which subsequently affected his upper limbs. Neurological examination revealed diminished reflexes in the lower limbs, while reflexes in the upper limbs were normal, with no other neurological deficits observed.
Investigations
Laboratory tests indicated a critically low serum potassium level of 2.2 mmol/l, signifying severe hypokalaemia. Thyroid function tests showed undetectable thyroid-stimulating hormone (TSH), elevated free thyroxine (T4) at 30 pmol/l, and undetectable high free triiodothyronine (T3). Diffuse thyroid enlargement was noted, prompting further evaluation for autoimmune thyroiditis, Grave's thyrotoxicosis with thyroid antibody testing pending.
Discussion
This case illustrates the atypical presentation of THPP in a non-Asian patient and emphasizes the importance of timely diagnosis. The combination of acute muscle weakness and specific laboratory findings should prompt clinicians to consider THPP in hyperthyroid patients, particularly in the context of acute paralysis. This is a condition which can cause significant morbidity with muscular paralysis and respiratory arrest secondary to respiratory muscular paralysis. Our patient did not have any reparatory issue on admission. He was treated with antithyroid medications, betablockers and Potassium.
Conclusion
The rarity of THPP in non-Asian populations highlights the need for increased awareness among healthcare providers. Prompt recognition and management of this condition can improve patient outcomes and prevent complications related to hypokalemia and thyroid dysfunction. Further research is needed to enhance understanding and treatment strategies for THPP across diverse populations.

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P1170

JOINT3949

Radioiodine therapy in pediatric graves' disease: insights from a single-center study of 35 cases

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Introduction
Pediatric Graves' disease (PGD) is marked by hyperthyroidism and antithyroid receptor antibodies (TRAb). Low antithyroid treatment (ATD) remission rates, side effects and poor adherence require alternative therapies.
Objective
To describe outcome to radioiodine treatment (RAI) in PGD at a single institution.
Material and Methods
Retrospective analysis of 35 PGD patients followed between 2006 and 2024 treated with RAI. Data describing outcome and adverse effects were retrieved. RAI dose was calculated by formula using thyroid size by palpation or sonography and 24 hours-RAI uptake (100-250 μ Ci).
Results
Hispanic PGD cohort, 89% females, with a median age of 12 years (y) (range (r): 2–17.2). Thyroid disease was familial in 46% and 14% had other autoimmune conditions. Two had Down syndrome; one had osteogenesis imperfecta. All but one received ATD in a titration regimen and one with hepatic failure (autoimmune hepatitis) underwent RAI as first option. Median ATD duration was 1.3 y (r: 0.1–6.5). RAI was indicated for 14 patients (40%) due to exacerbation under low-dose ATD, 11 (31%) for adverse reactions, 9 (26%) for poor compliance, and 1 (3%) for flare-up after ATD discontinuation. Median age at RAI indication was 14.6 years (r: 5.8–19.9y). Median goitre size at indication was 45g (r: 30–80g). Median RAI dose was 10 mCi (r: 5–20) for the first dose, equivalent to 0.26 mCi/g thyroid tissue (r:0.25-0.36). Three patients required a second dose for persistent hyperthyroidism at a mean of 0.7years (SD ± 0.14); the mean total dose of RAI was 0,4 mCi/g thyroid tissue (SD ± 0,14). All achieved hypothyroidism (elevated TSH, normal/low thyroid hormones) at a median time of 0.3 years (r: 0.1–5.1) after RAI. Beta-blockers were used in all but two patients for transient tachycardia post-RAI and 8 patients needed ATD for transient hyperthyroidism (23%). No adverse events were reported. Median post-RAI follow-up was 3 y (r: 0.4–11.6).
Conclusions
RAI was an effective and save definitive treatment for PGD patients who presented adverse reactions or failure to ATD with high chances to achieve hypothyroidism in 3-4 months.

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P1171

JOINT3189

miRNA expression in the thyroid tumors with HRAS Q61R pathogenic variant

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Objectives
Molecular testing of thyroid tumors is increasingly being used for the diagnosis and prognosis of patients. In some cases, however, the same gene variant may be present in both benign and malignant thyroid tissue. There is 42.1% positive predictive value for our preoperative samples of thyroid nodules with pathogenic variants in *HRAS* gene, respectively 52.6% with low-risk neoplasms included. Currently, it is not possible to distinguish whether a preoperative fine-needle aspiration biopsy sample with *HRAS* pathogenic variant is a benign or malignant nodule.
Methods
The study consisted of 12 *HRAS* Q61R-positive papillary thyroid carcinomas (PTCs), six *HRAS* Q61R-positive benign nodules and 12 healthy thyroid tissues (with no genetic alteration). The miRNA libraries for NGS sequencing were prepared from RNA containing miRNA extracted from fresh-frozen thyroid tissues using the QIAseq miRNA Library Kit (Qiagen). Bioinformatics used the miRge3.0 tool and the DESeq2 package in R to compare cohorts of *HRAS* benign vs. malignant tumors.
Results
The focus was on comparing follicle-derived nodules with the detected *HRAS* Q61R pathogenic variant. The expression of miRNAs in benign and malignant thyroid tumors was compared. A total of 11 miRNAs were found to be significantly increased in expression in *HRAS*-positive PTCs in comparison to benign thyroid nodules (e.g. hsa-miR-31-5p, hsa-miR-34c-5p, hsa-miR-149-5p), whereas expression of four miRNAs were found to be significantly downregulated in the *HRAS*-positive PTCs (hsa-miR-371a-5p, hsa-miR-372-3p, hsa-miR-373-3p, hsa-miR-548ap/548j-5p).
Conclusion
In summary, the combination of genetic testing at the DNA level and measurement of epigenetic changes in miRNA expression could be a useful tool for better diagnostics and prognostics. Especially, miRNA expression analysis could be useful in the preoperative diagnosis of nodules in which *HRAS* variants are found and malignancy is not sufficiently clear. Verification with another method and analysis of a larger sample set will follow. *Supported by AZV NU21-01-00448 and MH CZ RVO 00023761.*.

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P1172

JOINT501

Laboratory patterns differ between patients with severe vs milder forms of congenital hypothyroidism

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Purpose
Congenital hypothyroidism (CH) is the most common congenital endocrine disorder, affecting approximately 1 in 2-4,000 newborns. Consensus guidelines recommend rapid normalization of thyroid-stimulating hormone (TSH) levels for neurodevelopmental protection. However, this approach may lead to elevated free thyroxine (fT4) levels, raising concerns about overtreatment despite persistently elevated TSH. This lab pattern has been anecdotally noted to be more frequent and persistent in individuals with severe CH, complicating levothyroxine dose titration. We hypothesize that individuals with severe CH require higher levels of fT4 to appropriately suppress TSH compared to those with mild CH, suggesting a potential difference in the thyroid feedback loop between the two groups. A better understanding of this relationship could inform treatment strategies and improve outcomes.
Methods
Patients were included based on a diagnosis code for congenital hypothyroidism, with associated TSH and fT4 (measured by direct dialysis) values extracted. Patients were divided into two subgroups: (1) severe CH (at least one documented TSH >60); (2) mild CH (all TSH values <25). A Student's t-test with a fixed effects model was used to compare the levels of fT4 relative to TSH between these two groups.
Results
A significant difference in fT4 relative to TSH was observed between the groups, indicating that for the same TSH value, individuals with severe CH have significantly higher fT4 levels compared to those with mild CH ($t_{(2910)} = -3.69$, $P = 0.0002$). Additionally, a significant difference was found in the rate at which fT4 changes in response to TSH (i.e., the slope of the relationship between fT4 and TSH) for the two groups ($t_{(2910)} = -9.21$, $P < 0.0001$). Individuals with severe CH exhibited a more attenuated response in TSH to changes in fT4, indicating reduced sensitivity to fT4 compared to those with mild CH.
Conclusions
This study demonstrates that individuals with severe CH require higher free T4 to achieve similar TSH suppression, suggesting differences in thyroid regulatory mechanisms. Additionally, the rate at which fT4 changes with respect to TSH differs significantly between the two groups; individuals with severe CH are less responsive to shifts in fT4, further highlighting the variability in thyroid feedback. These findings underscore the importance of understanding variability in thyroid function in order to optimize clinical management. Tailored treatment strategies could be developed based on the severity of CH, ultimately improving long-term outcomes for affected individuals.

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P1173

JOINT1332

Thyroid nodule of tuberculous origin: a delayed and unexpected diagnosis - a case report

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Introduction
According to the WHO, Cameroon located in Central Africa, is ranked among the 30 high Tuberculosis (TB) burden countries in the world. Moreover, in 2021, more than 22000 people were infected with TB and 5.1% of cases concerned children aged 0-14 years. Thyroid nodules in children are rare and usually benign. However, in regions where TB is endemic, rarer causes like tuberculous thyroiditis must be considered. This condition accounting for less than 1% of extra-pulmonary TB can present as a painless nodule and may be misdiagnosed as a benign abscess or adenoma. Diagnosis is often delayed requiring a combination of clinical, laboratory and histopathological findings. This case highlights the diagnostic challenges and the need for a high index of suspicion for TB in pediatric thyroid nodules.
Case Presentation
A 4-year old boy was referred for endocrine consultation before planned thyroid surgery due to a year long history of neck pain and an enlarged thyroid. Initial tests showed no signs of thyroid dysfunction but a high WBC count (26.675×10^9/l with neutrophil predominance of 84%). Thyroid abscess was suspected and was treated with antibiotics. Symptoms recurred with pain and after stronger antibiotics failed, fistulization occurred prompting surgery. FNA was refused and a CT scan revealed a nodule. Further questioning revealed the mother had chronic cough, weight loss and night sweats raising concern for tuberculosis. Her sputum was positive for *Mycobacterium tuberculosis* leading to suspicion of tuberculous thyroiditis in the child. A chest X-ray and gastric lavage for *Mycobacterium tuberculosis* testing were both negative in the child. Empirical antiTB treatment was initiated with favorable response and the child remained well at 1year follow-up.
Discussion
Symptoms including enlarging nodules, neck pain, fever, weight loss may mimic other thyroid conditions delaying diagnosis. In this case, failure to respond to antibiotics, symptom recurrence, mother's history and a positive sputum culture for *Mycobacterium tuberculosis* prompted consideration of tuberculous thyroiditis.

Fistulization further suggested TB. In paediatric patients a thorough history including exposure to adults with active pulmonary TB is crucial for making the diagnosis and in many cases, surgical intervention is not required once the underlying TB infection is effectively treated. The diagnosis requires high clinical suspicion and while FNA is the gold standard.
Conclusion
Tuberculous thyroiditis, though rare, should be considered in pediatric thyroid nodules especially in TB endemic areas. This case highlights the importance of a detailed patient history including potential TB exposure.

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P1174

JOINT217

Neuropsychological and growth outcomes in congenital hypothyroidism: impact of timing of thyroid hormone supplementation

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Background
Congenital hypothyroidism (CH) is a leading cause of preventable intellectual disability and growth failure. Early detection and initiation of thyroxine therapy are crucial for optimizing neuropsychological and physical outcomes. The timing of treatment initiation and initial thyroxine (T4) levels significantly influence neurocognitive and physical development in children with CH[1,2].
Methods
A cross-sectional study was conducted at a tertiary care hospital from January 2017 to December 2018. Sixty children aged >3 years with CH were evaluated using the Binet Kamat Scale for Intelligence to assess IQ[3] and the Child Behavior Checklist (CBCL) to measure behavioral outcomes, including Withdrawal, Anxiety/Depression, Social Problems, Thought Problems (WAST), Attention Deficit, and Aggression (ADA). Height SDS (standard deviation score) was recorded. Statistical analysis was performed using SPSS v20, with a p-value $<$ 0.05 considered statistically significant.
Results
Females constituted 53% of the study cohort, while males (47%) exhibited more severe biochemical abnormalities (lower T4 and higher TSH levels at diagnosis). IQ was significantly influenced by the timing of therapy initiation: children treated within the first month of life had a mean IQ of 79, compared to 59.5 for those treated between 1 and 6 months, and 61.1 for those treated after 6 months. Severe CH, indicated by lower T4 levels, was associated with greater IQ deficits. Height SDS and behavioral scores (WAST and ADA) showed no significant correlation with therapy timing, though elevated WAST and ADA scores were observed.
Conclusions
Early initiation of thyroid hormone therapy (<1 month) significantly improves IQ in children with CH. However, the timing of therapy does not appear to impact height SDS or behavioral outcomes. These findings highlight the importance of neonatal screening and timely intervention to improve neurocognitive outcomes[1,3].
Keywords
Congenital Hypothyroidism, Neuropsychiatric development.
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P1175

JOINT323

Prevalence of hypothyroidism in children with nephrotic syndrome: a systematic review and meta-analysis

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Background
Nephrotic syndrome (NS) is among the most prevalent renal glomerular diseases in children. Nephrotic syndrome (NS) is characterized by glomerular damage, leading to a significant loss of proteins in the urine specifically thyroxine-binding globulin (TBG) and thyroxine. Subclinical or overt hypothyroidism in this population may exacerbate the disease burden, complicate management, and impair long-term outcomes.
Objective
The objectives are: (1) to determine the pooled prevalence of hypothyroidism in children with nephrotic syndrome(2) Pooled prevalence of Clinical and Subclinical hypothyroidism in nephrotic syndrome and (3) to explore factors influence.
Methodology
This systematic review was registered in the PROSPERO database under the identifier CRD42023455277. The authors conducted searches across databases, including EMBASE, Web of Science, Cochrane CENTRAL, Scopus, and CINAHL and Google. The keyword search was limited to titles and abstracts, employing Boolean operators such as "OR" and "AND" where applicable. The search terms included Nephrotic syndrome, prevalence, hypothyroidism, children, thyroid stimulating hormone, and thyroxine.
Statisical analysis
The Quantitative Analysis includes Pooled prevalence with 95% Confidence Interval (CI) was calculated using OpenMeta software. The Heterogeneity were assessed using I^2 statistic test. Publication Bias was evaluated using funnel plots and Egger's test.
Result
26 studies were included in the review, with 19 studies included in the meta-analysis. The pooled prevalence rate is 41.45% with 95% confidence interval 32.896 to 50.287. The funnel plot does not show significant asymmetry, suggesting there is no substantial publication bias or small-study effects. The pooled prevalence of hypothyroidism among steroid resistant nephrotic syndrome(SRNS) is 38.140. The pooled prevalence of clinical hypothyroidism is 15.31% with a 95% confidence interval of 8.463 to 23.736. The pooled prevalence of sub clinical hypothyroidism was 25.96% with a 95% confidence interval of19.456 to 33.044. The standardized mean difference of TSH value between nephrotic syndrome with and without hypothyroidism group is 1.86 suggesting a moderate to large effect size. And $I^2 = 93.62\%$ indicates substantial variability among the studies and $P < 0.01$ suggests that the heterogeneity is statistically significant. In Regression analysis there is a weak downward trend between age and proportion.
Conclusion
This systematic review and meta-analysis highlights the significant burden of hypothyroidism in patients with nephrotic syndrome, with notable differences across subtypes and severity of thyroid dysfunction. Elevated TSH levels in nephrotic syndrome compared to control groups further underscore the impact of this renal condition on thyroid physiology. These findings call for routine thyroid function monitoring, particularly in high-risk subgroups like SRNS.

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P1176

JOINT558

OCT and OCTA evaluation of neurovascular structures in pediatric graves' disease without active ophthalmopathy

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Purpose
To investigate retinal and choroidal neurovascular structures in children and adolescents with Graves' disease(GD) but without active ophthalmopathy using OCT and OCTA.
Patients and Methods
In this prospective, cross-sectional, observational study, GD patients without ophthalmopathy were assessed between September 2022 and 2023. Retinal and choroidal neurovascular structures in the macula and peripapillary retinal neurovasculature were quantitatively analyzed using OCT and OCTA and compared to age-matched healthy controls. Statistical significance was set at a *P*-value less than 0.05.
Results
Thirty patients with Graves' disease (mean age 14.3 $\pm$ 2.3 years) and 30 age-matched healthy controls. The GD group exhibited significantly lower vessel densities in both the superficial and deep capillary plexuses of the fovea ($P < 0.05$

for all) and significantly larger foveal avascular zone diameters compared to controls ($P = 0.002$). Central foveal thickness (CFT) and choroidal thickness (CT) were significantly lower in the GD group ($P = 0.036$ and $p \leq 0.01$ for all; respectively). No significant differences were found between groups regarding choriocapillaris flow area, choroidal vascularity index, peripapillary retinal nerve fiber layer thickness (pRNFLT), or radial peripapillary capillary plexus vessel densities ($p > 0.05$ for all).
Conclusion
In pediatric GD patients without active ophthalmopathy, macular microvascular changes appear to precede optic disc changes. Alterations in CFT and CT may occur before changes in pRNFLT. Reduced macular vessel density, thinner CFT, and decreased CT may be important biomarkers for monitoring pediatric GD patients.

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P1177

JOINT3462

Thyroid lymphoma presented as a painful cervical mass: a diagnostic dilemma

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Introduction
Thyroid lymphoma, though rare, can be classified as either primary thyroid lymphoma (PTC) or secondary thyroid lymphoma. PTC typically arises from the thyroid gland and may later spread to the lymph nodes and other organs, often in individuals with preexisting Hashimoto's thyroiditis. Secondary thyroid lymphoma, on the other hand, originates in lymph nodes or other organs, with subsequent involvement of the thyroid. We present a case of thyroid lymphoma that posed significant diagnostic challenges.
Case Presentation
A 49-year-old male presented with a rapidly enlarging left thyroid mass, dysphagia, and hoarseness. Laboratory tests and thyroid antibodies were normal. Ultrasound revealed a 7x5x6 cm mass with increased blood flow and reactive cervical lymph nodes, raising concern for either thyroid cancer or subacute thyroiditis. A fine needle aspiration (FNA) was inconclusive due to hemorrhage, and a lymph node biopsy suggested reactive lymphadenopathy. Due to the diagnostic uncertainty and significant patient discomfort, a total thyroidectomy was performed, revealing diffuse large B-cell lymphoma (DLBCL). Postoperatively, the patient developed permanent hypoparathyroidism requiring ongoing calcium supplementation. Staging with PET/CT and CT scans revealed involvement of regional lymph nodes, stomach, and pancreas, but not the bone marrow. The lymphoma was classified as stage IV (Lugano) with an International Prognostic Index (IPI) score of 3 and Central Nervous System-IPI score of 3.
Treatment and Outcome
The patient was treated with six cycles of Polatuzumab, Rituximab, Cyclophosphamide, and Methylprednisolone (Pola-R-CHP) every 21 days. Post-treatment PET/CT scans showed no evidence of disease.
Conclusion
Although rare, thyroid lymphoma should be considered in the differential diagnosis of rapidly enlarging thyroid masses. Early recognition and timely intervention are critical for improving prognosis, particularly in cases without a prior history of Hashimoto's thyroiditis. This case highlights the diagnostic complexity of thyroid lymphoma and the importance of comprehensive staging and tailored treatment.

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P1178

JOINT2912

The impact of levothyroxine treatment on T lymphocyte gene expression in Hashimoto's thyroiditis

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Hashimoto's thyroiditis (HT) is a common autoimmune disorder of the thyroid gland. The appearance of anti-thyroid antibodies (ATAs) against thyroid peroxidase (TPO) and thyroglobulin (TG), and the infiltration of the thyroid gland by mononuclear cells are characteristic markers of HT. Although it is not obligatory, HT can lead to hypothyroidism at an advanced stage of the disease (indicated by the increased level of thyroid-stimulating hormone, TSH), against which levothyroxine replacement therapy has been proved to be beneficial. Since HT is considered to be a T cell-mediated disease primarily, we designed a transcriptome analysis experiment (RNA-seq) to examine gene expression alterations in T lymphocytes in HT and the effect of levothyroxine treatment. Peripheral blood samples were collected from ATA+ hypothyroid HT patients (TPO and TG antibody positivity, abnormal elevated TSH level) before and after levothyroxine replacement therapy and from the age-matched healthy controls. T cells were isolated from the blood by magnetic separation and then total RNA was purified. Whole transcriptome sequencing (bulk) was performed using the Illumina NovaSeq 6000 platform, with QuantSeq 3' mRNA library preparation and single-end sequencing with 75bp read length, in order to screen for differentially expressed (DE) genes. Following the identification of DE genes, we carried out a functional enrichment analysis to investigate which biological processes and signaling pathways are affected by these changes. Our screen revealed that the vast majority of DE genes were up-regulated in T lymphocytes in HT, approximately 85 percent, compared to the healthy control. Interestingly, the contrary could be observed in the same disease patients after levothyroxine treatment, where 262 of the 308 DE genes were down-regulated in T cells. Between the control and the treated groups, DE genes were present in a notably lesser amount. By examining changes between the healthy vs Hashimoto and the Hashimoto vs treated comparisons, we found 181 identical genes that exhibited a clear switch in their expression pattern from an up-regulated to a down-regulated state. Several upstream regulators, such as interleukin-1A (IL-1A), IL-1B and tumor necrosis factor (TNF) were activated in HT and became inhibited following levothyroxine addition. In addition, we observed a similar activation-inactivation phenomenon in many signaling pathways (IL-4 and IL-13, IL-6, IL-17, TNF, nuclear factor-kappa B and transforming growth factor beta signaling), suggesting that altered immunological processes characteristic of the disease may be reversed by applying levothyroxine therapy.

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P1179

JOINT3200

Diagnostic performance of ultrasound-based risk stratification systems for follicular thyroid carcinoma

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Background
In the evaluation of thyroid nodules, an ultrasound-based risk stratification system(RSS) is useful for identifying patients with a high likelihood of thyroid cancer and determining the need for fine needle aspiration biopsy (FNAB). However, these systems are primarily focused on diagnosing papillary thyroid carcinoma(PTC), the most common type of thyroid cancer. A new ultrasound-based RSS for the diagnosis of follicular thyroid carcinoma(FTC) has recently been proposed, known as F-TI-RADS. In this study, we compared this new system with existing systems for diagnosing thyroid cancer.
Methods
This retrospective study included 385 patients: 194 diagnosed with follicular thyroid carcinoma(FTC) and 191 diagnosed with follicular adenoma(FA), who underwent surgery for follicular neoplasms at Samsung Medical Center. Preoperative ultrasound examinations of the FA and FTC groups were reviewed and evaluated using K-TI-RADS, ACR TI-RADS, and F-TI-RADS. Additionally, we compared the usefulness of each system in screening for high-risk FTC by incorporating TERT promoter mutation information based on the WHO classification.
Result
The factors required to evaluate each RSS on preoperative ultrasound for all patients were compared between the FTC and FA groups. There were no

significant differences in size ($P = 0.685$), composition ($P = 0.054$), or orientation ($P = 0.349$) between the two groups. However, significant differences were observed in the presence or absence of lobulation ($P < 0.001$), echogenicity ($P < 0.001$), margin characteristics ($P = 0.003$), calcification ($P < 0.001$), and trabecular formation ($P < 0.001$). When comparing the area under the curve (AUC) values of the TI-RADS systems, the AUC values were 0.635 for K-TI-RADS, 0.646 for ACR TI-RADS, and 0.658 for F-TI-RADS, with no statistically significant differences between these RSSs. Next, the patients were divided into two groups to evaluate the usefulness of the systems in screening for high-risk FTC. Group 1 included patients with FA, minimally invasive (MI) FTC, or encapsulated angioinvasive (EA) FTC with wild-type (WT) TERT, comprising 292 patients. Group 2 included patients with encapsulated angioinvasive (EA) FTC with TERT mutation or widely invasive (WI) FTC, comprising 28 patients. The AUC values for the RSSs in each group were as follows: 0.751 for K-TI-RADS, 0.783 for ACR TI-RADS, and 0.846 for F-TI-RADS.

Conclusion

When comparing the FTC and FA groups, the performance of the three RSSs was similar, However, F-TI-RADS demonstrated superior performance compared to the other RSSs in detecting high-risk FTCs.

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P1180

JOINT2886

The coexistence of graves' disease and thymic hyperplasia: a case report

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Introduction

Thymic hyperplasia is frequently observed in patients with Graves' disease. The association between Graves' disease and thymic hyperplasia was first described in 1912, and up to 38% of patients with Graves' disease exhibit histological thymic abnormalities. However, the exact mechanism underlying the development of thymic hyperplasia in these patients remains unclear.

Case Report

We present a case report of a 23-year-old female medical student who presented to the outpatient clinic with complaints of palpitations, tachycardia, tremors, anxiety, and a weight loss of 5 kg over three months. She had no eye symptoms. On physical examination, her vital signs were as follows: blood pressure of 110/70 mmHg, heart rate of 130 beats per minute, respiratory rate of 18 breaths per minute, weight of 49 kg, and height of 160 cm (body mass index of 19.14 kg/m^2). Laboratory tests revealed a suppressed TSH level of $<$0.005 μIU/mL (reference range: 0.27–4.2 μIU/mL), elevated free T4 of 4.47 ng/dl (reference range: 0.93–1.7 ng/dl), thyroperoxidase antibody of 397 IU/mL (reference range: 0–34 IU/mL), and thyrotropin-binding inhibitory immunoglobulins of 37 IU/l (reference range: 0–115 IU/l). The anti-TSH receptor antibody was also elevated at 20.5 IU/l (reference range: $<$1.22 IU/l). A thyroid ultrasound showed a heterogeneous and hypoechoic thyroid gland with increased vascularization. Additionally, a heterogeneous structure was observed below the left thyroid lobe. A CT scan of the neck and chest confirmed the presence of a hyperplastic thymus measuring 27 mm, located below the thyroid gland. Following a neurological evaluation, electromyography (EMG) was performed, and myasthenia gravis was ruled out. The patient was started on Methimazole 5 mg twice daily (2-0-2). After six weeks, she returned for follow-up with no symptoms of hyperthyroidism and a weight gain of 1.5 kg. Laboratory results showed TSH at 0.45 μIU/mL and free T4 at 1.1 ng/dl. A follow-up neck CT scan was scheduled for three months later.

Conclusion

Thymic hyperplasia is a common finding in patients with Graves' disease. It is important to consider this diagnosis in patients with thyrotoxicosis and a mediastinal mass to prevent unnecessary interventions that could lead to harm. The prognosis is excellent, and treatment with methimazole has been reported to contribute to thymic mass reduction.

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P1181

JOINT2467

Case report: misleading increase in thyroid-stimulating hormone receptor antibodies during pregnancy in graves disease: value of functional, cell-based assays

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Introduction

Graves disease is an autoimmune endocrinopathy caused by thyroid-stimulating hormone receptor antibodies (TSH-R-Ab). Classically, this results in hyperthyroidism as thyroid-stimulating autoantibodies (TSAb) predominate. Nevertheless, these antibodies can also exhibit blocking (TBAb) or neutral activity. The net activity determines the clinical presentation and approach. Specific consideration and monitoring in pregnancy is suggested due to TSH-R-Ab's ability to migrate transplacentally and affect the fetus' thyroid gland. However, conventional thyroid receptor binding tests detect all types of thyroid hormone receptor antibodies without differentiating between them.

Case Report

A 36-year-old woman with Graves disease without ocular involvement had been treated for 56-months with propylthiouracil (PTU) and L-T4 replacement therapy. The TSH-R-Ab titer, measured with two different chemiluminescence immunoassays during follow-up, remained persistently elevated. During the first trimester of her twin pregnancy, we noticed a tendency toward hypothyroidism and a remarkably increased TSH-R-Ab titer, considering the difference in immunoassay. The quantity and functional properties of TSH-R-Ab can be altered during gestation due to immunological changes. In classical Graves caused by TSAb, these antibodies will usually decrease during pregnancy. However, the antibodies may become blocking or neutral in rare cases. In consideration of hypothyroidism, the dose of PTU was reduced incrementally. L-T4 was associated given the low-to-normal T4-titer, where we aimed for higher values to sustain neurological fetal development. Ultimately, PTU was stopped and L-T4 progressively increased according to thyroid testing every two weeks. Development of both fetuses was normal with no evidence of hypo- or hyperthyroidism. Considering the appearance of TBAb would imply a risk of hypothyroidism in the fetuses, a functional TSH-receptor-antibody assay was requested to differentiate between all types of TSH-R-Ab. This test was performed by Prof. Dr. Kahaly at Johannes Gutenberg University. We concluded that neither thyroid-stimulating nor thyroid-blocking antibodies were present. Therefore, the measured antibodies were neutral. A favorable result given that these antibodies do not affect thyroid function, neither the mother's nor the fetuses'.

Conclusion

When observing a switch between hyper- and hypothyroidism in patients with known Graves disease, it is important to screen for functional TSH-R-Abs. This distinction is important during pregnancy because inadequate maternal L-T4 levels could irreversibly impair fetal neurological development. Other indications for screening could include Graves disease with positive TSH-R-Abs persisting after 18 months of block-replacement therapy, before pregnancy when there is a known history of auto-immune thyroid disease addressed with thyroidectomy or radioactive iodine and autoimmune thyroid dysfunction secondary to immune reconstitution therapy.

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P1182

JOINT2924

Thyroid dysfunction in children with nephropathic cystinosis- single center experience

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Background

Nephropathic cystinosis is a rare genetic disease characterized by defective lysosomal cystine transport due to mutation in CTNS gene and consequently increased lysosomal cystine. Hypothyrodism is a known complication of nephropathic cystinosis but the pathogenesis of thyroid dysfunction appears to be more complex than merely thyroid gland destruction by lysosomal cysteine.

Methodology

Prospectively fifteen patients with infantile nephropathic cystinosis had been recruited from Cystinosis Clinic, Children's Hospital, Cairo University. Laboratory assessment of thyroid profile included free T4, free T3, TSH, thyroid autoantibodies (anti-thyroglobulin antibodies, anti-peroxidase antibodies) were measured. Thyroid ultrasound was done to all patients by a single operator.

Results

The age of recruited patients ranged from 5 to 10 years with mean age of 7.87 + 1.7 years. The frequency of hypothyroidism among our cohort was 8 patients (53.3%). Most of the affected patients were males 75% with their mean age was 8.25 + 1.17 years old. However, the age of diagnosis of thyroid dysfunction ranged from 1 to 8 years old with mean age of 4.87 + 2.08 years. All patients

(100%) had negative anti- peroxidase antibodies (TPO). As regards anti thyroglobulin antibodies (TG), 2 patients among euthyroid group had positive titer and only 1 patient among hypothyroid group had borderline titer. All patients with hypothyroidism were on thyroid hormone replacement therapy in the form of Levothyroxine. The dose of replacement therapy ranged from 50 to 150 (μg/day) with mean dose of 71.8 +34.08(μg/day). Only 5 patients were compliant to treatment and well controlled but the remaining 3 patients were not controlled. Thyroid ultrasound revealed very small thyroid gland for age among both euthyroid and hypothyroid group.
Conclusion
Hypothyroidism is a frequently reported complication among our cohort of patients with nephropathic cystinosis. There is no role of autoantibodies (anti-thyroglobulin, anti-peroxidase) in the pathogenesis of thyroid gland destruction. Patients with nephropathic cystinosis have small volume thyroid gland regardless of their thyroid status.

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P1183

JOINT2998

Risk factors, clinical characteristics, and outcomes of pediatric thyroid cancer: an egyptian single center experience

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Introduction
Thyroid cancer is rare in childhood and adolescents representing about 0.7% of all malignant tumors in children. The incidence rate of pediatric thyroid cancer has been increasing over the last years. However, in comparison to adults, the pathophysiology, presentation, management, and long-term outcomes in children is different and not fully-known.
Aim of the work
The aim of this study is to describe clinical, laboratory, and radiological characteristics of pediatric thyroid cancer patients in a specialized tertiary-care center in Egypt. In addition, risk factors for thyroid cancer and its recurrence, treatment and outcomes were assessed.
Patients and Methods
This study was a retrospective cohort enrolling 17 children diagnosed with thyroid cancer at Alexandria Pediatric Oncology Center at age <18 years. Informed consent was obtained from parents of included children after approval of Alexandria University Ethical committee. Data was extracted from medical records of patients over a 5-year period. The following data was recorded: demographic characteristics, family history of malignancy or autoimmune thyroid disease and history of radiation exposure. Anthropometric measurements, clinical presentation, laboratory, and radiological findings, pathology results, treatment and outcomes were also reviewed.
Results
The patients' age at diagnosis ranged between 5-17 years (mean 10.41 yrs). Almost 53% were females, while 47% were males. One patient (5.8%) was exposed to neck radiotherapy, 5 patients (29.4%) had family history of autoimmune diseases, while 3 patients (17.6%) had family history of malignancy (other than thyroid cancer). Three patients had Hashimoto's thyroiditis with positive thyroid autoantibodies. All patients presented with neck swelling. At diagnosis, only one patient was short (-3.4 SD) and had severe hypothyroidism (TSH 106 mIU/ml), while 7 patients (41.1%) were obese. Sixteen patients (94.1%) had unilateral affection, with predilection to right side (82.3%). Fifty eight percent had nodal metastases, while 35.29% (6/17) had distant metastases including lungs. Surgery was performed in all patients; categorized into hemithyroidectomy (5.88%), total thyroidectomy (29.4%), and total thyroidectomy with nodal dissection (64.7%). The majority of patients had papillary carcinoma (94%), except one patient had follicular variant of papillary carcinoma. All patients received radioactive iodine therapy. Forty seven percent of patients developed hypoparathyroidism following surgery. As regards outcome, 4 patients (23.5%) had persistent/recurrent thyroid cancer.
Conclusion
Our study describes the outcomes of a cohort of pediatric thyroid cancer patients in a specialized center in Egypt. Children and adolescents are more likely to have more severe stages of disease with higher recurrence rate, compared to adults.

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P1184

JOINT3016

Spindle epithelial tumor with thymus-like differentiation: A rare thyroid entity

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Introduction
Spindle epithelial tumor with thymus-like differentiation (SETTLE) is a rare thyroid malignancy with fewer than 50 cases reported worldwide. Typically arising in children and young adults, it is believed to originate from remnants of the branchial pouch or thymic tissue. It is often misdiagnosed as medullary thyroid carcinoma (MTC) or differentiated thyroid malignancies. Despite its indolent growth, SETTLE has a notable propensity for late metastasis, necessitating early recognition and long-term monitoring.
Case Description
A 14-year-old boy presented with a left-sided neck swelling that rapidly increased in size over three weeks. Prior to presentation at our center, an ultrasound and fine-needle aspiration cytology (FNAC) were performed, which showed spindle cells and was reported as MTC. On examination, apart from the neck mass, the child had a marfanoid habitus. There was no significant family history. Based on these findings, we suspected Multiple Endocrine Neoplasia type 2B and proceeded with the estimation of calcitonin, carcinoembryonic antigen (CEA), and plasma fractionated metanephrines, all of which were within the normal range. Since non-secretory MTC is rare, we reviewed slides of the FNAC performed outside and also conducted a fresh FNAC, which was again reported as MTC. Imaging done to stage the tumor did not reveal any evidence of metastasis. We proceeded with a total thyroidectomy with central compartment lymph node dissection. Histopathological examination of the resected specimen showed a biphasic tumor with spindle cells and cystic areas lined by mucinous columnar cells, with no extrathyroidal extension. Immunohistochemistry showed positivity for CK7, CK5/6, vimentin, BCL2, and CD117. Tumor cells were negative for TTF1, calcitonin, and chromogranin. This led to a diagnosis of SETTLE, and the child is under follow-up.
Discussion
SETTLE is a rare thyroid neoplasm that poses a significant diagnostic challenge. Despite its indolent course, SETTLE carries a significant risk of late metastases, especially to the lungs, occurring years after the initial diagnosis. Definitive diagnosis often requires immunohistochemical examination of resected tissue. Complete surgical resection with long-term follow-up is the mainstay of treatment. Given the potential for late recurrence, close follow-up with periodic imaging is essential.

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P1185

JOINT1316

Using TSH-receptor antibody testing to guide antithyroid drug withdrawal reduces the early relapse rate - a population-based study

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Background
Cessation of methimazole treatment in Graves' Disease (GD) often leads to relapse. In February 2023, Clalit Healthcare Services (CHS), the largest health maintenance organization in Israel, began to provide thyrotropin receptor antibody (TRAb) testing for patients with GD to help guide when to withdraw methimazole treatment. This nationwide retrospective cohort study evaluated whether using TRAb testing to guide methimazole withdrawal reduces relapse rates compared to clinical judgment alone.
Methods
Using the MDClone platform, we identified CHS-insured patients diagnosed with GD between 01/2013 and 09/2023. The first day of remission was established three months following the last purchase of methimazole if euthyroid or hypothyroid thyroid function test results were documented during this timeframe. Exclusion criteria included prior thyroidectomy or radioactive iodine treatment, pregnancy, and elevated liver transaminases ($\geq$3 times the upper limit of normal), or neutropenia ($\leq 1{,}000 \times 10^3/\mu L$) within six months of methimazole cessation. Patients were grouped into two cohorts; one where TRAb titer was tested and

measured <2.5 UI/l (seronegative) within three months of the last purchase of methimazole ('TRAb assisted cohort'), and one where TRAb was not measured in this time period ('clinical assessment cohort'). Baseline characteristics and the primary outcome - GD early relapse, defined as subsequent thyrotoxicosis during one-year follow-up were compared. A frailty Cox regression assessed the association between TRAb seronegative status immediately prior to methimazole cessation and disease relapse, adjusting for potential confounders.
Results
The study included 3420 clinical episodes; 84 in the TRAb assisted cohort and 3336 in the clinical assessment cohort. Age (median 49 years, $P = 0.47$), gender (75% female, $P = 0.8$) and socioeconomic status (score of 3 when using a five-point scale, $P = 0.46$) were similar in the two cohorts. At the time of GD diagnosis, free triiodothyronine (T3) was above the upper limit of normal in 73% of patients in the TRAb assisted cohort and 66% in the clinical assessment cohort ($P = 0.4$). The proportion of patients with TSH above or within the normal range prior to methimazole cessation was similar (87% in both cohorts, $P > 0.99$). During one-year follow-up, 49/84 (55%) in the TRAb assisted cohort and 2606/3336 (78%) patients in the clinical assessment cohort relapsed ($P = 0.002$). TRAb seronegative status prior to stopping methimazole reduced the risk of relapse by 38% compared to clinical assessment alone (HR 0.62, CI 0.46-0.84, $P = 0.002$).
Conclusion
Seronegative TRAb status reduces the one-year relapse risk by 38% amongst patients presumed to be in remission.

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P1186

JOINT2591

Trapping-only nodules – are they higher risk for malignancy?

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Introduction
Trapping-only nodules, or "discordant" nodules, are thyroid nodules that exhibit increased uptake of radioiodine and decreased uptake of technetium-99m on thyroid scans. Unlike regular "hot" nodules, which actively synthesize and secrete thyroid hormones, trapping-only nodules simply trap the iodine but there is no organification or increased hormone synthesis, and consequently there is no hyperfunction. It has previously been proposed that this trapping-only phenomenon might be associated with higher risk of malignancy, and thus, these nodules often require careful evaluation.
Aim
Evaluate the risk of malignancy of trapping-only nodules.
Methods
All thyroid scans performed in our center from January 2020 to June 2024 reporting trapping-only nodules were reviewed ($n = 133$). Subsquently, pathology results from all the nodules that underwent fine-needle aspiration cytology and/or surgery were examined ($n = 41$). Characteristics of the nodules on ultrasound were also collected.
Results
Thirty-nine patients with 41 trapping-only nodules were included, 66.7% were female and the mean age was 59.0 ± 12.9 year. Thirty-one (75.6%) had subclinical thyrotoxicosis, and TSH nadir was 0.17 ± 0.13 mU/l. Twenty-five (64.1%) had uni- or multinodular toxic goiter and 8 (20.5%) had Graves' disease. Regarding ultrasound characteristics, the mean size of the nodules was 21.2 ± 9.9 mm, and most were classified as EU-TIRADS 3 (56.1%) and EU-TIRADS 4 (36.6%). Of the 33 nodules that underwent fine-needle aspiration cytology, 26 (78.8%) were benign, 5 (15.2%) were nondiagnostic, and 2 (6.0%) were suspicious for malignancy, according to the Bethesda system. Of the 14 patients that underwent surgery, 6 (75.0%) had pathology findings consistent with thyroid follicular nodular disease, 1 (12.5%) had a single adenomatous nodule, and 1 (12.5%) had a hyalinizing trabecular tumor, which is a low-risk follicular cell-derived neoplasia. Six nodules had both results from aspiration cytology and surgical histology. Of note, of the two patients with nodules suspicious for malignancy, one had follicular nodular disease and the second had the hyalinizing trabecular tumor.
Conclusion
Trapping-only nodules do not appear to carry an increased risk of malignancy, and their evaluation should be similar to "cold" nonfunctioning nodules. Larger studies are needed to assess the true prevalence of thyroid malignancy among trapping-only nodules.

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P1187

JOINT2821

From thyroid storm to cardiac recovery: the impact of hyperthyroidism on heart function

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Introduction
Hyperthyroidism is a systemic disorder with significant cardiovascular implications, including arrhythmias and structural heart changes. We report a case of a 27-year-old male with untreated hyperthyroidism presenting with thyroid storm and severe cardiovascular complications.
Case Description
A 27year-old male presented to the emergency room with worsening asthenia, palpitations, myalgia, diarrhea, and fever (39-40°C) over the past week. He was diagnosed with hyperthyroidism in 2019 but had not been taking any medications nor attending follow-up appointments. His clinical history included 25 kg weight loss, episodic palpitations, sweating, anxiety, and extremity tremor since 2019. On admission, he was alert, reactive, with marked exophthalmos and goiter. His blood pressure was 90/73 mmHg, heart rate of 180 bpm, corresponding to atrial fibrillation. Laboratory findings indicated severe hyperthyroidism: TSH <0.01 mUI/l (RV 0.27-4.20), T3 577 ng/dl (RV 80-200), fT4 6.03 ng/dl (RV 0.93-1.70); hepatocellular injury (ALT 167 UI/l, AST 126 UI/l, total bilirubin 1.7 mg/dl), mild systemic inflammation (CRP 3.47 mg/dl) and positive TRABs (17.7 UI/l). A diagnosis of thyroid storm was made (85 points on the Burch-Wartofsky Point Scale), and the patient was admitted to the intensive care unit, where treatment with propylthiouracil, hydrocortisone, potassium iodide, and propranolol was initiated. However, due to worsening hepatic cytolysis, therapy was switched to methimazole. A transthoracic echocardiogram revealed a severely dilated left atrium and severe mitral regurgitation, attributed to annular dilation, posterior leaflet hypomobility, and pseudo prolapse of the anterior leaflet (EROA 0.52 cm^2, regurgitant volume 63 mL). Right ventricular systolic function was impaired, and a mobile hypoechoic mass was noted near the superior vena cava, raising suspicion of thrombus formation. Anticoagulation therapy was initiated, and additional studies were performed to rule out other potential etiologies or complications. No other significant findings were identified. Heart rate control was challenging, necessitating additional digoxin before stabilizing with beta-blockers after euthyroidism was achieved. Follow-up echocardiography showed an improvement in mitral regurgitation severity from severe to mild-moderate.
Discussion
This case underscores the profound effects of hyperthyroidism on cardiovascular function, emphasizing the necessity of early diagnosis and intervention to avert life-threatening complications. The improvement in structural heart changes, such as mitral regurgitation, after achieving euthyroidism highlights the dynamic cardiovascular impact of thyroid dysfunction and reinforces the need for comprehensive endocrine and cardiac management.
Conclusion
Thyroid dysfunction can significantly impact cardiac structure and function. Early recognition and treatment of hyperthyroidism are crucial to prevent cardiovascular deterioration and improve patient outcomes.

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P1188

JOINT950

Decoding elevated tsh with normal free t4: a comprehensive guide to differentiation, genetic insights, and diagnostic strategies

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Background
Elevated thyroid-stimulating hormone (TSH) levels with normal free T4 can result from a variety of physiological or pathological causes. Differentiating these causes is crucial for effective diagnosis and management. Genetic factors further complicate this landscape, requiring careful evaluation using clinical and laboratory data.
Objective
To summarize key genetic factors, physiological and pathological causes, and diagnostic steps associated with high TSH and normal free T4, based on current studies.
Methods
Data from multiple studies were analyzed to identify genetic contributions, differentiate causes, and outline diagnostic steps. Key findings were summarized into structured tables.

Results

Table 1: Genetic and Differentiation Causes.

Category	Focus	Frequency	Key Studies (n)
Genetic Factors	TSHR, DUOX2, PAX8 mutations	Rare	15 studies (n = 3,150)
	Deiodinase polymorphisms (DIO1, DIO2)	10–15%	8 studies (n = 1,100)
	Thyroglobulin mutations (TG)	Rare	4 studies (n = 700)
Physiological	Transient elevation, lab variability	10–20%	18 studies (n = 3,200)
Pathological	Subclinical hypothyroidism, autoimmune	20–35%	28 studies (n = 3,500)

Table 2: Differentiation of Causes.

Cause Type	Specific Cause	Description
Physiological	Stress, lab variability	Non-pathological causes such as stress or circadian changes in TSH levels.
Pathological	Autoimmune, medications	TSH elevation due to thyroid dysfunction, drug side effects, or pituitary issues.

Table 3: Diagnostic Steps.

Step	Action	Purpose
Autoantibody Testing	Measure anti-TPO and anti-thyroglobulin antibodies	Detect autoimmune thyroid disease
Ultrasound	Evaluate for structural abnormalities	Identify nodules or Hashimoto's thyroiditis
Thyroid Function Tests	Repeat TSH and free T4 levels	Rule out transient changes
Family History & Genetics	Investigate familial patterns and genetic mutations	Uncover hereditary causes
Exclude Secondary Causes	Review medications and iodine exposure	Identify non-thyroidal factors

Conclusion

Elevated TSH with normal free T4 is multifactorial, encompassing physiological, pathological, and genetic components. Differentiation relies on targeted diagnostic steps including antibody testing, imaging, and genetic analysis. A structured approach aids in accurate classification and management.

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P1189

JOINT106

Ultrasonography and cytology previous results analysis in patients that have undergone thyroid surgery

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Objectives

To review the final pathological results in thyroid nodular disease surgeries and compare them with the previous ultrasonographic and cytological Results.

Patients and Methods

Among the patients that underwent surgery between January 2019 and June 2024, in our database we had at least one ultrasonography and one valid cytology of 304 nodules. EU-TIRADS classification has been used for ultrasound characteristics and the Bethesda system for cytology results.

Results

Among those 304 nodules, 229 (75.3%) had a non-malignant result and 75 (24.7%) malignant. Eleven out of 135 (8.1%) EU-TIRADS 3 were malignant, 22 out of 92 (23.9%) EU-TIRADS 4 and 40 out of 66 (60.6%) EU-TIRADS 5. None of 17 (0%) Bethesda I were malignant, 6 out of 90 (6.7%) Bethesda II, 11 out of 117 (9.4%) Bethesda III, 4 out of 21 (19%) Bethesda IV, 28 out of 34 (82.4%) Bethesda V and 26 out of 26 (100%) Bethesda VI. Combining the two classifications, it can be highlighted that among Bethesda V-VI nodules, 3 out of 7 (42.9%) EU-TIRADS 3 were malignant, 17 out of 19 (89.5%) EU-TIRADS 4, and 32 out of 32 (100%) EU-TIRADS 5. On the other hand, in Bethesda II-III nodules, 7 out of 111 (6.3%) EU-TIRADS 3 were malignant, 3 out of 63 (4.8%) EU-TIRADS 4, and 7 out of 29 (24.1%) EU-TIRADS 5.

Conclusions

The cytology results are highly reliable in our centre (equal or better than the theoretical in Bethesda I and Bethesda III-VI). The apparent high malignancy percentage among Bethesda II nodules can be explained because the reasons why these nodules undergo surgery may give them a higher malignancy risk than those that do not. The interactions between ultrasound and cytology classifications could be used to better assess the indication for surgical treatment.

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P1190

JOINT557

Thyroid peroxidase antibodies and their role in predicting outcomes in graves' disease treatment

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Introduction

Graveś disease (GD) is the predominant cause of hyperthyroidism. Treatment options include antithyroid drugs (ATD), surgery, and radioactive iodine ablation (RI). After treatment with ATD, both relapse and development of hypothyroidism are common. Although thyroid peroxidase antibodies (anti-TPO) are prevalent in patients with GD, their role in driving relapse or hypothyroidism after treatment in patients with GD remains unclear. This study aimed to determine if patients with anti-TPO at GD diagnosis are more likely to relapse after ATD or RI treatment, and if patients with anti-TPO are at increased risk of developing hypothyroidism post-ATD treatment.

Methods

This was an observational, non-interventional retrospective registry study, which included 712 patients treated for GD at a single center in Sweden during 2002-2018.

Results

After therapy with ATD, there was no difference in relapse rate between patients with (37.0%) or without (38.4%) anti-TPO at GD diagnosis. Age <40 years was a risk factor for relapse after ATD ($P < 0.0001$). Presence of anti-TPO at diagnosis was associated with reduced relapse rate after RI (13.9% vs. 24.6%; $P = 0.049$). Development of hypothyroidism after discontinuation of ATD did not correlate with anti-TPO status at diagnosis (with anti-TPO: 17.3%; without anti-TPO: 20.8%).

Conclusion

Anti-TPO positivity at diagnosis of GD did not affect the relapse rate after ATD treatment but could be associated with a better effect of RI. Anti-TPO did not increase the risk of hypothyroidism post-ATD. Understanding these and other risk factors can facilitate treatment choices and help physicians individualize management and follow-up strategies for patients with GD.

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P1191

JOINT1774

Admission and follow-up characteristics of pediatric and adolescent patients with hyperthyroidism

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Aim

Hyperthyroidism is rare in childhood, and its diagnosis may be delayed. The approaches to follow-up and treatment are varied, and evidence-based guidelines are lacking. This study aimed to evaluate the presentation and follow-up characteristics of patients with hyperthyroidism.

Material and Methods

Patients aged 1 to 18 years diagnosed with hyperthyroidism and admitted between September 2005 and January 2023, with complete data available, were included. Admission and follow-up characteristics were recorded from their files. The etiology of hyperthyroidism, treatment, response to therapy, and follow-up periods were evaluated. The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, Version 26.0, Chicago, IL).

Results

The mean age of the 63 patients included in the study was 11.7 ± 4.95 years, and the female/male ratio was 1.86. Forty-eight (76.2%) of the patients were

diagnosed with Graves' disease (GD), with Hashitoxicosis ($n = 9$, 14.3%) being the second most common diagnosis. The mean age was 12.03±4.52 years in patients with GD and 14.94±3.44 years in patients with Hashitoxicosis (p:0.04). Ophthalmopathy was found in seven patients (11.1%). Euthyroidism was achieved in 60 patients in whom antithyroid drug (ATD) treatment was initiated in a mean of 7±8.29 months (71.4% in the first six months). No side effects were observed with ATDs except allergic rash in two patients. The mean duration of treatment was 25.03±22.9 months and was longer in patients with GD than in patients with Hashitoxicosis (30±23.4 months vs. 6.1±6.6 months, $P = 0.002$). The mean follow-up period was 36.9±32.3 months. While the remission rate during the follow-up period was 22.9% in patients receiving ATDs for GD, 15 of 48 patients (31.3%) relapsed after a mean of 8.4±5.02 months. Thyroidectomy was performed in 11 (17.5%) patients (9 with GD, 2 with toxic adenoma). Thyroidectomy was more frequent in the presence of ophthalmopathy ($P = 0.018$) and in patients with larger thyroid gland volume ($P = 0.044$) and volume SDS ($P = 0.001$). It was found that the time to achieve euthyroidism ($P = 0.0015$) and the time to TRAb negativity ($P = 0.022$) were longer in those who underwent thyroidectomy compared to those who didn't.

Conclusion

In the majority of children with hyperthyroidism, euthyroidism can be achieved in the first six months with ATDs. In children with GD, the long-term remission rate with ATDs is low. Thus, permanent treatment is likely to be required in the presence of large goiter, ophthalmopathy, and in patients in whom biochemical euthyroidism and TRAb negativity cannot be achieved with long-term treatment.

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P1192

JOINT303

Hyperthyroidism and renal function: unravelling the diagnosotic dilemma in GFR estimation

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Summary and Background

Estimation of glomerular filtration rate(eGFR) is commonly based on biomarkers like creatinine(sCr) and cystatin C (sCysC), which are influenced by various factors, including muscle mass and thyroid status(1)(2). This case report presents a unique challenge in accurately assessing renal function in a patient with Chronic Kidney Disease(CKD) who developed severe hyperthyroidism and extreme weight loss. The patient's eGFR values significantly differed depending on the biomarker used. This disparity raises concerns about the reliability of these biomarkers in such complex clinical scenarios. While thyroid dysfunction is known to affect both sCr and sCysC levels, the aggregate impact of hyperthyroidism on eGFR in CKD patients remains poorly studied. Previous literature has highlighted the paradoxical effects of hyperthyroidism—where eGFR-Cr is often overestimated and eGFR-CysC is underestimated(3)—yet there is limited evidence to guide clinicians on how to reconcile these findings.

Investigations

Thyroid Function	- **TSH**: <0.01 μU/mL - **Free T4**: 49.0 pmol/l
Renal Function	- **Serum Creatinine(sCr)**: 102 μmol/l - **Serum Cystatin C(sCysC)**: 3.09 mg/l - **eGFR Cr(Creatinine-based)**: 56 mL/min/1.73m^2 (overestimated) - **eGFR CysC(Cystatin C-based)**: 16 mL/min/1.73m^2 (underestimated)

Discussion and Conclusion

To our knowledge, the 2015 study by Suzuki *et al*. is the only clinical study examining eGFR Cr-CysC in thyroid dysfunction (3). This study demonstrated that overestimation of eGFR-Cr and underestimation of eGFR-CysC in the presence of elevated thyroid hormones could be corrected when the condition was treated. Interestingly, the eGFR Cr-CysC derived from the CKD-EPI-Creatinine-Cystatin Equation remained largely unchanged after resolving the hyperthyroid state. This suggests that eGFR Cr-CysC may be independent of thyroid status, offering more accurate method for renal function assessment. In conclusion, healthcare professionals should be aware of the unreliability of Creatinine and Cystatin-C in hyperthyroid patients. The CKD-EPI-Creatinine-Cystatin Equation shows promise but requires further research to guide its use in patients with both CKD and thyroid disease.

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P1193

JOINT2253

Life saving Plasma exhchange in resistant thyroid storm with myocardial infacrtion

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Introduction

Thyrotoxic crisis is a rare, life-threatening emergency. Early diagnosis and prompt management reduces morbidity and mortality. We, hereby, report the case of a patient presenting with low GCS secondary to thyroid storm and consequently developed multi organ failure. Due to lack of clinical response to conventional treatment, plasmapheresis was carried out with a favorable outcome.

Case Presentation

A 65-year-old lady was diagnosed with hyperthyroidism while an inpatient in mental health care for worsening bipolar disorder. Two weeks later, she was transferred to our hospital with chest infection. She was withdrawn and non-compliant therefore, anti-thyroid treatment was frequently interrupted. Her condition rapidly deteriorated and she was transferred to ITU with respiratory failure and GCS of 7/15. Her HR was 148/min, BP-170/ 90 mmHg, RR-54/min, temperature 38.3^{0}C. She fulfilled the criteria for diagnosis of thyrotoxic storm as per Burch Wartofsky point scale (BWP) and Japan thyroid association (JTA). Her TSH was <0.05 μIU/ml; T4 61 ng/dl, T3 16 pg/ml. TRAb 9.6 IU/l. She was intubated and started treatment immediately including Propylthiouracil, Lugol's Iodine, Propranolol, Hydrocortisone and Cholestyramine. Then she developed type II myocardial infarction, complicated by acute kidney and liver injury due to cardiogenic shock in addition to coagulopathy. GCS remained low despite normal CT head and EEG. Conventional treatment failed to control her thyroid function after 6 days, so plasma exchange was commenced. She became euthyroid after 2 sessions. She successfully underwent total thyroidectomy. Her GCS started improving 7 days post-operatively and she was successfully weaned off ventilator and discharged.

Discussion

Thyroid storm is a rare presentation of hyperthyroidism with high mortality. The exact mechanism of this condition remains poorly understood. A potential explanation is reduced affinity of TBG for T4 leading to an increased level of freeT4. Moreover, an increase in target cell-β-adrenergic receptor or change in the signalling pathways can result in increased sensitivity to stimulation. Therapeutic plasma exchange (TPE) has been successfully utilised in a variety of diseases. It's a safe procedure, with overall incidence of adverse effects around 5%. Its use in treating thyrotoxic crisis has been demonstrated in a few case reports and case series globally. Despite its proven effectiveness, TPE is not yet included in recently published guidelines on management of thyrotoxicosis suggesting the need for further evaluation. However, in cases when conventional measures fail, plasmapheresis is a reasonable safe option to decrease circulating thyroid hormone levels and should be considered as a stabilising measure.

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P1194

JOINT2659

Thyroid cancer in thyroglossal duct cysts

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Introduction

Thyroglossal duct cyst (TGDC) is the most frequent cervical congenital anomaly. Thyroid carcinomas arising from these structures are rare, being present in approximately 1.5% of patients with TGDC. The diagnosis usually is done post-

operatively after the resection of the cyst. Due to the rare occurrence there is no definite consensus on the optimal treatment of thyroid cancer in thyroglossal duct cyst carcinomas (TGDCCs), namely the need of complementary thyroidectomy.
Objective
We aimed to assess tumor presentation, therapeutic strategy and follow-up in a series of patients with TGDCCs.
Methods
We performed a retrospective analysis of all patients with TGDCCs, selected from the pool of individuals with histological diagnosis of thyroglossal duct cyst established between 2010 and 2024 at our institution.
Results
From a total of 244 patients with thyroglossal duct cysts, 7 patients (2.9%) were identified with TGDCCs (5 females, 2 males), aged at diagnosis between 17 and 65 years (mean: 41,1; median: 41). In six patients clinical presentation was a cervical mass while the other was diagnosed by an ultrasound scan during follow up of a previous thyroid cancer. In all cases the diagnosis was established after surgery. Papillary thyroid carcinoma (PTC) was found in all samples (follicular variant PTC in 1 patient and classic PTC in 6 patients), sized between 0.1 and 1.4 cm, 5 of them being microcarcinomas. All patients were treated with Sistrunk surgery; one did total thyroidectomy at the same time for a suspicious nodule that histology confirmed as synchronous PTC with vascular invasion and was treated with radiodine ablation; the other two did a complementary thyroidectomy afterwards, both with no malignancy. None of the cases presented capsular invasion, lymphovascular invasion, soft tissue extension, lymph node metastasis or positive margins. No metastasis or recurrence was found in any of the cases after a mean follow up of 8.6 (4-14) years.
Conclusion
TGDCCs are a rare clinical entity with good prognosis. Despite the controversy regarding their therapeutic approach and follow-up, Sistrunk procedure alone with regular thyroid evaluation may be enough in low-risk patients. Further studies are needed to clarify this issue.

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P1195

JOINT698

Predictor of treatment outcome for pediatric Grave's disease

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Purpose
Graves' disease (GD), the most common cause of hyperthyroidism in children, is primarily and effectively treated with Antithyroid drugs (ATDs). The aim of this study was to evaluate the factors that could predict remission, relapse, and the need for persistent high-doses of methimazole (MMI) in pediatric GD.
Methods
This is retrospective study by medical records included GD diagnosed before 19 years of age from January 2004 to December 2023. Remission was defined as maintaining the euthyroid state for more than 6months after stop ATD. The high-doses group was defined as those receiving MMI doses more than 5mg/day at last follow-up, regardless of their euthyroid status.
Results
Of the 113 patients (95 girls and 18 boys), 47(41.6%) achieved remission at a mean of 37.17±29.01 months after treatment. Compared to the non-remission group, the remission group showed significant differences in T3, fT4 and TSH-binding inhibitor immunoglobulin (TBII) at diagnosis (330.92 ± 177.72 vs 413.75 ± 179.09 ng/dl, $P = 0.017$; 3.31 ± 1.39 vs 4.12 ± 1.34 ng/dl, $P = 0.002$; 15.68 ± 14.37 vs 23.37 ± 16.61 IU/l, $P = 0.012$, respectively), time to TBII normalization (25.26 ± 29.88 vs 45.33 ± 37.17 months, $P = 0.003$), and TBII ratio at 6 months (54.98 ± 42.04 vs 87.92 ± 55.94%, $P < 0.001$). 11 patients (11/47, 23.4%) experienced relapse at a mean of 17.91±16.81 months after remission. Compared to non-relapse group, relapse group was predominantly male (5.6 vs 45.5%, $P < 0.001$) and exhibited a higher TBII ratio at 12 months (36.64 ± 33.78 vs 87.18 ± 78.14%, $P = 0.025$). In non-remission group, 38/66 patients (57.6%) received persistent high doses of MMI, with a mean dose of 0.39 ± 0.17mg/kg/day at the last follow-up. Compared to low-dose group, high-dose group showed significant differences in time to T3, fT4 and TBII normalization (1.21 ± 0.69 vs 2.39 ± 1.76 months, $P < 0.001$; 1.50 ± 0.84 vs 2.61 ± 2.47months, $P = 0.013$; 7.00 ± 2.61vs 9.55 ± 5.14months, $P = 0.011$, respectively), and TBII ratio at 6 months (61.57 ± 36.96 vs 107.34 ± 59.90%, $P < 0.001$). Under the ROC curve for the TBII ratio at 6 months treatment, the cut-off value of remission was 62.5%, and the cut-off value of the need for persistent high-doses of MMI was 82.5%.
Conclusion
Thyroid hormone and TBII levels at diagnosis, time to thyroid hormone and TBII normalization, and the TBII ratio after ATD treatment can be used to predict remission, relapse, and the need for persistent high-dose MMI in pediatric GD patients.

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P1197

JOINT364

Prevalence of thyroid dysfunction in children with asthma in a tertiary care hospital of jharkhand, india - a cross-sectional study

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Background
Hyperthyroidism has been linked to asthma exacerbations, while some studies suggest an increased risk of hypothyroidism in individuals with asthma. Although several studies have shown a positive association between asthma and thyroid disorders, these findings are primarily focused on adult populations. Research exploring the prevalence of thyroid dysfunction and its impact on asthma control in pediatric populations remains limited.
Objective
To determine the prevalence of thyroid dysfunction in asthmatic children aged 6 to 15 years and to assess the relationship between thyroid function and the level of asthma control in this population.
Methods
A cohort of 80 children with BA (24 girls, 56 boys; mean age 111.3 ± 25.1 months) underwent comprehensive clinical evaluation, including spirometry, the Asthma Control Questionnaire (ACQ-5), and laboratory assessments of thyroid-stimulating hormone (TSH), free thyroxine (T4), and anti-thyroperoxidase antibodies (anti-TPO) via ELISA.
Results
Elevated TSH levels, indicative of subclinical hypothyroidism (maximum 11.45 mIU/l), were observed in 22 patients (27.5%), all without hypothyroid symptoms or anti-TPO elevation. TSH levels ranged from 3.16–5.74 mIU/l in other participants, while free T4 levels were mildly elevated in 18 patients but remained within clinically insignificant limits (maximum 23.1 pmol/l). A weak negative correlation was identified between TSH levels and ACQ-5 scores ($r = -0.29$, $P = 0.033$). Subclinical hypothyroidism was most prevalent (27.5%) in patients with fully controlled BA (mean TSH 3.39 ± 1.96 mIU/l) but absent in those with uncontrolled BA (mean TSH 1.87 ± 0.73 mIU/l). Patients with partially controlled BA exhibited intermediate TSH levels (mean TSH 2.93 ± 1.5 mIU/l), suggesting potential iodine deficiency. Despite these trends, group differences in TSH were not statistically significant ($F = 1.74$, $P = 0.1858$). Free T4 levels showed no significant variation across asthma control groups but negatively correlated with FEV1 ($r = -0.42$, $P = 0.01$). Normal TSH levels in poorly controlled BA may reflect suppression by stress-induced or exogenous corticosteroids rather than optimal thyroid function.
Conclusion
Subclinical hypothyroidism is common among children with well-controlled BA, occurring in 27.5% of cases. Further studies are needed to clarify the clinical significance and mechanisms underlying this association.

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P1198

JOINT569

Thyroid cancer in children: insights from an 18-year retrospective study at a tertiary center

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Background
Thyroid cancer is rare in children but represents the most common endocrine malignancy in this age group. Pediatric thyroid cancer exhibits distinct biological behavior compared to adults, characterized by higher rates of lymph node (LN) involvement and distant metastases, yet with a favorable overall prognosis. This study evaluates the clinicopathological features, treatment outcomes, and survival rates of children diagnosed with thyroid cancer.
Methods
A retrospective analysis was performed on pediatric patients ($\leq$18 years) diagnosed with thyroid cancer between January 2004 and December 2022 at King Hussein Cancer Center, Jordan. Data included demographics, clinical presentation, histopathology, staging, treatment details, and follow-up outcomes. Statistical analyses examined survival rates, recurrence patterns, and prognostic factors.
Results
The study included 25 children, predominantly female (n = 19, 76%). The median time to presentation was 2 months (range: 0.5–60). Papillary thyroid carcinoma (PTC) was the most common subtype (96%), with one case of medullary thyroid carcinoma, not MEN associated. Regional LN involvement was present in 84% of patients, and 16% (n = 4) had lung metastases at diagnosis. All patients underwent total thyroidectomy with LN dissection, and 92% received radioactive iodine therapy (median dose: 100 mci; range: 50–905 mci). After a median follow-up of 6.2 years (range: 0.5–20.1), the 5-year and 10 year overall survival rates were 100% and 93%, respectively. Recurrence occurred in 32% of cases (n = 8), primarily in regional LNs. Age, sex, LN metastasis, and distant metastases were not associated with increased risk of recurrence.
Conclusion
Thyroid cancer in children presents with unique clinical features, including high rates of LN involvement and distant metastases, yet it is associated with excellent long-term survival. Although recurrence is relatively common, it does not significantly affect overall survival. These findings emphasize the importance of comprehensive initial treatment and vigilant long-term follow-up to manage this disease effectively.

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P1199

JOINT613

Genetic landscape of goiterous hypothyroidism: key markers and clinical insights

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Background
Goiterous hypothyroidism, characterized by thyroid enlargement and impaired hormone production, arises from diverse genetic mutations affecting thyroid development and function. Advances in genetic analysis have expanded understanding of its molecular underpinnings, aiding early diagnosis and tailored interventions.
Objectives
To summarize the genetic markers associated with goitrous hypothyroidism and their clinical implications, focusing on recent findings and their impact on patient outcomes.
Methods
A systematic review of studies (1998–2024) was conducted to identify genetic markers, mechanisms, and clinical outcomes in goiterous hypothyroidism. Data from next-generation sequencing (NGS), linkage analyses, and case studies were analyzed for phenotypic correlations.
Results
1. Genetic Markers:.
• Thyroglobulin (TG) mutations (e.g., p.R277X, p.Val501Gly) impair hormone synthesis, contributing to congenital hypothyroidism (CH) and goiter (Caputo *et al*., 2007).
• Mutations in SLC5A5/NIS and DUOXA2 genes are linked to goitrous hypothyroidism, with severe phenotypes requiring long-term management (Stoupa *et al*., 2020; Jung *et al*., 2020).
• Oligogenic inheritance patterns were identified in congenital cases, emphasizing complex genetic contributions (Oliver-Petit *et al*., 2021).
2. Mechanisms and Clinical Impact:.
• Missense mutations in TG and TPO disrupt intracellular transport and hormone synthesis, causing thyroid enlargement (Hishinuma *et al*., 1998; Lee *et al*., 2013).
• Genome-wide studies identified loci on chromosomes 3q26.1-q26.3 and 14, linked to familial and autoimmune thyroid diseases (Takahashi *et al*., 2001; Tomer *et al*., 1998).
3. Therapeutic Outcomes:.
• Early hormone replacement therapy improved growth and cognitive outcomes in CH cases, while genetic insights informed precision medicine approaches (Li *et al*., 2021; Vincenzi *et al*., 2023).
• Novel interventions, such as combined selenium and myoinositol, showed promise in reducing thyroid antibodies in autoimmune thyroiditis (Ferrari *et al*., 2021).
Conclusion
Mutations in TG, TPO, DUOXA2, and other key genes shape the genetic landscape of goitrous hypothyroidism. Early diagnosis through advanced genetic tools enables tailored treatments, improving patient outcomes. Future research should focus on genotype-phenotype correlations and novel therapeutic strategies to enhance care for affected individuals.

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P1200

JOINT412

Ultrasound-based ultra-micro angiography for evaluating vascularity in diffuse thyroid disorders

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Background
Ultra-Micro Angiography (UMA) is an innovative Doppler ultrasound technique that significantly enhances the visualization of slow blood flow in small caliber vessels. The application of Subtraction UMA (sUMA) further refines this capability by eliminating background tissue interference, enabling a precise assessment of thyroid micro-vascularity. This study aimed to evaluate thyroid perfusion through sUMA in healthy individuals compared with those diagnosed with autoimmune thyroid conditions, while also exploring its potential implications in clinical practice.
Methods
This prospective, single-center study involved 70 participants, categorized into three groups: 18 healthy controls, 40 with chronic autoimmune thyroiditis (CAT), and 12 with Graves' disease (GD). All participants underwent multiparametric ultrasound followed by sUMA for microvascularity assessment. The Color Pixel Percentage (CPP) index was calculated to quantify the vascularity of the thyroid gland. Median CPP values were derived, and correlations with various clinical parameters were analyzed.
Results
The participant groups exhibited similar mean ages (ranging from 45.4 to 51.5 years), with a notable female predominance (72% to 80%). The median CPP values were significantly lower in controls (26.5; IQR [22-32.4]) compared to those with CAT (49.3; IQR [38.5-61.6]) and GD (54.5; IQR [41.7-64]; $P < 0.0001$). Within the control group, a moderate negative correlation between CPP and BMI was observed (r = -0.510, P = 0.032). In contrast, the CAT group demonstrated moderate positive correlations between CPP and TSH (r = 0.582, P = 0.002) as well as between CPP and thyroid volume (r = 0.492, P = 0.008).
Conclusions
sUMA is a reliable and effective modality for assessing thyroid vascularity in both healthy individuals and those with autoimmune thyroid disorders. The findings support the promising utility of sUMA in the diagnosis and clinical evaluation of thyroid diseases.

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P1202

JOINT2409

A less known cause of orbitopathy

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Introduction
IgG4-related disease (IgG4-RD) is a multisystemic fibroinflammatory condition characterized by clinical, histological, and serological markers. It presents with organomegaly, histological lymphoplasmacytic infiltration with IgG4+ plasma cells, varying degrees of storiform fibrosis, and elevated serum IgG4 levels. Most patients have multi-organ involvement, including the orbit. In cases of atypical orbital changes, besides thyroid eye disease (TED), IgG4-related orbital disease (IgG4-ROD) should also be considered.
Case 1
A 38-year-old female presented with eyelid swelling and hyperemia, conjunctival chemosis, and proptosis of the right eye, along with ipsilateral cheek swelling. Orbital MRI revealed right-sided exophthalmos (OD 25 mm, OS 17 mm), enlargement of the medial and lateral rectus muscles, borderline enlargement of the inferior rectus, and increased retrobulbar fat. Thyroid hormone levels were normal, and TRAb levels varied between $<$0.8–1.9IU/l (ref.range: 0.0-1.8IU/l). Serum IgG4 was elevated(2.87g/l). Her medical history is remarkable for atopy, nasal polyps, bronchial asthma, and surgery of the left submandibular salivary gland due to its enlargement, with extraction of regional lymph nodes. Due to persistently elevated liver enzymes and ASMA positivity with hepatomegaly, a liver biopsy was performed, showing severe steatohepatitis(NAS 7/8) but no signs of IgG4-RD. A review of the histopathology of a previously resected submandibular gland and lymph nodes confirmed probably IgG4-RD.
Case 2 A 43-year-old male presented with bilateral eyelid swelling, more pronounced on the right side, with an enlarged right lacrimal gland. Orbital CT revealed an enlarged right lacrimal gland and mild inflammation of the left lateral rectus muscle. His thyroid hormone levels were normal, TRAbs ranged from $<$ 0.8–2.4IU/l. Serum IgG4 was significantly elevated (6.09g/l). His medical history included bronchial asthma and nasal polyps. MRI with MRCP, performed due to abnormal liver function tests, revealed primary sclerosing cholangitis. Liver biopsy showed no histological characteristics of IgG4-RD.
Conclusion
Two patients were referred to our clinic with suspected TRAb-negative TED, but further investigations suggested IgG4-RD. Findings supporting IgG4-ROD included elevated serum IgG4, multi-organ involvement, and atypical orbitopathy (predominantly unilateral involvement, enlarged lateral rectus in both cases, and lacrimal gland involvement in the second patient). In the first case, histology of the salivary gland was used as a surrogate marker supporting IgG4-RD, increasing the likelihood that the ocular changes shared the same etiology. Features arguing against TED included normal thyroid function and morphology with negative to borderline elevated TRAbs, and the absence of a typical pattern of extraocular muscle involvement. TED and IgG4-ROD have overlapping orbital manifestations, making differential diagnosis challenging.

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P1203

JOINT245

An optimal capillary screen cut-off of thyroid stimulating hormone for diagnosing congenital hypothyroidism: gathering evidence

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Objective
To determine an appropriate cut-off of capillary Thyroid stimulating hormone (TSH) for congenital hypothyroidism.
Study design
Cross-sectional.
Participants
174,000 neonates born in different hospitals of Delhi, India, from November 2014 to October 2016.
Main outcome measures
Correlation between initial and repeat capillary TSH level and subsequent venous free thyroxine (fT4) level.
Results
102 newborns with initial/ repeat capillary TSH level of $\geq$20 mIU/l ($n = 174$) were confirmed to have congenital hypothyroidism at mean (SD) age of 5 (4) days. A good correlation between capillary TSH level and confirmatory venous fT4 level and postnatal age of sampling was obtained (r -0.6,-0.4). The area under the ROC curve (AUC) was 0.81 (95%CI 0.75 to 0.88), indicating referral capillary TSH level of 20 mIU/l to be a good predictor of subsequent high venous TSH level.
Conclusion
A cut off of $\geq$20 mIU/l for capillary TSH screening beyond 24 hours of life is optimal in the Indian setting for deciding further recall and workup, keeping a balance between sensitivity and recall rate.

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P1205

JOINT575

Nationwide web-survey on implementing the 2023 ETA guidelines for thyroid nodule management

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Background
Thyroid nodules are very common, and the European Thyroid Association (ETA) recently issued high-quality guidelines to standardize their management. However, the extent of guideline implementation and the barriers to adherence remain unclear. This study evaluates the application of the guidelines and identifies obstacles to their adoption among Greek endocrinologists.
Methods
Between November 2023 and April 2024, members of the Hellenic Endocrine Society (HES) completed a web-based survey on the management of a 2.5 cm thyroid nodule with fine-needle aspiration (FNA) cytology results of Atypia of Undetermined Significance (AUS). The scenarios varied by the nodule's sonographic risk classification: intermediate (EU-TIRADS 4) or high (EU-TIRADS 5). Participants also provided demographic information and reasons for non-adherence to the guidelines.
Results
The survey had a 25% response rate. For an EU-TIRADS 4 nodule with AUS cytology, 61% of respondents chose to repeat FNA, while only 23% opted to do so for an EU-TIRADS 5 nodule with AUS cytology, despite the 2023 ETA guidelines recommending repeat FNA in both scenarios. More experienced endocrinologists were less likely to select repeat FNA and more inclined toward total thyroidectomy in the EU-TIRADS 4 scenario. In contrast, experience had no significant impact on decision-making for the EU-TIRADS 5 scenario. Key barriers to guideline adherence included skepticism about the recommendations, limited access to reliable neck ultrasonography and molecular testing, and a shortage of high-volume surgeons.
Conclusions
Greek endocrinologists frequently deviate from the 2023 ETA guidelines for managing thyroid nodules with indeterminate cytology, citing challenges that may also affect clinicians in other countries. These findings highlight the importance of developing strong implementation strategies alongside guideline releases, particularly in anticipation of the upcoming American Thyroid Association guidelines for managing thyroid nodules in adults.

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P1206

JOINT1006

Riedl's thyroiditis arising from stable chronic atrophic Hashimoto's thyroiditis

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Background
Riedl's thyroiditis is a rare fibrosclerotic destructive thyroiditis of unknown etiology, arising either simultaneously or on preexisting autoimmune thyroiditis. We present a patient whose stable atrophic Hashimoto's thyroiditis "transformed" to Riedl's.
Case presentation
A 52-year-old woman with 3-year history of Hashimoto's thyroiditis presented because of gradually increasing TSH from high-normal to a recent 10.1mIU/l. The patient complained of mild discomfort on palpation and on swallowing over the left cervical area, starting a month before. She had previously been euthyroid on a stable replacement dose of L-thyroxine 75 mg daily. Thyroid ultrasound had also been stable, showing a small, slightly hypoechoic gland with increased vascularity. Past medical history was unremarkable and family history for autoimmune diseases was negative. On examination, the thyroid gland was visibly enlarged, hard and slightly tender on palpation. Ultrasound imaging showed marked change with bilateral hypoechoic avascular areas, measuring 23x 15 mm and 16x 14 mm, with a rim of hypervascular thyroid parenchyma. TSH was 8.14mIU/l, thyroglobulin 0.09ng/ml, CRP 2 mg/l (0-8) and ESR 8 mm/1hr. The findings were not consistent with subacute thyroiditis and an ultrasound-guided FNA was performed, (2 passes with a 23G needle and one pass with a 21G needle), with complete absence of material for cytology. Subsequently a core biopsy was performed, with findings consistent with Hashimoto's thyroiditis, while symptoms remained stable. A six-week trial of oral methylprednisolone had no effect. Finally, the decision was made to proceed to surgery due to diagnostic uncertainty and unremitting disease. The left lobe of the gland was removed piecemeal, without adverse events. The procedure was not completed because of significant risk of complications. Histopathologic diagnosis showed complete absence of follicles, diffuse fibrous tissue infiltrating parathyroid tissue and striated muscle, IgG4 positive plasmatocytic infiltrate and eosinophils, consistent with Riedl's thyroiditis. The patient remains stable on follow-up without systemic manifestations.
Conclusion
The diagnosis of Riedl's thyroiditis must be included in the differential diagnosis when a change in thyroid appearance or size associated with compressive symptoms occur in a patient with Hashimoto's thyroiditis. Awareness of this condition is important for appropriate management.
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P1207

JOINT1813
The clinical impact of vitamin D supplementation on thyroid eye disease outcome
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Introduction
Thyroid eye disease (TED) is the most common extraocular manifestation of Graves' disease. Recent reports demonstrate that low serum vitamin D levels is associate with TED diagnosis. The aim of our study is to evaluate whether low serum vitamin D levels are associated with active thyroid eye disease and whether or not supplementation potentially improves the clinical course of the disease for patients with TED as an adjuvant treatment.
Material and Methods
We have recruited 115 patients with TED from the Outpatient Clinic of Autoimmune Endocrinopathies, Department of Pathophysiology of the University of Athens, Greece. The analyzed data were respectively collected from the patients' medical record from the same investigator. We recorded a comprehensive personal and family medical history. Magnetic resonance imaging was performed in all patients. Serum vitamin D was measured for all patients. Patients already receiving vitamin D supplementation or received during the last 8 months were excluded from the study.
Results
Regarding demographic characteristics of study population mean age was 56.18 $\pm$ 1.63 years, the majority of the patients (74.8%) were females and 82.8% were smokers. Median CAS was 3/7 (1-7) and 19.6% of study population presented with unilateral disease. Active disease was present in 58.3%. Regarding disease severity 26.6% had mild disease, 52.3% moderate to severe and 21.1% had severe-sight threatening TED. We conducted subgroup analysis and compared the above characteristics between patients with active and inactive disease. Mean 25(OH) vitamin D levels for patients with active TED were 25.82$\pm$10.15 ng/ml whereas for patients with inactive TED mean levels were 24.83$\pm$12,88 ng/ml ($P = 0.677$). Moreover, we compared all variables between patients with disease duration <6 years and ≥ 6 years in an attempt to establish clinical factors contributing to disease chronicity. Mean 25(OH)vitamin D levels for patients with disease duration <6 years were 24.79 $\pm$11,68 ng/ml and for patients with disease duration $\geq$ 6 years were 28.12 $\pm$9,07ng/ml ($P = 0.261$).
Conclusion
We found higher levels of serum vitamin D concentration in patients with active and therefore more severe TED. However, the comparison does not reach statistical significance. Similarly patients with longer disease duration have higher vitamin D levels. As a result, vitamin D supplementation in patients with active TED is not strongly indicated. Further prospective studies are required to determine which subgroup of TED patients will potentially benefit from vitamin D supplementation as an adjuvant treatment.
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P1208

JOINT2714
Association of thyroid cancer risk with plasma 25-hydroxyvitamin D levels in multinodular goiter patients
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Introduction
Multinodular goiter (MNG) is a common thyroid disorder, often associated with an increased risk of differentiated thyroid cancer (DTC). Vitamin D insufficiency and multinodular goiter are prevalent worldwide, including in the Romanian population. Recent research has highlighted the potential role of vitamin D in various malignancies, but its influence on thyroid cancer development remains inconclusive. Given the high prevalence of both vitamin D deficiency and thyroid disorders, investigating their possible relationship is crucial. This study aims to assess the association between plasma 25-hydroxyvitamin D (25OHD) levels and the risk of DTC in patients with MNG, providing insight into potential endocrine and oncologic implications.
Material and Methods
We performed a retrospective study which included 351 patients evaluated for thyroid nodular goiter with fine needle aspiration (FNA) in a tertiary Endocrinology Department between 2022-2024. Mean age of the study group was 53.56$\pm$13.6 years (range 17-83 years), (16.8% males). The following data were collected from medical files: age, body mass index, serum 25OHD, freeT4, TSH, ATPO, anti-TG, ultrasound features of the thyroid nodules, Bethesda class at FNA.
Results
No significant differences were found in terms of age, body mass index and thyroid nodule dimensions between Bethesda subgroups. Patients with Bethesda class 3 or higher ($n = 72$) had significantly lower levels of 25-hydroxyvitamin D (22.6$\pm$10.58 ng/ml) in comparison with patients with Bethesda class 2 ($n = 279$, 25.5$\pm$11.6 ng/ml, $P = 0.043$). Moreover, serum 25-hydroxyvitamin D level was associated with ultrasound characteristics of the thyroid nodule. Thus, the presence of irregular margins was associated with significantly lower levels of serum 25 hydroxyvitamin D (22.42$\pm$11.53 ng/ml) in comparison with patients with nodules with regular margins (25.56$\pm$11.39 ng/ml, $P = 0.041$), and marginal vascularization was more frequently found in patients with 25-hydroxyvitamin D below 30 ng/ml (51%) in comparison with those with 25-hydroxyvitamin D above 30 ng/ml (39.6%, $P = 0.05$). Moreover, we found a tendency that patients with 25-hydroxyvitamin D below 20 ng/ml to present more frequently with incomplete hallo (19.1%) in comparison with patients with 25-hydroxyvitamin D above 20 ng/ml (12.3%, $P = 0.068$).
Conclusion
Our study suggests that lower levels of serum 25-hydroxyvitamin D might be associated with increased risk of thyroid malignancy.
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P1209

JOINT2005
MCT8 deficiency - a pathway of the "floppy baby" from thyroxine treatment to tiratricol
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Monocarboxylate transporter 8 (MCT8) deficiency known as Allan-Hernon-Dudley syndrome is an X-linked disorder caused by an impairment of the transcellular transportation of thyroid hormones into neurons due to SLC16A2 gene mutations. Clinical symptoms are a consequence of developing hypothyroidism in the brain and signs of hyperthyroidism in peripheral tissues. Affected patients develop mental retardation, axial hypotonia, peripheral spasticity, involuntary movements that may be paroxysmal. New treatments are being applied. We report a patient, who was born from an uneventful pregnancy in the 37th week of gestation, Apgar score 8/9, eutrophic. Shortly after birth suffered from pneumothorax, which was drained, he was dismissed with slight proximal and axial hypotonia. Neurological follow up showed deterioration of axial muscle tone around 5 months, but till 8 months there was evident regression in psychomotor development, pronounced hypotonia. EMG and EEG showed no pathology. SMA screen was negative. At 13 months MRI: delayed white matter myelinisation. EEG: unspecific abnormal activity. Endocrine assessment at 8 months was appropriate, but at 13 months showed signs of primary hypothyroidism and Thyroxin was started. After 5 months on medication there was no change. At 23 months NGS revealed mutation in SLC16A2 gene (c.940C T (p.Arg314Ter): Allan-Herndon-Dudley syndrome i.e. MCT8 deficiency. Endocrine tests on Thyroxin were broadened to fT3 and showed TSH 2,7 mIU/l, fT4 11 pmol/l fT3 8,35 pmol/l (2,5 – 5,8), Thyroxin was stopped. Vomiting led to elimination diet, which helped but he didńt gain weight, while growing normally. At 32 months TSH: 4,52 mU/l [0,70..5,97], Ft4: 6,61 pmol/l [10,45..22,35], fT3 14,72 pmol/l [3,69..8,46], with pronounced clinical picture. We started treatment with Tiratricol 350 ug daily, increasing the dose during 6 weeks to 75mg/kg daily, when the boy started to gain weight, slightly improved the axial muscle tone. But in another 8 weeks, he started vomit, was constipated, lost weight. At this time TSH was supressed. The dose was lowered and has been kept till now with normalised fT3. Evidence of epileptic encephalopathy on EEG and seizures led to antiepileptic treatment with good response. He is improving now his psychomotor development, slowly gaining weight on 5O ug /kg of Tiratricol.

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P1210

JOINT1936

A report on an unusual source of heterophilic antibodies interfering with thyroid function tests

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Introduction

Interference in thyroid function tests is a relative frequent condition that can lead to improper diagnosis and treatment. Interference can be multiple and involve certain drugs or patient-specific factors such as antibody production. These interferences can produce both false-positive and false-negative Results.

Case Report

We report a case of a 65-year-old man suffering from Waldenstrom macroglobulinemia (WM). During a hospitalisation for subacute neurological impairment, thyroid function tests were performed as a screening. Blood tests showed TSH of 0.79 mUI/l [0.27-4.2 mUI/l], total T4 >320 nmol/l [66-181 nmol/l], free T4 >100 pmol/l [11.2-24.1 pmol/l], total T3 >10 nmol/l [1.3-3.1 nmol/l], free T3 15.5 pmol/l [3.1-6.8 pmol/l]. Further workup revealed high titers of anti-TPO antibody (1231 kUI/l [<34 kUI/l]), anti-thyroglobulin (21.4 kUI/l [<33 kUI/l]) and TRAb (143.2 UI/l [<1.75 UI/l]). The patient was clinically euthyroid and without previous thyroid history or treatment known to cause thyroid dysfunction. This biochemical pattern in an asymptomatic patient raised suspicion of interference in thyroid function tests. This suspicion was supported when another laboratory platform was used to re-analyse thyroid function and showed values in the normal range. Biotin levels were normal. Tests repeated after serum pretreatment in heterophilic blocking tubes (HBT) showed normal values. The interference in this case is due to heterophilic antibodies. We hypothesised that the IgM production in WM can interfere with the immunoassay with the same mechanism of endogenous antibodies.

Discussion

This case report demonstrates a rare cause of heterophilic antibodies interference due to excessive monoclonal immunoglobulin M (IgM) production. It highlights the importance of considering the patient's history, clinical examination and collaboration with the laboratory. When an interference is suspected, changing the manufacturer assay or re-measuring the analyte after dilution, precipitation or adding of blocking agents, can suggest an interference. However, a lack of effect from these methods does not rule out interference.

Conclusion

Heterophilic antibody-like behavior of WM-associated IgM can complicate diagnosis and interpretation of various laboratory tests. It must be considered when interpreting results in known WM patients, to avoid misdiagnosis and mistreatment. In our patient, it affected thyroid function tests, but many interferences have been reported for other endocrine tests (cortisol, testosterone, prolactin), tumoral markers (AFP, PSA) and cardiac markers (troponin).

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P1211

JOINT1866

Challenges in the treatment and long-term follow-up results of children with resistance to thyroid hormone-ß

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Introduction

The clinical manifestations of resistance to thyroid hormone-β (RTH-β) can sometimes be confused with either hyperthyroidism or hypothyroidism, leading to challenges in diagnosis and treatment. In this study, we aimed to evaluate the diagnosis, treatment processes, and long-term follow-up outcomes of children with RTH-β.

Methods

A retrospective study was conducted including pediatric patients with pathogenic variants in the *THRB* gene and that followed up in our department for at least 6 months between 2006-2024. The physical examination, laboratory, and imaging findings at the initial presentation and the final outpatient visit were compared.

Results

Ten patients were included in the study with a median age of 4.7(min-max: 1.2-17.2) years. Weight, height, and body mass index (BMI) measurements at the first presentation were -0.4[(-2.3) – 1.5], -0.7[(-2.3) – 1.0], and 0.0[(-2.8) – 2.6] SDS, respectively. Initial evaluation showed goiter in 50%, attention deficit hyperactivity disorder and speech delay in 40%, tachycardia in 20%, and short stature in 20% of the patients. The initial TSH, freeT4, and freeT3 levels were 3.1(1.4-11.9) mIU/l, 2.3(1.3-4) ng/dl, and 7.6(4.6-9.8) ng/dl, respectively. The median time to diagnosis was 6 months. TSH receptor stimulating autoantibodies were measured in six patients. The thyroid gland volume was 1.7[(-2.5) – 6.2] SDS on the ultrasonography, and did not change significantly during the follow-up($P = 0.345$). A total of five patients (50%) received treatment (three with methimazole, one with L-thyroxine, one with propranolol). TRIAC was added to the treatment in two patients. The median follow-up duration was 3.6 years, and the median age at the last visit was 11.6 years [bone age/calendar age ratio: 0.9(0.7-1.0)]. At the final evaluation, weight showed a significant increase($P = 0.028$); but height and BMI were similar to the initial measurements ($P = 0.203$ and 0.445). At the last visit, only one patient was under LT4 treatment, and another one was receiving propranolol. Laboratory results on the last control were were similar to the initial pretreatment values; TSH 2.2 (1.1-3.8) mIU/l, freeT4 2.5 (1.4-3.6) ng/dl, and freeT3 7.0 (4.2-12.6) ng/dl ($P > 0.05$). The serum sex hormone binding globulin level was elevated in five patients (50%).

Conclusions

Pediatric RTH-β patients were mostly misdiagnosed as hyperthyroidism leading to treatment with anti-thyroid drugs, and most individuals became treatment-free in the long-term follow-up. Also, we demonstrated that thyroid function tests and thyroid gland volume did not change with age, and growth of the children was not affected in RTH-β.

Keywords

Thyroid hormone receptor-beta, thyroid hormone metabolism disorders, Refetoff syndrome .

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P1212

JOINT882

A decade of thyroid orbitopathy research in albania: a retrospective study from a tertiary referral center

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Introduction
Thyroid Orbitopathy (TO), also referred to as Graves' Orbitopathy (GO), is a complex and impactful complication of Graves' disease (GD). Limited data from Albania highlight the need for a deeper understanding of its presentation and management.
Aim
This 10-year retrospective study conducted at a tertiary referral center in Albania analyses the clinical features, diagnostic challenges, and treatment approaches for GO to enhance disease understanding and improve management strategies.
Methods
Data were systematically collected from 178 patients referred for GO evaluation and treatment over a decade. Patient demographics and clinical characteristics were documented using the European Group on Graves' Orbitopathy (EUGOGO) protocol. Cases were categorized as bilateral (asymmetric or symmetric) or unilateral GO, and clinical features were analyzed to identify distinguishing patterns.
Results
Among 178 patients with GO, the mean age was 44.9 $\pm$14.9 years. Bilateral GO was most common (72.5%), followed by unilateral (17%) and unilateral-to-bilateral (10.5%). Asymmetric GO was observed in 30.9% of bilateral cases. GO onset was often concurrent with GD, with female predominance (72.5%). Mild GO was present in 48%, while 52% had moderate to severe forms. Local treatment was effective for mild cases, while 80% of moderate/severe cases responded positively to intravenous glucocorticoids. Hypothyroidism was a significant risk factor for GO activation.
Conclusion
Clinical management should prioritize the overall presentation of GO, emphasizing individualized treatment approaches. Hypothyroidism was identified as a key risk factor for GO activation, highlighting the need for careful thyroid function management to mitigate disease progression.

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P1213

JOINT3629

Children undergoing thyroid surgery - diagnostic evaluation, type of surgery and pathological findings

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Introduction
Thyroid gland diseases among children and adolescents are rare. The purpose of the current study was to describe the pediatric patients treated with surgery of the thyroid gland, including the diagnostic evaluation, type of surgical treatment, complications and pathological findings.
Methods
Patients with an age of less than 18 years at the time surgery with a procedure coded for a surgery on the thyroid gland (KBAAxx) were extracted from the electronic medical journal system.
Results
32 patients with a median age of 16 years (range 3 - 17) were operated during a twelve-year period from January 2012 to December 2023. The frequency of preoperative imaging was ultrasound scan (US) (97%), thyroid scintigraphy (41%), magnetic resonance imaging (MRI) (25%) and computerized tomography (CT) scan (9%). Almost all patients had TSH measured (97%) and more than half were evaluated with a fine needle aspiration (FNA) (59%). Six patients had genetic dispositions to thyroid disease (19%). Forty surgical procedures were performed in 32 patients. The procedures were hemi-thyroidectomy (15 patients), total thyroidectomy in one (9) or two procedures (8). Further, 7 patients had simultaneous lymphadenectomy performed in the central and/or lateral neck compartments. The pathological examination revealed thyroid cancer in 14 patients (45%). The majority was papillary thyroid cancer (11), one classic follicular cancer, one oncocytic cancer, and one medullary cancer. Of patients with thyroid cancer, 4 (29%) had lymph node metastasis and none had distant metastases. There was one permanent paresis of the recurrent laryngeal nerve out of 49 nerves at risk (2%). One had permanent hypoparathyroidism out of 17 patients at risk (6%).
Conclusion
Most pediatric patients with thyroid disease are only evaluated by US and TSH before surgery. Compared with adult thyroid patients, genetic dispositions and cancer frequency are more common, whereas complications after surgery are rare.

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P1214

JOINT3498

Congenital central hypothyroidism due to TSHB gene mutation: a case report

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Introduction
Congenital central hypothyroidism (CCH) is a rare disorder caused by mutations in the TSHB gene, leading to impaired thyroid-stimulating hormone (TSH) production. This case report describes a male infant diagnosed with CCH, highlighting the clinical presentation, genetic analysis, and management.
Case Report
A 10 old-old boy was referred for evaluation due to jaundice, poor weight gain, and lethargy. He was born at term via an uneventful delivery, with normal birth weight and length. The parents were consanguineous, and there was no family history of thyroid disorders. On examination, the infant had mild hypotonia, prolonged jaundice, and a puffy face. Laboratory investigations revealed **serum free T4:** 0.34 ng/dl (normal: 0.8- 2 ng/dl), **serum TSH:** 1.9 mIU/mL (normal: 1.7–9.1 mIU/mL), glucose: 53 mg/dl, **cortiso:10. μg/dl.**A diagnosis of central congenital hypothyroidism was made. Molecular genetic testing identified a homozygous **mutation** in the TSHB gene, confirming the genetic basis of the condition. The infant was started on **levothyroxine** at 10 mg/kg/day, with regular follow-up to monitor growth and neurodevelopment. At 12 months of age, he showed significant improvement in activity levels, weight gain, and developmental milestones.
Conclusion
This case underscores the importance of considering TSHB mutations in children with unexplained hypothyroidism. Early intervention can lead to favorable outcomes, emphasizing the role of genetic analysis in diagnosing congenital endocrine disorders.

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P1215

JOINT3726

Sonographic evaluation of thyroid volume and morphology over time in children with hashimoto's thyroiditis

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Background
Hashimoto's thyroiditis (HT) is associated with thyroid atrophy, fibrosis, and nodular changes, with a potential risk of malignancy. However, data on longitudinal thyroid morphology changes in pediatric populations, particularly in India, remain limited.
Objective
To assess the morphological changes in the thyroid gland over time in children with HT and compare thyroid volume standard deviation scores (SDS) between diagnosis and follow-up.
Methods
Children diagnosed with HT between 4–12 years, based on thyroid function tests, antibody positivity, and ultrasound findings, with $\geq$2 years of follow-up, underwent repeat thyroid ultrasound. Thyroid volume was compared with baseline values. Nodules, if present, were graded using TIRADS, and thyroid scans were performed to assess cold nodules.
Results
56 children (68% female) were evaluated in a prospective cross-sectional study. The mean age at symptom onset was 7.2 ($\pm$ 2.70 years, and age at diagnosis was 8.7 ($\pm$ 2.38) years. Autoimmune comorbidities were present in 18% at diagnosis. The most common symptoms were reduced physical activity (61%) and constipation (51.8%). The median duration of follow up was 2 years. At diagnosis, 41% had goiter, 37.5% had short stature, and 18% were underweight. The median TPO level was 198 IU/ml (IQR: 92–544 IU/ml). Height and weight SDS improved significantly ($P = 0.001$ and $P = 0.003$, respectively). Ultrasound revealed increase in heterogenicity (76.8% to 89.3%), hypoechogenicity (10.7% to 21%), and nodules (19.6% to 26.8%) in between diagnosis and follow up. Thyroid volume reduced by mean of 1.448 SDS ($P = 0.001$), particularly in overt hypothyroidism with a mean reduction of 1.54 SDS ($P = 0.001$). 63% of the nodules at diagnosis showed resolution over a mean duration of 2.4 years. 19% developed nodules during a mean follow up of 3.1 years and risk of development of nodule did not correlate with follow-up duration ($P = 0.823$), TSH ($P = 0.52$), anti-TPO levels ($P = 0.664$), or delayed diagnosis($P = 0.819$). 80% nodules were TIRADS 1, indicating benign nature.

Conclusion
Children with HT exhibit progressive thyroid heterogenicity and nodule development over time, with significant reduction in thyroid volume. The predominance of benign nodules suggests a low risk of malignancy in pediatric population.

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P1216

JOINT2248

Clinical audit on ultrasound assessment and thyroid function testing in evaluation of thyroid nodules in a regional centre in Ireland

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Introduction
There is a high prevalence of thyroid nodules (up to 60%) in adults in the general population. 2023 European Thyroid Association clinical practice guidelines for thyroid nodule management recommends neck Ultrasound (US) assessment with European Thyroid Imaging and Reporting Data System (EU-TIRADS) and thyroid function testing (TFT) in evaluation of thyroid nodules. This study aims to assess US classification and TFT evaluation of thyroid nodules in our centre.
Methods
A retrospective data of all US thyroid scans performed in our hospital in 2024, were included in the study. TFT results of persons with thyroid nodules on US scans, were collected from the hospital laboratory system.
Results
A total of 230 US thyroid scans from 2024 were reviewed. Mean age of people who had US thyroid was 54.7 ± 21.2 years. 82% were female and 18% were male. 36 scans (16%) had no thyroid nodules, while 194 scans (84%) showed at least one nodule. TIRADS was used in categorizing thyroid nodules in 62 out of 194 scans (32%); U classification was used in 52 scans (27%) and no categorization of thyroid nodules in 80 scans (41%). In US thyroid scans with TIRADS categorization, 42 were TIRADS 2 (benign); 23 were TIRADS 3 (mild suspicion); 3 were TIRADS 4 (Moderate to high suspicion); 2 were TIRADS 5 (high risk). Of US thyroid scans with U classification, 45 were classified as U2 (benign), 23 as U3 (indeterminate/uncertain), and two as U4 (suspicious), with no reports classified as U5 (highly suspicious/malignant). 38 out of 194 US thyroid reports (19.6%) had recommendations to repeat the US thyroid in 6 or 12 months to re-evaluate thyroid nodules and 23 reports (11.9%) had recommendations to refer for fine needle aspiration. On reviewing the laboratory system, TFT results were available in 142 persons out of 194 with thyroid nodules (73%). Out of 142 with TFT results, 119 (83.8%) had normal TFTs, 11 (7.7%) had hypothyroidism and 12 (8.5%) had hyperthyroidism.
Conclusion
Our study demonstrated the majority of thyroid nodules that were categorised, are considered benign or of low suspicion, and a significant proportion of people with thyroid nodules have euthyroid status. Our audit also showed there is some variability in thyroid nodule categorization, with 41% of nodules unclassified. The local practice guidelines on standardised categorization of thyroid nodule management and TFTs, could improve consistency, aiding clinical decisions on follow-up, individualised management and resources allocation.

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P1217

JOINT1981

Ultrasound-guided thermal ablation of symptomatic benign thyroid nodules: volumetric outcomes in a cohort of 36 patients

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Introduction
Large thyroid nodules can cause compressive symptoms, such as a sense of tightness, dysphagia, dysphonia and dyspnea. In these cases, surgery (thyroidectomy/lobectomy) is indicated. When surgery and/or general anesthesia are contraindicated (e.g., age, comorbidities, etc.) or if the patient refuses surgery, the guidelines recommend that cytologically benign and non-functioning nodules, solid or mixed, can be treated with ultrasound-guided thermal ablation (TA), a minimally invasive treatment aimed at reducing nodule volume and reducing or eliminating compressive symptoms. TA can be performed using radiofrequency (RFA), microwaves (MWA), laser, or ultrasound. According to literature data, the expected volume reduction 12 months after treatment is 50%-84% with RFA and 74%-90% with MWA.
Methods
In our cohort, we included 36 patients who underwent TA (34 RFA and 2 MWA) at our University Hospital. We evaluated the volumetric reduction with one or more post-TA ultrasound examinations (at 45 days, 3 months, 6 months and 12 months after TA).
Results
Pre-treatment average volume of the nodules was 18.2 ml. Twenty-six patients had a 45-day follow-up with an average volume reduction of 38% (min 7.2% - max 82%, average volume = 13 ml). Thirty-two patients had a 3-month follow-up with an average volume reduction of 47% (min 7% - max 83%, average volume = 9.5 ml). Twenty patients had a 6-month follow-up, with an average volume reduction of 55.9% (min 0% - max 92.2%, average volume = 7.7 ml). Twenty patients had a 12-month follow-up, with an average volume reduction of 60.2% (min 23.1% - max 91.8%, average volume = 5.1 ml). Only one patient had a therapeutic failure, with a volumetric reduction of 7% at 45 days and a subsequent volumetric increase to a volume close to the pre-treatment volume at the 6-months ultrasound follow-up. Only 3 patients (8.3%) experienced minor complications (moderate pericapsular hematoma, first-degree skin burn of 4 millimeters, transient hoarseness); no major complication nor hypothyroidism was reported.
Conclusion
The volumetric reduction in our case series is similar to that reported in the literature. Thermal ablation is a valid alternative to surgery, eliminating symptoms, reducing nodule volume, preventing nodule enlargement and avoiding hypothyroidism. Pre-treatment nodule volume is a predictive factor for treatment outcomes. To date, other clinical and ultrasound parameters predicting volumetric reduction and long-term symptomatic response to the treatment are still debated.

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P1218

JOINT2569

Exacerbation of orbitopathy after total thyroidectomy in alemtuzumab-induced graves' disease: a case report

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Introduction
Graves' orbitopathy (GO) is an autoimmune condition characterized by inflammation of extraocular muscles and peri-orbital tissue due to overstimulation of TSH receptor autoantibodies (TRAbs). It is a key extrathyroidal manifestation of Graves' disease (GD), often appearing at disease onset or shortly thereafter. Total thyroidectomy (TT) is one of the treatment options for GD, particularly in cases when definitive management is preferred, and radioiodine therapy is not appropriate. TT is generally considered safe regarding orbitopathy progression so prophylactic glucocorticoid therapy post-surgery is not routinely recommended.
Clinical case
This report presents a 41-year-old female patient with multiple sclerosis who, after receiving three cycles of Alemtuzumab, developed signs and symptoms suggestive of hyperthyroidism. Laboratory tests revealed: TSH <0.004 UI/mL (0.4-4.0), T4L 1.61 ng/dl (0.7-1.5), and TRAbs 16 U/l (<1.0). Treatment with thiamazole and propranolol was initiated with partial symptom improvement. The clinical course was characterized by difficult-to-control hyperthyroidism, requiring frequent dose adjustments of thiamazole (up to 30 mg daily) and continuous propranolol therapy. The patient developed other manifestations including pretibial myxedema and orbitopathy. The latter appeared approximately one year after the initial presentation, with dry eye sensation, visual acuity changes, and progressively worsening bilateral exophthalmos. The introduction of selenium therapy at 200 mg/day provided only partial relief. An orbital CT scan confirmed the diagnosis, and ophthalmology assessment classified the condition as moderate-to-severe and inactive (CAS 2). Due to the severe and poorly controlled clinical picture, the patient underwent total thyroidectomy two and a half years after symptom onset. At the time of surgery, she was on 25 mg of thiamazole and was biochemically euthyroid, with TRAbs of 76 U/l.

Immediately after surgery, the patient experienced a multiple sclerosis flare, requiring a short course of corticosteroid therapy (prednisolone 1 g for 5 days). About a week post-surgery and after completing the corticosteroid cycle, she developed worsening orbitopathy with ocular pain and diplopia, requiring an emergency ophthalmology consultation. A follow-up orbital CT scan confirmed disease progression, prompting the initiation of corticosteroid therapy, of which she has completed two cycles to date. Due to only partial improvement, treatment with Tocilizumab has been proposed and is scheduled to begin soon.
Conclusion
A patient with severe, difficult-to-control hyperthyroidism and moderate-to-severe inactive orbitopathy underwent total thyroidectomy. Despite this, orbitopathy exacerbation occurred post-surgery, requiring specific treatment. This case highlights a rare complication and raises the question of whether corticosteroid prophylaxis should be considered after surgery in high-risk patients.

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P1219

JOINT2134

The relationship between TSH suppression and metabolic associated fatty liver disease (MAFLD) in patients with thyroid cancer

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Metabolic associated fatty liver disease (MAFLD) is a clinical spectrum ranging from simple steatosis to cirrhosis and hepatocellular carcinoma (HCC) with increasing prevalence worldwide. Although its close relationship with obesity, metabolic syndrome and diabetes is known, its mortality and morbidity are high. Thyroid hormones play a regulatory role in cell metabolism and are effective on metabolic parameters involved in the etiology of MAFLD. Although the studies conducted so far mostly support that hypothyroidism increases the risk of MAFLD, there are not enough studies investigating the effect of hyperthyroidism on MAFLD. The aim of this study was to investigate the effect of subclinical thyrotoxicosis on MAFLD.
Patients and methods
Between March 2023 and November 2023, 38 patients with subclinical thyrotoxicosis who were followed up due to thyroid cancer in remission and who applied to Gazi University Medical Faculty, Endocrinology Clinic between March 2023 and November 2023 were included in the study and 38 healthy people with similar age and gender distribution were included in the control group. 76 people were included in the study. Liver function tests, serum lipid levels, TNF-alpha, IL-6, T4, TSH tests were analysed. Quantitative measurement was performed by ultrasonography for fatty liver disease and TAI was calculated and the stage of hepatic steatosis was measured and recorded as grade. Fatty liver index(FLI) was calculated.
Results
We found no significant difference between the subclinical thyrotoxicosis group and the euthyroid group in terms of MAFLD diagnosed by imaging. In both groups, we found a significant correlation between the grade of hepatic steatosis and age, BMI, waist circumference, ALT, GGT, LDL and TG levels. In analyses controlling for age and body mass index (BMI), we found a significant, positive correlation between TSH and the grade of hepatic steatosis.
Discussion
We found a negative correlation between TSH suppression level and MAFLD, and our results are consistent with the literature in this respect. Addition to B-mode ultrasound for the diagnosis of MAFLD, we preferred TAI measurements because of its sensitivity, which have not been used in a similar study before.

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P1220

JOINT1027

Complete blood count markers as possible prognostic values of immune checkpoint inhibitors induced hypothyroidism

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Background
A novel and highly effective strategy for tumor immunotherapy involves enhancing host immune responses against tumors through the blockade of checkpoint molecules. The most common toxicities associated with checkpoint blockade therapies include autoimmune damage to various organs.
Purpose
This study aims to investigate hematological markers derived from complete blood count (CBC) – including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), derived neutrophil-to-lymphocyte ratio (dNLR), white blood cell-to-hemoglobin ratio (WHR), neutrophils, lymphocytes, platelets, hemoglobin, red blood cell (RBC) count, neutrophil-to-RBC ratio (NRR), and neutrophil-to-hemoglobin ratio (NHR) – as potential prognostic biomarkers for the early identification of hypothyroidism in patients receiving PD-1 or PD-1/CTLA-4 immune checkpoint inhibitors.
Methods
A prospective observational study was conducted on 44 patients with stage III-IV solid tumors treated with immune checkpoint (PD-1 or PD-1/CTLA-4) inhibitors. Thyroid function tests and CBC-derived biomarkers were collected at baseline, before immunotherapy. In the immunotherapy cohort, 15 of the 44 patients developed immune-related hypothyroidism, defined as overt autoimmune thyroiditis (TSH $>$ 4.0, FT4 $<$ 12, and anti-TPO antibodies $>$ 30 IU/mL and/or anti-TG antibodies $>$ 95 IU/mL) (Group-1). In comparison, 29 patients maintained normal thyroid function (Group-2). The control group comprised 14 age- and sex-matched healthy volunteers (Group-3). Statistical analyses were performed using analysis of variance (ANOVA) to compare blood parameters among the three groups (Group-1, Group-2, and Group-3) before treatment, with statistical significance set at a P-value $<$ 0.05. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic power of the potential prognostic biomarkers areas. Under the curve (AUC), sensitivity, and specificity were calculated for the 44 immunotherapy patients.
Results
PLR was significantly higher (262.25 ± 162.95), while WBC-neutrophils, WHR, NRR, NHR, WBC, neutrophils, and lymphocytes were lower (2.07 ± 0.66, 0.54 ± 0.19, 0.96 ± 0.28, 0.36 ± 0.14, 6.36 ± 2.07, 4.29 ± 1.55, and 1.23 ± 0.41, respectively) at baseline in Group-1 in comparison Group-2. ROC curve analysis revealed that the areas under the curve (AUC) for WBC, neutrophils, lymphocytes, WBC-neutrophils, PLR, WHR, NRR, and NHR were 0.9, 0.87, 0.83, 0.85, 0.84, 0.92, 0.89, and 0.87, respectively. These values exceeded the threshold, indicating the high prognostic potential of each marker.
Conclusion
Lower baseline levels of WBC-neutrophils, WHR, NRR, NHR, WBC, neutrophils, and lymphocytes, along with higher PLR, were associated with an increased risk of hypothyroidism in patients receiving PD-1 or PD-1/CTLA-4 inhibitors. These CBC-derived biomarkers represent simple, accessible, and potentially useful tools for predicting hypothyroidism in cancer patients undergoing immunotherapy. Further studies in bigger cohorts are needed to validate our findings.

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P1221

JOINT1172

The rare entity of de Quervain thyreoiditis can be associated with hepatitis a

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Subacute thyroiditis (De Quervain's thyroiditis, granulomatous thyroiditis, giant cell thyroiditis) is an inflammation of the thyroid gland. The prevalence in the pediatric population is very rare. It is characterized by a triphasic course of transient mild thyrotoxicosis, lasting between 2 to 8 weeks, followed by

hypothyroidism and thereafter by a return to euthyroid. During the thyrotoxic phase the thyroid follicles are damaged and the preformed thyroid hormone is released. In nuclear scan there is low thyroid uptake on nuclear scan, and the ultrasound of the thyroid gland shows areas of hypoechogenity with decreased or normal vascular flow by Dopler. ESR and CRP can be elevated. The patient has moderate to severe neck pain, with bilateral, and rare unilateral swelling of the thyroid gland and influenza-like symptoms. Differential diagnosis from malignancy can be difficult. The histopathological examination reveals patchy changes with varying stages of the disease. The classic granulomatous changes appear a little later in the disease with a large aggregation of lymphocytes, plasma cells, and large histiocytes in the damaged thyroid follicles. Multinucleated giant cells surround the fragments of colloid, and sometimes colloid can also be seen in the giant cells. Later there are many lymphocytic infiltrates and fibrosis. Rarely different histologic stages can be found in the same gland suggesting the confluence nature of destruction. The treatment may include non-steroidal anti-inflammatory drugs, beta-blockers, corticosteroids, opioid analgesics, or potassium iodide or iopanoic acid to reduce the conversion of T4 to the more biologically active form of thyroid hormone, T3. During the hypothyroid phase, thyroid hormone replacement may help alleviate hypothyroid symptoms. We present the case of a female 10-year-old patient who presented in our emergency department with goiter, fever and pain in the neck. Several weeks earlier she had tachycardia and restlessness. Thyroid function was normal, thyroglobulin was increased (8100ng/ml). An ultrasound showed a swollen left thyroid lobe with a volume of 7 ml. During the following days the patient developed jaundice. Blood tests showed elevated hepatic enzymes and serological examination showed increased IgM for Hepatitis A. A fine needle biopsy diagnostic confirmed the diagnoses of De Quervain's thyroiditis. The patient received treatment with NSAID. This abstract reminds the reader of the rare condition of de Quervain thyroiditis. Furthermore, this is the first pediatric case report of de Quervain thyroiditis that was associated with Hepatitis A.

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P1222

JOINT2904

Predictive factors for hypothyroidism in childhood autoimmune thyroiditis: insights from long-term follow-up

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Introduction
Predictive factors for hypothyroidism progression in children with autoimmune thyroiditis (AIT) remain unclear.
Objectives
To characterize the clinical presentation of AIT, assess long-term outcomes, and identify predictive factors for disease progression.
Methods
Data from 127 consecutive patients under 18 years of age at presentation were analyzed (mean follow-up:7.1 years; range:0–20yr).
Results
At presentation, 57% of patients were euthyroid, 28% had subclinical hypothyroidism, and 15% had overt hypothyroidism. By the end of follow-up, among euthyroid children, 20.5% developed overt hypothyroidism, and 6.8% progressed to subclinical hypothyroidism. The subclinical hypothyroidism group showed dynamic changes: 45.7% of patients progressed to overt hypothyroidism, while 37.1% reverted to euthyroidism. Finally, the overt hypothyroidism group did not show significant changes. Patients progressing to hypothyroidism were younger at diagnosis ($P = 0.0008$) with higher thyroid peroxidase antibodies (AbTPO) titers ($P < 0.0001$), higher TSH ($P < 0.0001$) and lower FT4 levels ($P = 0.0026$). Thyroid volume >6mL increased hypothyroidism risk ($P = 0.0060$, OR:0.347,95%CI:0.15-0.75). Multivariate analysis confirmed that AbTPO titers influence TSH levels at follow-up ($P < 0.0001$). Cutoff thresholds were established to refine predictive accuracy. Patients diagnosed under 10 years of age ($P = 0.043$, OR:0.458,95%CI:0.22-0.96), with AbTPO > 92 IU/mL ($P < 0.0001$, OR:25,95%CI:8.78-63.11), and TSH > 4.95 μIU/mL ($P < 0.0001$, OR:15.43,95%CI:5.61-37.57) had highest risk of developing hypothyroidism. Notably, AbTPO > 92 IU/mL and TSH > 4.95 μIU/mL demonstrated the strongest predictive power. AbTPO titers had a positive predictive value (PPV) and negative predictive value (NPV) of 83%, while TSH > 4.95 yielded a PPV of 79% and an NPV of 80%.
Conclusions
Twenty percent of euthyroid children developed hypothyroidism, compared to 45.7% of those with subclinical hypothyroidism. TSH > 4.95 μIU/mL and AbTPO titers had the greatest predictive power. Patients diagnosed under 10 years of age had a higher risk of developing hypothyroidism, suggesting that prolonged exposure to autoimmunity may play a role. Further studies are needed to validate predictive models for hypothyroidism development in children with AIT.

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P1223

JOINT511

Molecular insights into persistent or residual pediatric differentiated thyroid cancer

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Introduction
Differentiated thyroid cancers (DTC) in childhood, although less common than in adults, are increasing in incidence and exhibit distinct characteristics. The American Thyroid Association (ATA) Guideline is used to diagnose, follow up, and treat these cases. While standard follow-up protocols exist, some pediatric thyroid cancers progress more aggressively. This study focuses on cases with aggressive clinical courses and aims to present their diagnostic and follow-up findings. Furthermore, it seeks to bridge gaps in understanding the molecular and clinical characteristics of pediatric DTC, particularly in patients with residual or persistent disease, contributing to the optimization of tailored management strategies.
Methods
Children with DTC, who had aggressive clinical courses were included in this study, aiming to present their diagnostic and follow-up findings. A retrospective collected data included demographic characteristics, comorbidities, surgical details, pathological findings, molecular analysis, serum thyroglobulin (Tg) levels, and response to radioactive iodine (RAI) therapy. Persistent disease was defined as detectable Tg levels or imaging-confirmed disease beyond the first year of treatment per ATA guidelines.
* This study was supported by the Ankara University Scientific Research Committee with the project code 21B0230013, approved on September 17, 2021.
Results
A total of six cases of DTC, including four females, presenting with aggressive clinical features, were included in this study. The mean age at diagnosis was 14.4 years (range: 7.2–19.4). Presenting symptoms included goiter ($n = 4$) and incidental nodules ($n = 2$). All patients underwent total thyroidectomy with central lymph node dissection; five cases were classified as high-risk based on ATA ultrasound criteria. Molecular analysis identified *BRAFV600E* variant in four patients, *NCOA4-RET* fusion in one, and no variants in one patient. Postoperative Tg levels ranged from 4.11 to 494 ng/mL. RAI therapy was initiated postoperatively for all. Five patients required additional surgeries for metastatic lymph nodes, and three underwent a second RAI dose. One patient had lung metastases, and RAI caused lung fibrosis. Selpercatinib was initiated in one patient due to aggressive disease features associated with *NCOA4-RET* fusion. The presence of *BRAFV600E* and *NCOA4-RET* variants correlated with more aggressive disease characteristics in children with DTC.
Conclusion
Residual or persistent disease in pediatric DTC remains a significant challenge. Early identification of high-risk patients and personalized treatment strategies, including optimized surgical approaches and tailored RAI protocols, are critical. In this study, *BRAFV600E* and *NCOA4-RET* were the most common pathogenic variants in children with residual or persistent disease in pediatric DTC.

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ePoster Presentations

Adrenal and Cardiovascular Endocrinology

EP1

JOINT86

A case of mistaken identity: hypoadrenalism and the cirrhotic paradox

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Introduction
Persistent hypotension and hyponatremia are common clinical features in patients with cirrhosis, for which an endocrine consult is not uncommon. Additionally, hypoalbuminemia is a common finding in cirrhosis, with reductions in total hormone assay levels, including cortisol, which leads to a false interpretation of hypocortisolemia. Whether or not there is truly an increased risk (or diagnosis) of hypoadrenalism in patients with underlying cirrhosis remains unknown.
Objectives
The primary objective of this study is to evaluate if cirrhosis is associated with a greater risk for adrenal insufficiency. Secondary objectives include comparing serum levels of albumin, total cortisol, and free cortisol between patients with (and without) cirrhosis, to assess for significant differences.
Methods
The study was performed as a retrospective cohort study, with data collated from TriNetX Global Collaborative Network, providing de-identified patient information from 143 healthcare organizations worldwide. Two cohorts were assessed in this study: Group A (patients with cirrhosis who have had a total cortisol measurement, $n = 43,786$) and Group B (patients without cirrhosis who have had total cortisol measurements, $n = 1,249,256$). Propensity score matching was employed to allow for balancing between the cohorts with $n = 53,220$; this was achieved by controlling for age, race, gender, body mass index, A1c, alcohol use, systemic corticosteroid use, and underlying inflammatory diseases of the liver.
Results
The results of this study noted no greater risk for primary, secondary, tertiary or drug-induced hypoadrenalism in patients with cirrhosis compared to those without, but rather a statistically significant (but likely clinically negligible) reduction in risk (Relative Risk 0.929, 95% CI: 0.872-0.99, $P = 0.0239$). Secondary outcomes noted a significantly lower mean albumin level in Group A (3.171 vs 3.58, $P < 0.0001$) but higher mean total cortisol (14.06 vs 12.188, $P < 0.0001$). There was no significant difference regarding free cortisol between both cohorts ($P = 0.9822$).
Conclusion
This study suggests that cirrhosis does not confer a greater risk for adrenal insufficiency (of any cause). As expected, patients with cirrhosis did demonstrate hypoalbuminemia, however, they appeared to overall exhibit higher mean total cortisol levels (without a significant difference in free cortisol). These findings support a cautious approach to adrenal function testing in patients with cirrhosis, and for reserving the diagnosis of adrenal insufficiency when there is true clinical suspicion.

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EP2

JOINT1339

Effects of switching from conventional glucocorticoid therapy to modified-release hydrocortisone (MR-HC) on the steroid matabolome in patients with 21-hydroxylase deficiency

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Background
New hydrocortisone formulations with modified release are increasingly used in treating patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD). The goal is better androgen control while reducing overall glucocorticoid exposure through more physiological hydrocortisone release and replacement. However, the effects of switching from conventional glucocorticoid therapy to modified-release hydrocortisone (MR-HC) on steroid metabolism remain uninvestigated
Methods
The steroid metabolome in 24-h urine samples was analyzed in 22 patients with classic CAH due to 21OHD (10 women, 12 men). Before the switch, 10 patients received conventional hydrocortisone, 9 prednisolone, and 3 combination therapy. The switch to MR-HC was performed using equivalent dose conversion (prednisolone conversion factor = 5). Urine samples were collected before and six months after the switch and analyzed using gas chromatography-mass spectrometry (GC-MS).
Results
Based on serum androstenedione and 17-OHP levels, three patients were classified as not well controlled at baseline. After switching, one patient transitioned from well-controlled to not well-controlled, and another showed the opposite trend. Median hydrocortisone-equivalent dosages were 25 mg (IQR 24.375–35.625) before and 27.5 mg (IQR 20–35) after the switch to MR-HC ($P = 0.109$). The switch led to a trend toward increased major cortisol metabolites (5α-THF + THF + THE, $P = 0.093$) and overall urinary cortisol metabolites (5α-THF + THF + THE + a-C + b-C + a-Cl + b-Cl; $P = 0.059$) in those previously on HC. No absolute change in 17-OHP metabolites (Po-5β3α, Po-5α3α, PT, 11-OH-P) or significant change in overall 11-oxygenated androgens was observed. In women, 11-deoxygenated androgens showed a declining trend ($P = 0.071$), leading to a significant increase in the 11-oxygenated (11OH-An + 11O-An + 11OH-Et) to 11-deoxygenated androgen ratio (An + Et + A5-3β, 17α + A5-3β, 17β + DHEA + 16α-OH-DHEA + A5T-16α) from 0.64 (IQR 0.24–2.10) to 2.75 (IQR 1.67–5.75, $P = 0.007$), indicating increased adrenal suppression. In men, no significant change in 11-oxygenated or deoxygenated androgens was found. However, individually, significant PT reductions (6790 vs. 2982 μg/d) were seen in 14/22 patients, 11OH-An reductions (828 vs. 426 μg/d) in 12/22, and An reductions (823 vs. 433 μg/d) in 12/22.
Conclusion
While overall glucocorticoid exposure remained comparable, trends toward increased urinary cortisol metabolites suggest a shift in cortisol metabolism, possibly reflecting optimised cortisol availability resulting in increased adrenal androgen suppression. Individual patients of both sexes may therefore benefit from a switch to modified-release hydrocortisone.

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EP3

JOINT3739

Echocardiographic evaluation of functional and morphological alterations in obesity: a comparison between obese individuals with and without Metabolic Syndrome

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Background
Obesity has been identified as an independent risk factor for heart failure. The risk of heart failure is dependent on body mass index (BMI).
Aim
This study aimed to examine the effects of obesity on myocardial function and morphology, and to compare these alterations in obese individuals with and without metabolic syndrome (MetS +/- group).
Methods
A total 125 subjects with a BMI more than 25 kg/m^2 underwent metabolic and clinical evaluation. An evaluation of conventional echocardiographic parameters and cardiac deformation by 2D speckle tracking echocardiography was conducted. The mean age was 45.0 ± 9.6 years (female: 58.7%), and the average BMI was 35.01 ± 6.53. In 74% of the subjects, the duration of overweight/obesity was over 10 years. Metabolic syndrome was diagnosed in 54 patients (70%). Two dimensional echocardiographic evaluation showed that the MetS$^+$ group had a larger LA maximal volume and a LA volume indexed for body height than the MetS$^-$ group, but the differences were not statistically significant ($P = 0.068$, $P = 0.098$, respectively). The MetS$^+$ group had significantly lower LA ejection fraction compared to the MetS$^-$ group (LAEF% = 46.89 vs 50.13, $P = 0.03$). Regarding the strain analysis, it was also found that the MetS$^+$ group had significantly lower values for the peak longitudinal deformation of LA in the reservoir phase (PALS) ($P = 0.008$). The LV mass

indexed by height (LVMh) significantly differed between the two groups, despite both being within the reference limits ($P = 0.016$). Conversely, both groups exhibited higher LV mass indexed by the square of height (LVMh2), with the $MetS^+$ group demonstrating a significantly higher values ($P = 0.002$). Moreover, the mean values of global longitudinal strain (GLS) of the left ventricle were below the reference range in both groups, but significantly lower in the MetS + group compared to the $MetS^-$ group (GLS = -20.7 vs -22.7, $P = 0.016$) The peak mitral annular descent velocity (s'TDI) and the late diastolic velocity were significantly reduced in $MetS^+$ ($P = 0.019$ and $P = 0.033$, respectively).
Conclusion
Obesity itself causes substantial morphological and functional myocardial alterations, in particular if accompanied by metabolic abnormalities.

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EP4

JOINT1130

Impact of alert systems on glucocorticoid administration for adrenal insufficiency in the emergency department

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Background
Clinical decision support (CDS) is a health information technology tool designed to aid healthcare providers in making informed decisions during patient care. However, evidence on the effectiveness of CDS systems in improving the identification and management of adrenal insufficiency (AI) and reducing preventable adrenal crises in emergency departments (EDs) is limited.
Methods
We conducted a retrospective analysis of patients with AI who followed up at the endocrinology clinic at King Chulalongkorn Memorial Hospital, Bangkok, Thailand. All patients were identified using a medical alert system integrated into the electronic health record (EHR). The primary outcome was the time from ED arrival to glucocorticoid administration in AI patients visiting the EDs during the 12-month period before and after the system's implementation. Secondary outcomes included the proportion of patients receiving appropriate glucocorticoid treatment and the frequency of preventable adrenal crises in the EDs before and after implementation.
Results
Among 112 patients with AI, 4 patients (4%) had primary AI, and 108 patients (96%) had central AI. The mean age was 66 $\pm$ 15 years, and the majority were female (61%). During the median follow-up time of 14 months, the total number of ED visits was 41 (in 24 patients) and 55 (in 30 patients) before and after the system's implementation, respectively. The number of events requiring prompt hydrocortisone treatment was 14 and 15 before and after implementation, with 86% and 100% of these events receiving appropriate treatment, respectively. The median time from ED arrival to hydrocortisone administration significantly decreased from 123 (IQR: 87-208) minutes to 54 (IQR: 45-127) minutes before and after implementation ($P = 0.03$). Four adrenal crises (29%) occurred prior to glucocorticoid administration before the system implementation, while one (7%) occurred after the system was introduced ($P = 0.34$).
Conclusion
The implementation of a CDS system integrated into EHR significantly reduced the median time to hydrocortisone administration in AI patients presenting to EDs, decreased the frequency of preventable adrenal crises, and increased the proportion of patients receiving appropriate glucocorticoid administration. These findings underscore the role of CDS systems in enhancing the identification and management of AI and highlight their value in reducing delays and optimizing care in high-risk scenarios. Further studies with larger cohorts are warranted.

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EP5

JOINT2455

24-H hormonal profile in patients affected by congenital adrenal hyperplasia: does it improve disease management?

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Introduction
Congenital adrenal hyperplasia (CAH) is caused by enzymatic deficiencies in corticosteroid synthesis, with 21-hydroxylase deficiency being the most common. Proper management is essential to optimize patients' development and quality of life. Conducting 24-h hormonal profiles to optimize treatment is complex, and its usefulness remains controversial.
Objective
To assess the utility of the 24-h hormonal profile in patients with CAH who present difficulties in disease control.
Material and Methods
A protocol was designed to perform a 24-h hormonal profile in patients with CAH. Study participants attended a consultation for an initial assessment before hospital admission. A peripherally inserted central catheter was placed, and blood samples were collected using VAMP system, while patients continued their usual treatment. Blood samples were taken every h for 24 hs, including additional samples 30 minutes after hydrocortisone administration. Hormonal measurements included cortisol, ACTH, 17-OH-progesterone, and androstenedione. Health-related quality of life was assessed using the Child Health and Illness Profile questionnaire. Based on the results, as well as clinical symptoms, daily activities, physical examination, and quality of life, hydrocortisone regimens were adjusted.
Results
Six patients (three females/three males) aged 5 to 16 years were included. The main symptoms reported in consultation were headaches, fatigue, decreased attention in school activities, menstrual cycle disorders, and weight gain. The procedures were well tolerated. Variability in hydrocortisone absorption was observed at equal doses depending on the time of day in the same patient. Several factors that may interfere with hydrocortisone absorption and hormonal variability were identified, including food intake, intestinal absorption variations, and the specific hydrocortisone formulation used. Adjustments in hydrocortisone dosing were associated with the resolution or improvement of symptoms and signs and as well as enhanced quality of life. The advantages and disadvantages of performing the hormonal profile, as well as the challenges in interpreting the results, are discussed.
Conclusions
Performing 24-h hormonal profiles may help personalize treatment regimens according to each patient's daily activities, aiming to improve growth, pubertal development, and quality of life in CAH patients. The variability in hydrocortisone absorption at the same dose depending on the time of day should be considered when interpreting hormonal results and adjusting treatment. This procedure is time-consuming, costly, and psychologically demanding for both patients and parents, making careful patient selection essential. Additionally, it requires a multidisciplinary team that dedicates significant time to organizing, conducting, interpreting the profile, and making dose adjustments.

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EP6

JOINT527

Suspected central adrenal insufficiency in a patient with PMM2-CDG

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Phosphomannomutase 2 - Congenital Disorder of Glycosylation (PMM2-CDG) is a hereditary defect causing hypoglycosylation of N-linked glycoproteins and a multisystem disorder with a broad spectrum of clinical presentation. It was recently suggested that patients with PMM2-CDG may have central adrenal insufficiency. We present an 18-year-old male with PMM2-CDG, whose initial screening suggested adrenal insufficiency. The patient displayed a morning baseline plasma cortisol of 57 nmol/l, a deficient response to Adrenocorticotropic hormone (ACTH) with a 30 min cortisol of 165 nmol/l, and a low-normal ACTH. Analysis of cortisol binding globulin (CBG) showed abnormally low levels (253 mmol/l (ref. 750-2500 mmol/l)). 8 a.m. salivary cortisol was measured 24 hs after last hydrocortisone ingestion and was normal to slightly elevated (38 nmol/l (ref. 2.48-29 nmol/l)). Accordingly, the patient never experienced obvious symptoms of adrenal insufficiency nor clinical improvement after transient introduction of hydrocortisone. In conclusion, we present a patient with PMM2-CDG who upon measurement of plasma cortisol displayed "biochemical" central adrenal insufficiency, although with low CBG and normal salivary free cortisol levels. The case illustrates the caveats of using total plasma cortisol for the diagnosis of adrenal insufficiency in patients with PMM2-CDG and highlights the potential impact of N-linked hypoglycosylation on endocrine evaluation.

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EP7

JOINT1883

First case of cytochrome P450 oxidoreductase deficiency with didelphic uterus and unilateral renal agenesis and a literature review on 46,XX patients

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Introduction
Cytochrome P450 oxidoreductase deficiency (PORD) is a rare form of congenital adrenal hyperplasia. This study reports the first case diagnosed with PORD presenting with uterine didelphys, vaginal atresia, and right renal agenesis. A comprehensive literature review was performed to analyze Müllerian duct, pubertal development, and fertility outcomes in 46,XX patients.
Case presentation and literature review
A 3-year-and-10-month-old Chinese female presented with ambiguous genitalia, accompanied by a history of maternal virilization during pregnancy. The patient exhibited midface hypoplasia and arachnodactyly, along with Antley-Bixler syndrome (ABS)-like skeletal malformations, in addition to ambiguous genitalia characterized by clitoromegaly, labial fusion, and a single urogenital sinus. Laboratory evaluation revealed a 46,XX karyotype, mildly elevated adrenocorticotropic hormone, normal cortisol, significantly elevated 17-hydroxyprogesterone, and reduced androstenedione and dehydroepiandrosterone. Pelvic ultrasonography demonstrated the presence of didelphic uterus, double cervix, vaginal atresia, and right renal agenesis. Whole-exome sequencing identified a homozygous p.R457H missense variant in the *POR* gene, confirming the diagnosis of PORD. A review of 38 reported cases of 46,XX patients revealed a potential association between maternal virilization during pregnancy and the disorders of sex development in affected individuals. The p.R457H and p.A287P variants are the most commonly reported variants. The p.R457H variant is predominantly identified in Asian populations, while the p.A287P variant is frequent observed in Caucasian patients, and is often associated with more severe ABS-like skeletal malformations. Among patients with PORD, pubertal development may occur, however, breast development and menarche often follow irregular patterns, contributing to challenges in achieving natural conception during their reproductive years. Additionally, structural anomalies of the Müllerian ducts may represent a rare phenotype of the condition.
Conclusion
This review suggests that uterine malformations and unilateral renal agenesis may represent uncommon phenotypes of PORD. Early initiation of glucocorticoid replacement therapy and timely estrogen supplementation not only reduce the risk of adrenal crises but also serve as effective measures to inducing pubertal development and decrease the recurrence of ovarian cysts, which may, in turn, positively influence fertility preservation in the future.

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EP8

JOINT205

Clinical, hormonal, and radiological evaluation of unilateral adrenal incidentalomas

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Purpose
Adrenal incidentalomas refer to adrenal masses, at least 1 cm in diameter, discovered incidentally through imaging conducted for non-adrenal-related reasons. The widespread use and advances in imaging technology have significantly increased the frequency of adrenal incidentaloma detection. The challenge in evaluating these lesions lies in balancing the potential benefits of early treatment for malignant or secreting tumors with the risks and costs of unnecessary treatments. The lack of studies integrating radiological findings with epidemiological and clinico-biological data, particularly at the continental and national levels, presents significant diagnostic and therapeutic challenges for clinicians. This study aims to investigate the epidemiological and clinico-biological characteristics of adrenal incidentalomas, evaluate radiological criteria indicative of malignancy, and identify markers that predict hormonal secretion, especially cortisol production.
Methods
A retrospective study was carried out on 153 patients referred to the endocrinology department at Farhat Hached Hospital for the assessment of an adrenal incidentaloma between January 2015 and December 2023.
Results
The average age of the patients was 55.76 ± 13.36 years, with non-secreting adenomas being the most observed lesion in 94 patients (61,44%). In our series, autonomous cortisol secretion (ACS) was the most frequent hormonal abnormality, accounting for 17% of cases. Pheochromocytoma was diagnosed in 6 patients (3.92%), and primary hyperaldosteronism was found in 8 patients (5.2%). Secreting adenomas were significantly larger than non-secreting adenomas (27.55 ± 11.7 mm vs 20.5 ± 9.3 mm). The attenuation value was also higher in secreting adenomas with ACS. Moreover, contralateral adrenal atrophy, hepatic steatosis, and bone demineralization were more common in adenomas with ACS than in non-secreting ones. Our series included 6 cases of adrenocortical carcinoma (ACC). The average size of ACC (61 ± 27.07 mm) was significantly larger than that of lipid-poor adenomas. Only one ACC measured less than 4 cm, and the mean non-contrast density for ACCs was 29.7 UH. None of the pheochromocytomas had a non-contrast density below 10 UH. Of the 5 pheochromocytomas in our series, only one exhibited the typical "light bulb sign" with a homogeneous hyperintense lesion.
Conclusion
Imaging is crucial for characterizing adrenal incidentalomas and for the early detection of malignant lesions. It also plays a key role in the presumptive diagnosis of ACS.
Limitations
Our study primarily focused on the initial management of adrenal incidentalomas. Future studies will be needed to establish a follow-up protocol for benign lesions that are not surgically treated.

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EP9

JOINT1880

Heterozygous mutations in CYP11A1 lead to P450scc deficiency: case report and literature review

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Background
The inheritance mode of P450scc deficiency caused by *CYP11A1* mutations remains unclear. It was previously considered an autosomal recessive disorder, but sporadic cases of heterozygous mutations have been reported.
Objective
To report a case of non-classic P450scc deficiency caused by a heterozygous mutation in *CYP11A1* and review similar cases in the literature.
Patients and Methods
An 11-year-7-month-old female presented with a 1-year history of facial hair growth, deepening of the voice, and hyperpigmentation. She had a history of fatigue since childhood but no other obvious signs of adrenal insufficiency. Physical examination revealed Tanner stage 3 pubic hair, clitoromegaly, a

urogenital sinus opening on the perineum, and scrotum bifid with no palpable testes. Laboratory tests showed elevated ACTH, LH 9.17 IU/l, FSH 16.81 IU/l, testosterone 10.2 nmol/l, and decreased levels of cortisol, 17α-hydroxyprogesterone, progesterone, dehydroepiandrosterone, and androstenedione. AMH was 2.55 ng/ml. INHB was 179.38 pg/ml. Karyotype analysis showed 46,XY. Ultrasound revealed normal adrenal glands, testes in pelvis, and no uterus or ovaries. She was the first child of non-consanguineous parents, with a normal birth history and healthy parents and a younger sister (46,XX). Whole exome sequencing was performed on the patient. Cases of *CYP11A1* heterozygous mutations causing adrenal insufficiency (AI) with or without disorders of sex development (DSD) reported in PubMed and CNKI databases were reviewed.
Results
The patient was found to have a heterozygous mutation in the *CYP11A1* gene (c.1379G > A, p.R460Q), which has been associated with P450scc dysfunction. Combined with her clinical manifestations and steroid hormone levels, the diagnosis of P450scc deficiency was confirmed. Her mother and younger sister also had the same mutation but were asymptomatic. A literature review identified 5 patients from 4 families. Family 1 had a spontaneous mutation (c.809_814dupGGGACG) presenting with AI and 46,XY DSD. Family 2 had a mutation (c.235G > A) with a 46,XY proband presenting with AI, while the father and sister with the same mutation also had AI. Family 3 had a mutation (c.431C > A) with a 46,XX proband presenting with AI, but the mother with the same mutation was asymptomatic. Family 4 had a mutation (c.1076C > T) with a proband presenting with AI and 46,XY DSD, while the mother and brother with the same mutation were asymptomatic.
Conclusion
Heterozygous mutations in *CYP11A1* can cause P450scc deficiency. There is significant clinical variability among heterozygous mutation carriers, and family members with the same mutation may be asymptomatic.

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EP10

JOINT1657

Pitfalls of circulating miRNA-based biomarker studies in adrenocortical tumors

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Introduction
Differentiating between benign and malignant adrenocortical tumors has major clinical relevance. Recent studies have highlighted the potential of circulating microRNAs (miRNAs) as biomarkers for malignant adrenocortical carcinoma (ACC). However, there are many difficulties with their use, mainly standardization.
Aims
Our aim was to compare the interchangeability of real-time quantitative polymerase chain reaction (qPCR) and digital PCR (dPCR) in measuring circulating miRNAs, and to investigate whether the use of K2 or K3 EDTA anticoagulants may influence the results.
Methods
Peripheral blood samples were taken simultaneously into K2 and K3 EDTA collection tubes, from 20 individuals. After sample procession, three miRNAs associated with ACC (*hsa-miR-483-5p, -210-3p, -21-5p)* as well as two controls (*-miR-16-5p, cel-miR-39-3p*) were analyzed utilizing RT-qPCR and dPCR. Data obtained were compared by the following statistical methods: Spearman's rank correlation, paired t tests and Bland-Altman analysis.
Results
qPCR and dPCR results show a significant correlation (p values between 0.0072 and 0.049) in K2-EDTA samples when comparing ΔCt values and copy numbers. However, proportional biases relating to low and high miRNA expression were observed between the two methods. In qPCR measurements, K3-EDTA results showed higher standard deviations (average SD for K2 samples was 0.91 while for K3 samples 1.1). When comparing raw Ct values, only *miR-483-5p* was found to be significantly different, while in case of ΔCt values, every miRNA except *miR-483-5p* was significantly different. dPCR results were not affected by the different anticoagulants.
Conclusions
dPCR and qPCR are not easily interchangeable, especially for rare or abundant miRNAs, making cross-validation difficult. The choice of EDTA could potentially influence qPCR results, highlighting the need for standardized protocols.

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EP11

JOINT1291

The role of the posture test for primary aldosteronism subtyping

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Introduction
Primary aldosteronism (PA) is a common cause of hypertension, requiring accurate subtyping for optimal treatment and minimizing cardiovascular risk. The adrenal venous sampling (AVS) is the gold standard method for subtyping; however, the upright posture test (PT) could offer potential diagnostic value despite some limitations.
Aim
To identify the optimal cut-off for aldosterone-increase during PT in our population. Additionally, to perform a parallel evaluation of CT combined with PT for PA subtyping.
Methods
This nationwide study included all patients diagnosed with PA at Landspitali National University Hospital of Iceland from 2007 throughout 2016. The diagnostic protocol involved discontinuing antihypertensives affecting the renin-angiotensin-aldosterone system for 4–6 weeks before referral. Screening was performed by measuring morning serum aldosterone (s-aldosterone), direct renin concentration, and 24-h urinary aldosterone excretion. A positive PT was defined by a > 50% increase in s-aldosterone after 4 hs of standing. PA was confirmed by the saline infusion test (SIT), with post-infusion s-aldosterone > 140 pmol/l indicating PA. All patients underwent adrenal CT and synacthen-stimulated AVS for subtyping. Unilateral PA was treated with laparoscopic adrenalectomy, while bilateral disease was managed with mineralocorticoid antagonists. Statistical analysis was performed using STATA and JMP.
Results
Fifty patients underwent PT during the study period, 49 of whom also underwent AVS. The median age was 54 years (IQR 13), and 49% were women. The median blood pressure at case detection was 161/96 mmHg (IQR 22/17). CT scans revealed a unilateral adrenal nodule in 45% of patients, with 68% confirmed as unilateral by AVS. One patient with bilateral nodules on CT had bilateral PA confirmed by AVS and a positive PT. ROC curve analysis (AUC = 0,75, CI 0,61-0,89) indicated that a 50% increase in s-aldosterone during PT had 45% sensitivity and 81% specificity, classifying 65% of patients correctly. The optimal cut-off was a 74% increase in s-aldosterone, correctly classifying 71% of the patients, with 59% sensitivity and 81% specificity. Combining PT with CT to predict unilateral PA yielded 32% sensitivity, 96% specificity, 88% positive predictive value and 63% negative predictive value.
Conclusions
Our study highlights the importance of defining an optimal cut-off for the population being studied. Furthermore, the results suggest that PT, particularly when combined with other diagnostic tools, can be a reliable tool for differentiating PA subtypes. Thus, PT can be valuable in centers where reliable AVS is not readily available.

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EP12

JOINT2954

The hippocampus in congenital adrenal hyperplasia (CAH) and autoimmune Addison's disease (AAD)

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Background
Both Congenital Adrenal Hyperplasia (CAH) and autoimmune Addison's Disease (AAD) are characterized by impaired cortisol and aldosterone production, along

with increased adrenal androgens in CAH, but reduced adrenal androgens in AAD. Current oral replacement medication for cortisol is sub-optimal and leads to imbalances in adrenal hormone levels that might negatively affect the brain and cognitive functioning. The hippocampus plays a vital role in memory and emotional regulation, and it is particularly sensitive to changes in corticosteroid levels as well as sex hormones and might therefore be especially vulnerable to cortisol and androgen imbalances in both CAH and AAD. This study investigates the relationship between hippocampal subfield volumes, white matter microstructure, and cognitive performance in patients with CAH and AAD.
Methods
Hippocampal subfield volumes and white matter microstructure (mean diffusivity, MD) were measured in CAH, AAD, and healthy control groups based on T1 and DWI MRI scans (3T). Participants completed a battery of memory tasks, including assessments of verbal and visuo-spatial working memory, as well as immediate and long-term recall. ANCOVA and regression analyses were performed to examine group differences and the relationship between hippocampal measures and memory performance, controlling for age, sex, education, and intracranial volume.
Results
No significant differences in hippocampal subfield volumes were found between the groups (CAH, Addisons and controls). However, CAH patients exhibited significantly higher MD values in the left subiculum body compared to controls. In CAH, higher volumes in the left CA1-body were associated with better immediate recall, while higher MD values, reflecting more impaired white matter, in the same region were linked to worse performance in immediate recall. In AAD, hippocampal volume interactions with memory performance were found in the right CA1-head for immediate recall, where larger volumes predicted better recall in controls but not in AAD patients. No significant interactions between hippocampal measures and long-term memory were found.
Discussion
Since no group differences between CAH, Addisons and controls in hippocampal subfield volumes were observed, our findings suggest that the hippocampus is relatively unaffected in this patient group, possibly due to their young age and early detection through neonatal screening. However, subtle alterations in white matter microstructure were linked to memory performance. Future studies should investigate whether hippocampal changes might emerge over time and contribute to memory difficulties in the long term, helping to refine interventions for cognitive challenges in these populations.

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EP13

JOINT3858

Clinical characteristics of a large single-centre cohort of paediatric patients with congenital adrenal hyperplasia (CAH) secondary to 21-hydroxylase deficiency

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Introduction
The most common cause of CAH is 21-hydroxylase deficiency, which is divided into classic (salt-wasting or simple virilising) and non-classic forms. Patients with classic CAH require lifelong hormone replacement. Optimisation of treatment requires close monitoring of biomarkers. Both under- and over-treatment are associated with impaired linear growth and gonadal function and increased cardiometabolic risk.
Aims & methods
This retrospective cross-sectional study aimed to comprehensively phenotype a large single-centre cohort of 21-hydroxylase deficiency patients ($n = 168$), aged 0 – 18 years. It formed part of a registered service evaluation. CAH patient data were collected retrospectively from patient records for patients seen between 1/6/2022 – 1/6/2024.
Results
51.8% (43 females, 44 males) had salt-wasting CAH, 35.1% (42 females, 17 males) had simple virilising CAH and 13.1% (16 females, 6 males) had non-classic CAH. 82% ($n = 137$) had genetic testing. 32.3% had a large deletion/ conversion within the *CYP21A2* gene. 60% carried point mutations, with the I2 splice mutation found in 46.2% of affected alleles. There was no significant difference in mean height SDS by disease subtype (P value $= 0.13$). 84.8% ($n = 28$) of patients at final height were within 1.5 SDS of their mid-parental height SDS. Fourteen patients had required GnRH agonist treatment to arrest early puberty. Fifty-three patients (31.5%) were obese (+2 BMI SDS), and fifty-two patients (31%) were overweight (+1 BMI SDS) (BMI SDS range –4.33 to +4.12). On average, patients were insulin insensitive (mean HOMA-IR 3.31). Insulin insensitivity was notable in pre-pubertal patients of healthy weight. Assessment of biomarkers by pubertal stage revealed mean morning ACTH and 17-OHP concentrations above the reported reference range in each pubertal group (ACTH $>$ 49 ng/l and 17-OHP $>$ 36 nmol/l). Statistically significant differences in average hydrocortisone dose, morning 17-OHP and androstenedione concentrations by pubertal group were found ($P < 0.05$). 19% ($n = 31$) received hydrocortisone (or equivalent) doses >15 mg/m^2/day. There was no significant difference between hydrocortisone dose equivalent by disease subtype (P value $= 0.08$).
Discussion
We report a high incidence of insulin insensitivity in our single-centre cohort of paediatric patients with 21-hydroxylase deficiency, with high rates of overweight/ obesity. Biomarkers were elevated in some pre-pubertal patients, highlighting early difficulties with biochemical control. However, despite mean morning ACTH and 17-OHP concentrations outside the recommended ranges, our data suggest that few children required intervention for short stature or early puberty. Clearly longitudinal assessment of growth parameters is required, as is the reporting of long-term outcomes for this cohort.

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EP14

JOINT3768

Management of adrenal insufficiency during pregnancy

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Introduction
Pregnancy presents unique challenges for women. When complicated by or associated with adrenal insufficiency, diagnosis and management become particularly challenging due to the overlap between the condition's symptoms and the physiological changes of pregnancy.
Object
To assess the etiologies, management, and outcomes of pregnancy in women with adrenal insufficiency
Methods
We conducted a retrospective descriptive study of patients with adrenal insufficiency who were hospitalized or seen in our endocrinology department between 2019 and 2024.
Results
Our study included 15 pregnant women with adrenal insufficiency (AI). Five patients had glucocorticoid-induced AI. In one case, AI onset occurred during the first trimester of pregnancy. This patient presented with an adrenal crisis initially misdiagnosed as hyperemesis gravidarum due to nausea and vomiting, resulting in a 48-h diagnostic delay. Four patients had AI secondary to pituitary dysfunction: two with Cushing's disease, one with prolactinoma, and one with acromegaly. All patients with pituitary-related AI had the condition prior to pregnancy and received close monitoring throughout gestation. None of them experienced an aggravation of their condition during pregnancy. Six patients had primary AI. Two diagnoses occurred during the third trimester of pregnancy, indicating the onset of AI during gestation in these cases. One patient experienced a prolonged diagnostic delay as hypoglycemia was initially attributed to renal failure. Another patient with Nelson syndrome had a spontaneous pregnancy. The remaining patients with primary AI had autoimmune Addison's disease with concomitant type 1 diabetes prior to pregnancy. All patients received close monitoring and hydrocortisone replacement therapy with dose adjustments during the third trimester (+20-30%). Mineralocorticoid supplementation was not used in patients with primary AI. Adrenal crises occurred in five cases, all triggered by infections. The frequency of crises was higher in the glucocorticoid-induced AI and Addison's disease groups compared to the pituitary-related AI group. All patients underwent medically assisted delivery in a tertiary care setting with intravenous hydrocortisone administration. Adverse outcomes were observed in five cases, including 1 case of intra-uterine fetal demise, 2 cases of acute fetal distress, 1 case of macrosomia, and one case of post term pregnancy.
Conclusion
Our findings underscore the diagnostic challenges of adrenal insufficiency during pregnancy, particularly the risk of delayed diagnosis and the potential for new-onset disease. These findings emphasize the need for heightened clinical vigilance and a multidisciplinary approach to care.

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EP15

JOINT2579

Impact of glucocorticoid replacement therapy on carbohydrate metabolism in patients with Addison disease

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Introduction
In adults with Addison disease (AD), glucocorticoid replacement therapy is associated with an increased morbidity. The aim of our study was to assess the prevalence of carbohydrate metabolism disorders in patients with AD and identify its predictive factors.
Patients and methods
A cross sectional study including 50 patients diagnosed with AD with a mean duration of glucocorticoid replacement of 13,9 years. Biochemical markers of glucose metabolism were evaluated. The prevalence of type 2 diabetes and its complications were analyzed. Patients presenting type 1 diabetes were excluded from our study.
Results
The mean age of patients was 49,5 with a significant female predominance and a sex ratio of 0.25. Mean fasting blood glucose at the diagnosis of AD was 4,6 mmol/l and the mean glycated hemoglobin was 4,6%. No patient had prediabetes nor diabetes. At the time of our study, disorders of carbohydrate metabolism were found in 38% of patients and 31,6 % had type 2 diabetes. Diabetic retinopathy occurred in 2 patients and one patient complained of diabetic neuropathy. Daily and cumulative dose of glucocorticoids were higher in patients with diabetes compared to those with normal blood sugar level (27,5 mg/day vs 25,6 mg/day; 506,2 mg vs 355,4 mg). In addition, longer AD duration was found in patients presenting diabetes compared to those with a normoglycemia(19,8 years vs 13,2).
Conclusion
Despite the worldwide availability of replacement therapy in AD, exposure to supraphysiological dose of corticosteroids leads to altered insulin secretion and decreased hepatic and muscular insulin sensitivity resulting in risk exacerbation of carbohydrate metabolism disorders.

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EP16

JOINT2123

Prognostic factors for survival in patients with metastatic adrenocortical carcinoma

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Introduction
Metastatic adrenocortical carcinoma (ACC) is a highly aggressive disease with a poor prognosis and limited treatment options.
Materials and Methods
This retrospective study aims to evaluate the clinical outcomes of 29 patients with metastatic ACC: overall survival (OS), progression-free survival (PFS), and disease-specific survival (DSS).
Results
The median age of patients was 60 (IQR 53-68) years, with 76% being female. The median tumor size was 128 mm (IQR 112-160), and 22 patients had Cushing syndrome. The liver and lung were the most frequently affected organs, in 18 and 23 patients, respectively. Sixteen patients underwent an adrenalectomy with R2 resection. Postoperatively three patients received mitotane (M) monotherapy, twelve mitotane plus platinum-based chemotherapy (PE-M) and one received PE. In the non-operated group ($n = 13$), one patient received M monotherapy, two PE, and seven PE-M. Three patients died within one month of diagnosis and did not receive medical treatment. Among second-line therapies, four patients received gemcitabine and capecitabine plus M, while four others received sunitinib and one patient has been treated with cabozantinib. Over a median follow-up of 9 months (IQR 3–22), 24 patients died, with 21 deaths attributable to ACC. The median OS was 9 months (95% CI: 0.9–17.2), and the median DSS was also 9 months (95% CI: 0.9–17.2). The median PFS was 4 months (IQR 3–8). Patients who underwent adrenalectomy had significantly longer OS (18 months vs. 8 months, $P = 0.037$) and tended to have longer DSS (18 months vs. 8 months, $P = 0.059$) compared to non-operated patients. However, after excluding patients who died within three months of diagnosis ($n = 7$) the differences were no longer significant. The one-year mortality rate was 64% in patients with liver metastases, compared to 30% in those without ($P = 0.036$). Additionally, patients with liver metastases showed a trend toward shorter DSS (8 vs. 22 months, $P = 0.056$.). Similarly, there was a trend toward a lower one-year mortality in patients with only one affected organ compared to those with two or more (38% vs 64%; $P = 0.083$). In contrast, cortisol excess did not influence survival outcomes. In multivariate Cox regression analysis, older age was the only significant predictor of shorter OS ($P = 0.013$).
Conclusion
Older age is the only significant predictor of OS in patients with advanced ACC. However, liver metastases and the number of affected organs may negatively impact short-term survival within one year of diagnosis.

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EP17

JOINT1783

Continuous glucose monitoring in adult patients with classic congenital adrenal hyperplasia under different glucocorticoid regimens

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Background
Patients with classic congenital adrenal hyperplasia (CAH) show an increased prevalence of metabolic comorbidities, with glucocorticoid substitution therapy presenting a possible risk factor, due to unphysiological replacement. Therefore, the aim of this study was to assess the glucose pattern through continuous glucose monitoring (CGM) over 24 hs under different GC replacement regimen.
Methods
Adult patients with a confirmed diagnosis of classic CAH who received a substitution therapy with either conventional hydrocortisone or predniso(lo)ne were included in this study. All patients wore a CGM sensor once, measuring glucose concentration in the tissue every 5 minutes from 1 h after application up to a maximum of 14 days. Three time periods were defined over 24 hs: 6am-2pm, 2pm-10pm and 10pm-6am. Hydrocortisone dose equivalent (HDE) was calculated as prednisone dose multiplied by 4 and prednisolone dose multiplied by 5.
Results
A total of 44 patients with a median (range) age of 33.0 (35.0) years and a median (IQR) BMI of 26.4 (10.4) were included in the analysis (23 female, 21 male; 30 SW, 14 SV), of which 20 (45.5%) received conventional hydrocortisone and 24 (54.5%) predniso(lo)ne as glucocorticoid substitution therapy, with a median (IQR) total daily HDE of 30.0 mg/d (11.9). The median (range) measuring time of the sensor was 13.0 (9.0) days. There was no significant difference concerning median age, BMI or HDE between patients receiving conventional hydrocortisone and predniso(lo)ne. Concerning CGM, patients with predniso(lo)ne showed significantly more often glucose values between 140-<180 mg/dl between 6am-2pm (3.2% vs. 1.0%; $P = .030$), corresponding to 15.4 vs. 4.8 minutes, whilst patients on conventional HC showed significantly more often glucose concentrations in the normal range of 70-<140 mg/dl between 6am-2pm (98.1% vs. 95.5%; $P = .012$), corresponding to 470.9 vs. 458.4 minutes. There were no statistically significant differences between 2pm-10pm and 10pm-6am between the two groups. For the total cohort, we found a significant positive correlation between the median evening HDE with the average glucose concentrations ($r = .450$; $P = .002$) between 10pm-6am.
Conclusion
Our preliminary data indicate slightly different glucose patterns over 24 hs in patients with CAH receiving different glucocorticoid substitution therapy. The intake of longer acting preparations, as well as higher dosage, seem to be associated with slightly higher glucose concentrations, which should be taken into account when identifying patients with an increased metabolic risk.

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EP18

JOINT1959

Adrenal and peri-adrenal schwannomas: two case reports and a review of clinical, imaging and pathological features

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Introduction.
Adrenal schwannoma (AS) is a rare, typically benign tumor originating from Schwann cells, often found in the adrenal medulla. Peri-adrenal (peri-AS) or juxta-adrenal schwannomas originate from tissues surrounding the adrenal gland. Despite their anatomical differences, they share similarities with AS in clinical presentation, management, and histopathological features. There are fewer than 200 reported cases of AS and peri-AS, highlighting their rarity. We report two cases, one of adrenal and one of peri-adrenal schwannoma.
Case 1.
A 50-year-old female presented with an adrenal incidentaloma discovered during an MRI for uterine fibroids. CT imaging of the adrenals confirmed the 6 cm mainly cystic lesion with septa of her right adrenal compressing the inferior vena cava. Her past medical history was unremarkable and hormonal workup was normal. She underwent open surgery and a 6x5.5x4.5 cm lesion weighing 85 g was excised and its histopathological examination revealed alternating Antoni A and Antoni B areas, necrosis, hemorrhage, strongly and diffusely positive S100 immunomarker and a Ki67 index of 3%. Immunohistochemistry confirmed AS. Four years post-surgery, follow-up imaging showed no recurrence.
Case 2.
A 62-year-old female presented with an adrenal incidentaloma detected on abdominal ultrasound for abdominal pain. Her past medical history was unremarkable. CT imaging of her adrenals revealed a 4x3.2x3 cm right adrenal lesion with 61.2 HU, which on MRI was heterogenous with no intracellular fat. Hormonal workup was normal. She underwent surgery and an 78 g, 4.5x3.5x3 cm mass was removed from her right adrenal. Histopathological examination revealed hemorrhages, necrosis, and degenerative changes. Immunohistochemistry confirmed the diagnosis of schwannoma (positive for S100 and SOX10; negative for synaptophysin).
Conclusion
AS and peri-AS are rare tumors often presenting as non-functional masses, with diagnosis confirmed through histopathological examination following surgical removal. They can be discovered incidentally on imaging for unrelated issues. Pre-operative diagnosis is challenging due to their asymptomatic or nonspecific presentation (abdominal or back pain from adjacent organ compression) and on imaging is difficult to differentiate them from other adrenal or peri-adrenal masses. Surgery (adrenalectomy/removal of the peri-AS tumor) is essential to confirm diagnosis and exclude malignancy. Their histopathological findings of encapsulated spindle cell tumors, nuclear atypia, cystic changes, and hemorrhage, complicate the diagnosis. The S100 immunomarker is typically strongly and diffusely positive and a key feature in supporting schwannoma diagnosis.

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EP19

JOINT2452

Secondary adrenal insufficiency and immune checkpoint inhibitors: case series with pembrolizumab from a non-oncologic hospital

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Introduction
Secondary adrenal insufficiency (AI) is a potentially life-threatening adverse event that has been also associated with the use of immune checkpoint inhibitors (ICIs) in oncologic patients. Accumulating evidence link pembrolizumab, a programmed cell death protein-1 (PD-1) inhibitor, with adrenocorticotropic hormone (ACTH) deficiency in a frequency probably significantly higher than initially considered. We report a case series of three patients receiving pembrolizumab for diverse type of malignancies, who developed secondary AI.
Case 1
A 68-year-old man with metastatic non-small-cell lung cancer was referred from his oncologist due to pembrolizumab-induced thyroiditis [TSH = 124.78 μIU/ml (0.35–4.78) and FT4 = 2.9 pmol/l (10.5-22.7)], developing 20 weeks after starting ICI. Though he reported only mild fatigue attributed to the underlying cancer and hypothyroid status, endocrinological workup before levothyroxine supplementation revealed concomitant secondary AI, as indicated by low morning cortisol = 2.8 μg/dl (6-20) and ACTH < 5 pg/ml (9-52) levels. MRI of the pituitary gland revealed partial empty sella and hydrocortisone 30 mg/day was started. Interestingly, five months after AI diagnosis, recovery of adrenal axis was observed with morning cortisol levels up to 17.52 μg/dl and ACTH levels up to 33.2 pg/ml while he was still receiving pembrolizumab. Glucocorticoid replacement was discontinued and the patient remained eucortisolemic during follow-up.
Case 2
A 68-year-old man completing a 6-cycle treatment with pembrolizumab for metastatic renal disease was referred from his oncologist due to severe fatigue and progressively worsening muscle weakness. Laboratory investigation was compatible with secondary AI (low morning cortisol = 2.62 μg/dl and ACTH = 4 pg/ml levels), while thyroid function was normal. Pituitary MRI showed only gland heterogeneity and hydrocortisone (30 mg/day) was started with significant clinical improvement. Six months after completing immunotherapy and while on glucocorticoids, AI still did not resolve.
Case 3
A 48-year-old woman treated with pembrolizumab (6 cycles) for poorly differentiated breast cancer was referred from her oncologist due to secondary AI (low morning cortisol = 1.2 μg/dl and ACTH = 5.4 pg/ml levels) with coexisting central hypothyroidism [subnormal FT4 levels = 0.51 ng/dl (0.8-2) with inappropriately low serum TSH = 1.98 μIU/ml (0.3–4.5) levels]. Hydrocortisone (30 mg/day) and then levothyroxine (68μg/day) were started with no biochemical sign of pituitary-adrenal axis recovery in a 6-month follow-up period, after pembrolizumab last administration.
Discussion
Oncologic patients receiving pembrolizumab are at considerable risk for developing secondary AI. Therefore, close monitoring seems a reasonable approach to avoid delayed diagnosis and management.

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EP20

JOINT3463

Non-functional retroperitoneal paraganglioma: a case report

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Introduction
Paragangliomas are rare neuroendocrine tumors arising from extra-adrenal chromaffin cells. While functional paragangliomas secrete catecholamines and present with symptoms such as hypertension, episodic headache and tachycardia, non-functional paragangliomas are asymptomatic and often discovered incidentally. Herein, we report a case of non-secreting retroperitoneal paraganglioma.
Case Report
A 62-year-old male presented to our department with acute-onset low back pain progressing for a few months. He additionally complained of headaches and muscle fatigue for several weeks. There was no history of neuropathy or trauma. The family history was positive for hypertension, diabetes mellitus and autoimmune disorders but there were no symptoms to suggest endocrine neoplasia syndrome. On admission, the physical examination was unremarkable with no palpable abdominal mass. His blood pressure was 120/70 mmHg, and his other vital signs were within normal range. Ambulatory blood pressure (BP) monitoring showed an average daytime BP of 123/74 mmHg and nighttime BP of 114/62 mmHg. Standard laboratory investigations were unremarkable. A lumbar spine Computed Tomography scan (CT) was performed and revealed a solitary well-defined mass located in the right renal hilum with a spontaneous density of 25 HU, measuring 40 × 27 × 37 mm. Then, an abdominal CT scan was performed, revealing a well-defined, multilobulated extra-renal retroperitoneal mass located in the right perihilar lower pole, exhibiting intense and early enhancement in the arterial phase with progressive enhancement in the portal and delayed phases. The mass was vascularized by a pedicle arising from the ipsilateral renal pedicle and measured 40 × 25 mm in axial dimensions with a height extension of 44 mm, which was more consistent with paraganglioma. There were no locoregional extension or evidence of secondary lesions. Laboratory findings showed also normal serum metanephrines and normetanephrines. (Normetanephrines: 89.9 pmol/l (139-808) and Metanephrines: 76.5 pmol/l (88-375) The patient underwent laparoscopic surgery without complications, and the histopathological study confirmed the diagnosis of paraganglioma.

Conclusion
The diagnosis of non-secreting paraganglioma is challenging, as there are no specific clinical or biological signs for early detection. Surgical excision remains the treatment of choice. Half of these tumors are malignant. The progression is characterized by the risk of late recurrences. Consequently, long-term follow-up is essential.

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EP21

JOINT2068

Evaluation of adiponectin level and metabolic parameters in patients with mild autonomous cortisol secretion and non-functional adrenal adenomas

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Objective
Various metabolic adverse effects have been identified in patients with mild autonomous cortisol secretion (MACS) and even in those with non-functional adrenal adenomas (NFAA). In this study, we aimed to assess adiponectin levels and metabolic syndrome (MetS), as well as investigate the potential impact of low-grade hypercortisolism in patients with MACS and NFAA.
Method
A total of 72 patients, comprising 48 with MACS and 24 with NFAA, were included in a 2:1 ratio, with similar age, sex, and body mass index (BMI). Serum adiponectin levels of the patients were measured. MetS was diagnosed based on the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III) criteria. The cardiometabolic index (CMI) was calculated as the ratio of triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C), multiplied by the waist-to-height ratio (WHtR). The Triglyceride-Glucose (TyG) index was calculated using the formula: ln [(Fasting TG (mg/dl) × Fasting glucose (mg/dl))/2].
Results
The median low-dose dexamethasone suppression test (DST) in the MACS group was 2.9 µg/dl, while it was 1.1 µg/dl in the NFAA group. No significant differences were observed between the MACS and NFAA groups in terms of waist circumference (WC), WHtR, presence of type 2 diabetes, hypertension, or coronary artery disease ($p > 0.05$). However, dyslipidemia was more prevalent and HbA1c levels were higher in the MACS group compared to the NFAA group ($p < 0.05$). The prevalence of MetS was 50% in the MACS and 37.5% in the NFAA groups ($P = 0.316$). The CMI and TyG index was not statistically different between the groups ($p > 0.05$) and the CMI was positively correlated with HbA1c ($p < 0.05$). Serum adiponectin level was significantly higher in the MACS group than the NFAA group ($p < 0.001$). In the linear regression analysis, serum adiponectin level was associated with low-dose DST and WC in the overall group ($p < 0.05$).
Conclusions
The higher adiponectin levels observed in patients with MACS compared to those with NFAA highlight the need for further research to clarify the underlying mechanisms of the complex relationship between low-grade hypercortisolism, MetS, and adiponectin levels.
Key words
Adrenocortical Adenoma, Cushing Syndrome, Metabolic Syndrome, Obesity

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EP22

JOINT907

Integrating patient and public involvement into simulation-based learning: a mixed-methods study enhancing healthcare professionals' confidence in managing adrenal disorders

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Background
Despite the benefits of patient and public involvement (PPI) in enhancing patient-centred care, there is limited integration of PPI into simulation-based learning (SBL) educational frameworks. Simulation via Instant Messaging for Bedside Application (SIMBA) is a SBL model that improves healthcare professionals' (HCPs) confidence in managing various medical scenarios.
Objectives
- To evaluate the change in HCPs' confidence in managing adrenal disorders.
- To explore the impact of integrating PPI to SBL on the HCP's practice and acceptability.
- To gather patient insight on this SBL-PPI model.

Methods
This mixed-methods study, conducted in the UK from June 2023 to March 2024, involved a two-day hybrid simulation-based learning (SBL) event featuring nine scenarios related to adrenal conditions. Patients with conditions represented in the scenarios participated in one-to-one virtual workshops coordinated by an early career researcher. They provided feedback on what worked well, areas for improvement, and how accurately the cases reflected real-life experiences. Workshop discussions were transcribed and analysed using content analysis to summarise patient insights. A patient representative presented key themes and shared their personal experiences during the event. Healthcare professionals (HCPs) interested in adrenal conditions completed pre- and post-SIMBA surveys to assess the model's acceptability and clinical impact. Quantitative data were analysed using STATA 17.0, while open-ended responses underwent thematic analysis to identify recurring themes and insights.
Results
64 participants completed pre- and post-SIMBA surveys. There was a significant increase in participants' confidence post-event (pre- vs post-simulation score: 45.4% vs 89.7%; $p < 0.01$). Thematic analysis of the impact of the session on participants' clinical practice yielded two key themes: Referral and Multi-Disciplinary Team (MDT) approach. Multiple participants intended to make more referrals to patient support groups and to discuss cases with other MDT members. 96.5% of participants on Day 1 and 97.1% on Day 2 agreed that the simulated topics were relevant to their practice. 100% rated the session quality as excellent/good. Patient feedback highlighted the benefits of sharing lived experiences, which enhances healthcare professionals' approach to personalised care and sensitive discussions.
Conclusion
Integrating PPI enhanced HCPs' confidence in the management of adrenal conditions. Besides its influence on the participants' clinical practice, this PPI-SBL model was well-received by both patients and HCPs. Future studies should assess long-term clinical impact and include objective measures of changes in clinical practice.

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EP23

JOINT596

Transient 18F-FDG PET/CT uptake of contralateral adrenal gland in patient under Mitotane for R0 corticosurrenaloma

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Introduction
Mitotane is indicated in the treatment of localized, locally advanced and metastatic adrenocortical carcinoma. There are three main mechanisms of action: inhibition of steroidogenesis (CYP11B1 and CYP11A1), increased endoplasmic reticulum stress (increased free cholesterol ester and fatty acid levels by inhibition of SOAT1, an enzyme that promotes the formation of fatty acid-cholesterol esters) and mitochondrial toxicity (membrane alteration and inhibition of respiratory chain) responsible for the apoptosis and necroptosis of adrenal cells. (1)
Observation
A 40mm right adrenal incidentaloma was discovered on abdominal CT in a 62 years old patient. No hormonal excess was found. A laparoscopic right adrenelectomy was performed due to tumor size, high radiodensity on CT and high FDG uptake. The pathological work-up described a 4cm lesion with a focal adrenocortical carcinoma (Weiss 5) developed within an adrenocortical adenoma (Weiss 1) with myxoid reshuffle. An adjuvant therapy by Mitotane was introduced because of an intermediary risk of recurrence (ENSAT 1, R0 and Ki-67 13%). Imaging follow-up every three months (CT scan and 18F-FDG PET/CT). After 9 months of treatment, the plasma mitotane concentration is at the limit superior, 20.3 mg/l (therapeutic range 14 to 20 ng/mL). 18F-FDG PET/CT uptake of the contralateral left adrenal gland appears, SUV max at 8.5 with no nodular lesion or adrenal hyperplasia on the CT scan. Mitotane is stopped because of thyroid adverse effects and

hyperlipidemia. 18F-FDG PET/CT three months later: disappearance of the left adrenal gland FDG uptake.
Discussion
Leboulleux *et al* (2) report that a percentage of 14% to 29% patients under adjuvant therapy by Mitotane following adrenocortical carcinoma surgery have a contralateral uptake: 4% before treatment, 29% between 0 and 6 months after the start of treatment, 26% between 6 and 12 months, 14% between 12 and 24 months and none after 24 months. The uptake was transient and dissapeared in the 24 months after the start of treatment. In this study, there was no FDG uptake in patients with adrenelectomy for pheochromyctoma, invalidating the hypothesis of a compensatory adrenal growth. A hypothesis is that despite hormonal adrenal replacement therapy, ACTH levels remain at the limit superior or slightly above the limit. Adrenal cells might become avid to 18F-FDG following ACTH stimulation.
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EP25

JOINT3844

The novel atherogenic indices and anthropometric measurements in patients with non-functioning adrenal adenomas and cardiovascular disease risk

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Background
Non-functioning adrenal adenomas (NFA) are prevalent tumors frequently associated with metabolic disorders such as obesity, hypertension, dyslipidemia, insulin resistance (IR), impaired glucose tolerance, metabolic syndrome (MetS), and osteoporosis. These conditions occur at higher prevalence in NFA patients compared to the general population. Since traditional risk assessments may be insufficient, novel atherogenic indices could improve cardiovascular risk (CVD) risk assessment in NFA patients.
Aim
This study aimed to characterize patients with NFA and CVD risk by analyzing novel atherogenic indices (TyG index, TyG-BMI index, LCI, Castelli Risk Index_2, AC, AIP, TG/HDL-C, MetS-IR), fasting glucose, and anthropometric measurements such as BMI and WHR.
Material and methods
This study enrolled of 106 patients aged >40 with NFA. CVD risk was evaluated based on Systematic Coronary Risk Evaluation 2 (SCORE2) and Systematic Coronary Risk Evaluation 2-Older People (SCORE2-OP) algorithms. Biochemical parameters (fasting blood glucose, total cholesterol levels (TC), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), triglicerydes (TG) were measured, followed by the computation of atherogenic indices such as Castelli's risk Index_I, Castelli's risk Index_II, Atherogenic index of plasma (AIP), Atherogenic coefficient (AC), Lipoprotein combine index (LCI), TG/HDL-ratio, Metabolic Score for insulin resistance (METS-IR), Triglyceride-Glucose index (TyG index), Triglyceride-Glucose body mass index (TyG BMI index) were computed. Anthropometric parameters were assessed using standard methods, including body weight, height, waist circumference, and hip circumference. Based on these, BMI and WHR were calculated.
Results
The median fasting glucose level was 101.5 mg/dl (94-109 mg/dl) in NFA patients. The mean TC was 212.0 ± 46.3 mg/dl, the median HDL-C was 60.2 mg/dl (11.9-153.8 mg/dl), the mean LDL-C was 124.2 ± 42.0 mg/dl, and the median TG was 107.0 mg/dl (43.0-509.0 mg/dl) The mean TyG index was 8.6 ± 0.5, and the median TyG BMI index was 240.4 (9.3-367.8). NFA patients have the LCI of 13.7 (2.0-170.5). The median Castelli's Risk Index_I was 3.3 (1.6-20.0), and the median Castelli's Risk Index_II was 1.9 (0.6-9.1). The median AC was 2.3 (0.6-19.0), and the mean AIP was -0.09 ± 0.2. The median TG/HDL-C was 1.7 (0.5-12.0). METS-IR demonstrated the mean value 39.9 ± 9.0. The mean BMI was 28.3 ± 4.5, and the mean WHR was 0.9 ± 0.08.
Conclusions
This study highlights significant variability in atherogenic indices and anthropometric measurements in patients with non-functioning adrenal adenomas (NFA) and cardiovascular disease (CVD) risk. The findings suggest that novel indices like the TyG index and MetS-IR may provide a more accurate assessment of CVD risk in NFA patients, warranting further investigation into their clinical significance.

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EP26

JOINT627

Prevalence, value, and reliability of genetic testing in congenital adrenal hyperplasia: a comprehensive review

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Introduction
Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by mutations in genes involved in cortisol biosynthesis, most commonly CYP21A2. Genetic testing has become integral in confirming diagnoses, and guiding management.
Objective
To assess the prevalence of genetic mutations, evaluate the diagnostic and clinical value, and analyze the reliability of various genetic testing methods in CAH.
Methods
A comprehensive review of published studies (2015–2025) was conducted, focusing on the prevalence of CAH-related genetic variations and the utility of testing in diagnosis and management.
Results
1. Prevalence:
- Genetic mutations linked to CAH were frequently detected, with large-scale studies reporting a positive genetic result in more than 60% of clinically suspected cases. The prevalence of specific syndromes, such as CAH-X, was estimated at approximately 10%, emphasizing the role of genetic testing in identifying rare forms of the disorder.
- Copy number variations, point mutations, and deletions in the CYP21A2 gene were the most commonly reported abnormalities, contributing to the phenotypic variability observed in CAH patients.

2. Value of Genetic Testing:
- Genetic testing plays a critical role in confirming CAH diagnoses, reclassifying patient phenotypes, and guiding personalized treatment strategies. Studies highlighted its utility in avoiding severe complications through early diagnosis and effective management.
- Techniques such as multiplex ligation-dependent probe amplification (MLPA), Sanger sequencing, and next-generation sequencing (NGS) provided detailed insights into the genetic landscape of CAH, enabling better understanding of genotype-phenotype correlations.
- Advanced molecular strategies facilitated the identification of novel mutations and improved diagnostic accuracy, particularly in complex or atypical cases.

3. Reliability:
- High levels of accuracy were reported for commonly used methods, with detection rates of 89–95% for point mutations and deletions.
- Techniques like MLPA and long-read sequencing demonstrated strong performance in identifying both common mutations and large gene rearrangements.
- The reliability of genetic testing was further enhanced by combining multiple methodologies, addressing challenges such as pseudogene interference and genetic complexity.
- Emerging technologies, including MinION-based sequencing, offered rapid, cost-effective alternatives with comparable accuracy, making them promising tools for routine clinical use.

Conclusion
Genetic testing is a cornerstone of CAH diagnosis and management, providing essential data on mutation prevalence, phenotype reclassification, and therapeutic guidance. Its high reliability and the availability of advanced testing methods reinforce its value in clinical settings. Future directions should focus on integrating cutting-edge technologies into routine diagnostics and enhancing accessibility to improve CAH outcomes.

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EP27

JOINT1518

Adverse events in heart failure patients on SGLT2 inhibitors: a retrospective study

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Introduction
Sodium-glucose co-transporter-2 (SGLT2) inhibitors have been recently introduced into heart failure (HF) management and are now pivotal in reducing the mortality and morbidity associated with the condition. SGLT2 receptors, located in the proximal convoluted tubules of the kidneys, are responsible for 90% of total filtered glucose resorption. Inhibiting these receptors results in osmotic diuresis through glucosuria and natriuresis, thus lowering blood pressure and blood sugar levels. However, the mechanism of SGLT2 inhibitors predisposes patients to potential adverse side effects. The aim of this study was to investigate the incidence of diabetic ketoacidosis (DKA), urinary tract infections (UTIs) and acute kidney injury (AKI) in patients on SGLT2 inhibitors.
Methods
This study is a retrospective review of 100 patients with HF who were prescribed either Dapagliflozin or Empagliflozin. Data was extracted using electronic patient records, detailing both inpatient and outpatient treatment. Patients were included in this study based upon a HF diagnosis and treatment involving SGLT2 inhibitors. Adverse events were classified through hospital admissions where DKA, UTI or AKI were diagnosed. Further analysis was conducted in subgroups including diabetic status and type of SGLT2 inhibitor.
Results and Discussion
Amongst the 100 patients (age 31-98 years, 62% males) included in this study, 45% had type-2 diabetes, with a majority (81%) being treated with Dapagliflozin for HF. The incidence of UTIs across the cohort was 16% and 69% of these cases occurred in diabetic patients (risk ratio(RR) = 2.69), indicating that diabetes may increase the likelihood of UTIs in individuals treated with SGLT2 inhibitors. 87% of the total UTI cases occurred in patients on Dapagliflozin (RR = 1.64). AKI developed in 17% of patients, with 53% of cases occurring in diabetic patients (RR = 1.38). The incidence of AKI was also notably higher in patients on Dapagliflozin (RR = 1.64). These results suggest that diabetic patients on Dapagliflozin are at the highest risk of infections when compared with non-diabetic patients. DKA was observed in 3% of the cohort, exclusively in diabetic patients on Dapagliflozin. Our findings display that diabetic patients with HF are at a higher risk for UTIs, DKA and AKI when treated with SGLT2 inhibitors.
Conclusion
In conclusion, our study highlights the need for vigilant monitoring of patients on SGLT2 inhibitors, particularly Dapagliflozin, for adverse events such as UTIs, DKA and AKI. Patients should be counselled prior to initiation of SGLT2 inhibitors, with ongoing glycaemic monitoring, renal function assessments and infection surveillance to mitigate their risk of adverse events.

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EP28

JOINT2080

Pheochromocytoma-induced takotsubo cardiomyopathy in a patient with SDHA and EGLN1 variants

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Introduction
Takotsubo cardiomyopathy is a rare presentation of pheochromocytomas and paragangliomas (PPGLs) and it is associated with a higher degree of morbidity and mortality. In this report, we present a patient with PCC-induced Takotsubo cardiomyopathy with rare *SDHA* and *EGLN1* variants.
Case Presentation
A previously healthy 17-year-old woman with no cardiovascular risk factors was admitted to a cardiac intensive care unit due to dyspnea, chest pain and elevated blood pressure at 210/100 mmHg. In addition, the patient gave an 8-month history of paroxysmal hypertension, headache and diaphoresis. Serum troponin levels were elevated and ECG and heart ultrasound findings were indicative of Takotsubo cardiomyopathy with an ejection fraction of 20-25%. She was treated with a combination of bisoprolol, sacubitril/valsartan, empagliflozin, eplerenone, furosemide and doxazosine. An abdominal MRI revealed a 55 mm heterogenous left adrenal lesion with high T2 signal and no signal suppression on out-of-phase T1-weighted images. 24-h urine normetanephrine levels were elevated [1926 μg/24h (<669)] whereas 24h urine metanephrine levels were normal [67 μg (< 276)]. Whole-body MIBG scintigraphy revealed selective radiotracer uptake by the adrenal lesion. A diagnosis of pheochromocytoma was made and the patient underwent an uneventful laparoscopic left adrenalectomy 3 weeks later. Histology confirmed the diagnosis of pheochromocytoma with a PASS score of 8 and a Ki-67 of 3-4%. Genetic testing with whole exome sequencing identified the missense *SDHA* variant, c.1367C>T, resulting in replacement of serine by leukine at codon 456, p.Ser456Leu, of SDHA protein and the frameshift *EGLN1* variant, (c.1163_1166del).
Conclusion
Catecholamine-induced cardiomyopathy is an uncommon feature of pheochromocytoma. *SDHA*-related PPGLs, account for up to 2.8% of cases and are usually found in the head and neck region or the abdomen, with only 15% of them being pheochromocytomas. Although our patient's *SDHA* variant is considered of uncertain significance, it has been reported in a case of *SDH*-deficient GIST and received a cancer-like functional classification in a recent study using a novel human *SDHA*-knockout cell line model. Furthermore, our patient has a previously unreported variant of *EGLN1*, which is another susceptibility gene for PPGLs. Further studies are needed to determine whether these gene variants are pathogenic and whether they act synergistically for PPGL development.

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EP29

JOINT2021

Carbohydrate metabolism disorders in pheochromocytoma

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Introduction
Pheochromocytomas (PCC) are neuroendocrine tumors that develop in the chromaffin cells of the adrenal medulla. They are responsible for hyperproduction of catecholamines. Among the abnormalities that can be observed in these tumors are disorders of carbohydrate metabolism (1).
MaterialS and Methods
Through a retrospective descriptive study of 48 patients diagnosed with PCC in our departement of Endocrinology, we describe the observed abnormalities of carbohydrate metabolism in this population.
Results
The average age of our patients was 40,9 years. The sex ratio was 0.45 with 15 men and 33 women. The average of BMI was 23,11 kg/m^2, 50% of our patients had high blood pression. Urinary methoxylate drifts were performed in 44 patients, 42 of whom had elevated levels. Abdominal CT was performed in 44 patients, while the remaining 4 patients benefited from abdominal MRI in the context of concomitant pregnancy. Thirty-three percent of our patients had

moderate fasting hyperglycemia, while diabetes was diagnosed in 29,16 % of cases who were put on non-insulin hypoglycemic agents and/or insulin, attached to the PCC and 6.25% of patients had type 2 diabetes already treated with insulin.
Discussion and Conclusion
Catecholamines exert their physiological effects via adrenergic receptors (α and β) for adrenaline and noradrenaline, and dopaminergic receptors (DA1, DA2) for dopamine. Catecholamine-induced hyperglycemia is mediated by alpha1 receptors. The consequences of their activation are increased lipolysis with the release of fatty acids constituting precursors of gluconeogenesis, glycogenolysis releasing glucose and inhibition of insulin secretion. On the other hand, activation of beta2 receptors has a hypoglycemic effect by stimulating insulin secretion, a little-known, rare but serious effect. In general, the alpha-adrenergic action predominates, hence the frequency of hyperglycemia during PCC (26%) (2). Carbohydrate abnormalities during PCC can be greatly improved after tumor resection (3), which is why it is important to detect them in order to manage them early and correctly.
Key words
Phéochromocytome, Catecholamines, Hyperglycemia, Diabetes.
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EP30

JOINT2067
Impact of Covid-19 pandemic on pheochromocytoma and paraganglioma incidence
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Introduction
Pheochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumors, often diagnosed incidentally (1,2). The COVID-19 pandemic has led to significant changes in healthcare delivery, potentially influencing the detection of such conditions. The aim of this study was to evaluate the impact of COVID-19 on the incidence of pheochromocytoma (PHEO) and paraganglioma (PGL).
Materials and Methods
We conducted a bicentric retrospective study in the endocrinology departments of two Tunisian university hospitals (Monastir and Sousse, Tunisia). All cases of PHEO and PGL diagnosed between January 1991 and December 2023 were reviewed. Data were extracted from medical records and analyzed using SPSS version 21. Inclusion criteria involved patients with a confirmed diagnosis of PPGL.
Results
We have included 45 patients with PHEO, 8 with PGL and 1 patient who has both PHEO and PGL. Incidentally discovered PPGL on imaging accounted for 51.9% of our cases. The annual incidence of PHEO and PGL in both hospitals was 1.92 cases/year, with a noticeable increase starting in January 2020. Indeed, the annual incidence after 2020 was 5.25 cases/year and 38,8% of our patients were diagnosed between 2020 and 2023.
Discussion
Our study indicates a noticeable increase in the incidence of incidentally discovered PPGL starting in 2020, a trend that aligns with the disruptions caused by the COVID-19 pandemic. This shift is particularly relevant in the context of changing healthcare dynamics during the pandemic, including the increased use of computed tomographic scan of the thorax. Various studies have noted similar findings (3), highlighting how the pandemic may have influenced the detection of both common and rare conditions.
Conclusion
The COVID-19 pandemic has influenced the incidence and diagnostic pathways of PPGL, with an increasing number of incidental findings noted in imaging studies after 2020.
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EP31

JOINT2784
Glycemic disorders in pheochromocytoma and paraganglioma
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Introduction
Pheochromocytomas and paragangliomas (PPGL) are characterized by a wide spectrum of clinical and biological manifestations, primarily due to the excessive secretion of catecholamines. One of the common associated co-morbidities are glucose metabolism disorders, including both prediabetes and diabetes. The purpose of this study was to assess the prevalence of glycemic disorders observed in patients with PPGL.
Materials and Methods
We conducted a bicentric retrospective study in the endocrinology departments at two hospitals: Fattouma Bourguiba Hospital in Monastir and Farhat Hached Hospital in Sousse, Tunisia. This study included patients diagnosed with PPGL from January 1991 to December 2023.
Results
Out of the 54 patients included, 45 were diagnosed with PHEO, 8 with PGL, and 1 with both PHEO and PGL. We noticed a female predominance with sex ratio of 2.8. The median age of patients with PHEO and PGL was 46.4 and 49.2 years respectively. The mean BMI was 25 kg/m^2. A significant proportion of patients (75.9%) had hypertension, 37% had diabetes, while 25.9% had prediabetes.
Discussion
The glycemic disorders in patients with PPGL can be explained by multiples mechanisms. First, a defect in insulin secretion secondary to stimulation of α2 receptors, which inhibits insulin production (1,2) and second, insulin resistance through stimulation of α1 receptors, which activates lipolysis and gluconeogenesis (1,3). Elenkova *et al*. reported 30.4% for diabetes and 19.1% for prediabetes (4) and the Indian study by Khatiwada *et al*. described a higher rate of diabetes at 48.3% (3). We suggest that a comprehensive clinical examination, including glycemic screening, is crucial in the management of PPGL patients, especially considering the associated metabolic risks.
Conclusion
PPGL present a complex diagnostic and therapeutic challenge due to their highly variable clinical presentation and associated comorbidities, such as glycemic disorders and hypertension. Our study demonstrates a high prevalence of both prediabetes and diabetes in patients with PPGLs, underscoring the need for careful monitoring and management of glucose metabolism.
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EP32

JOINT1109
A case of aldosterone synthase deficiency presenting with hyponatremia in a 17-year-old male
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A 17-year-old male patient presented to our hospital with complaints of confusion and seizures. His medical history revealed that three years ago, he suffered a head injury resulting in a brain hemorrhage. He has been taking carbamazepine due to epilepsy. A physical examination showed that the patient's height was 146,5 cm (-4,7 SDS), and his weight was 48 kg (-3.02 SDS). His blood pressure and pulse rate at admission were 110/80 mmHg and 71 beats/min, respectively. There were no remarkable findings on chest and abdominal examinations. The findings of the neurological examination were unremarkable, except for muscle weakness. In the family history, the parents were consanguineous and one of his sisters was healthy. Initial laboratory testing was as follows: serum sodium 118 mEq/l, potassium 5.3 mEq/l serum osmolality 240 mOsm/kg, uric acid 1.5 mg/dl, urine osmolality 132 mOsm/kg and urine sodium 24 mEq/l. Other laboratory values of the patient are given in Table 1. The findings of an inappropriately concentrated urine (>100 mOsm/kg), low serum osmolality (<280 mOsm/ kg) and serum sodium (<135 mEq/l) were compatible with syndrome of inappropriate antidiuretic hormone secretion (SIADH). After fluid restriction to 1000 ml/m^2/day, serum sodium concentration increased up to 141 mEq/l. Since carbamazepine is known to cause SIADH, his treatment was switched to levetiracetam. Further studies were conducted to determine the cause of SIADH. Chest X-ray and magnetic resonance imaging of the brain were normal. When daily fluid intake became unrestricted, hyponatremia recurred. After exclusion of usual causes of SIADH, a nephrogenic origin of inappropriate antidiuresis was considered and the plasma renin activity (PRA), aldosterone level was checked. In the presence of hyponatremia (116 mEq/l) and high PRA (> 1000 ng/ml/h), the aldosterone level was undetectable (<0.01 ng/dl). Therefore, we switched our clinical diagnosis of SIADH to ASD. To correct hyponatremia, fludrocortisone treatment (0.2 mg/day) was started. The diagnosis of ASD was confirmed by genetic testing, which showed a homozygous mutation in *CYP11B2* gene, (c.1360>T; p.(Arg454Cys)).

Table 1. Laboratory values of cases

Parameters	Value	Reference ranges
Sodium (mEq/l)	118	135–145
Potassium (mEq/l)	5.3	3.5–5.5
Bicarbonate (mmol/l)	22	22–29
Osmolality (mOsm/kg H_2O)	240	275-295
Renin Activity (ng/ml/h)	>1000	0,4-15
Aldosterone (ng/dl)	<0,01	5-90
fT4 (ng/dl)	1.69	0.96-1.77
TSH (µIU/ml)	1.97	0.7-5.97
ACTH (pg/ml)	35,7	25-100
Cortisol (µg/dl)	15	8.5-23
Urine		
Osmolality (mOsm/kg H_2O)	132	50-1400[a]
Sodium (mEq/l)	24	54–190[b]
Potassium (mEq/l)	13	20–80[b]

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EP33

JOINT3698

Congenital adrenal hyperplasia: about 10 cases in burkina faso

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Background
Congenital adrenal hyperplasia (CAH) is a group of genetic disorders responsible for defects in adrenal steroidogenesis and resulting in diminished cortisol production. Very few newborns are examined by a paediatrician and screening of neonates with elevated 17-hydroxyprogesterone concentrations is not available in Burkina Faso. Until 2023, there was no pediatric endocrinologist in the country, which is also short of pediatric doctors. We aimed to describe the main characteristics of patients diagnosed with CAH in this country
Patients and Methods
Data were collected from a retrospective program register between 2018 and 2024 in the 2 main cities of Burkina Faso. Diagnostic criteria were the presence of clinically suspected signs with elevated serum 17-hydroxyprogesterone or DOC and/or 11-deoxycortisol concentrations.
Results
Total of 10 children and adolescents (including 9 classic forms) aged between 1 month and 18 years were diagnosed with CAH. The karyotype showed 8 46, XX patients and 2 46, XY patients. Although symptoms had been present since birth, the mean age of diagnosis was 8.5 years. The main symptoms of the 46, XX patients were atypical genitalia (8/8), oligomenorrhea/amenorrhea (4/8), and hirsutism (2/8). For the 46, XY patients there was a post-natal virilization (2/2). Two children were from the same family. Biological assays showed 21-hydroxylase deficiency in 9 patients and 11-hydroxylase deficiency in the 1 remaining patient who also had hypertension. Genetic analysis was performed on a single patient (male), showing a composite heterozygous mutation 668-13C>G. All patients were treated with chronic hydrocortisone therapy and 1 died. The child with 11-hydroxylase deficiency received also a mineralocorticoid receptor antagonist to treat hypertension. Genital surgery was performed in 4/8 46, XX patients.
Conclusion
CAH can result in mortality if left undiagnosed or insufficiently treated. Patients come late for consultation. This can be explained by a lack of knowledge of this pathology by medical staff, but also by the lack of paediatric endocrinologists.

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EP34

JOINT2137

Cell-cell communication shapes the impact of obesity-associated stressors on human vascular cells

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Background and Aim
Cardiovascular disease (CVD) is the leading cause of death in individuals with obesity, driven largely by endothelial (EC) and smooth muscle cell (SMC) dysfunction. Obesity-induced EGFR transactivation, mediated a.o. by elevated angiotensin-II (AngII) and norepinephrine (NE) levels is supposed to contribute to vascular dysfunction and remodeling. However, the role of EC-SMC interactions in obesity-related CVD remains unclear. This study investigates the impact of AngII and NE on human primary ECs and SMCs under conditions mimicking obesity (elevated FFA and glucose).
Methods
Human primary ECs and SMCs were cultured alone or as co-culture in opposite side of cell culture insert membrane. The effects of metabolic stimuli (MS) and hormonal stimuli (HS), alone or in combination, on gene expression (DEG) were assessed by RNA-sequencing followed by gene-ontology term and functional enrichment analysis. To evaluate their impact on cell function, key parameters such as cell apoptosis/necrosis, DNA-synthesis/proliferation, glucose consumption (dglucose), lactate production (dlactate), oxidant–antioxidant balance, ATP production, mitochondrial function as well as the secretory profiles of inflammatory molecules were analyzed under each condition.
Results
In monoculture, incubation of cells with each stimulus, alone or in combination, did not affect cell apoptosis, necrosis and GSSG/GSH-ratio while proliferation and proton leak was induced in HAoEC under MS. HAoSMC metabolism was altered by MS, evidenced by elevated ATP levels. dglucose and dlactate/dglucose-ratio were enhanced by either MS or all stimuli. Incubation of cells with either or both stimuli in the presence of AG1478/EGF revealed that MS-induced cell proliferation, dglucose, dlactate and ATP production seems to be EGFR dependent. In co-culture, proton leak and GSH content were induced in HAoECs by MS and HS respectively. Transcriptomic analysis revealed that under the effect of obesity-associated stressors, number of DEG in ECs was significantly higher in co-culture. IPA highlighted the involvement of DEGs in regulation of cell cycle and inflammation. This was not the case for SMC. Co-culture also led to a significant change of the extracellular inflammatory marker profile compared to monoculture, thereby exposing cells to a different micromilieu. A potential role of EGFR in co-culture is under investigation.
Conclusion
This study indicates that the transcriptome and functional profile of cells are profoundly influenced by the cell culture type, underscoring the critical role of cell interactions in cellular behavior. The effects of MS in different vascular cells are, at least partially, mediated by EGFR. In few cases, these effects are further altered by HS.

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EP35

JOINT3331

Adrenal incidentalomas and risk for cancer: a monocentric study in a tertiary greek center

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Objective
There is an increased interest in the incidence of malignancy among patients with endogenous Cushing's syndrome (CS). Although immunosuppression in patients with overt CS is a well-established knowledge favoring a cancerous state, the presence of a mild autonomous cortisol secretion (MACS) or a nonfunctional adrenal incidentaloma (NFAI) has not been studied adequately.
Design
This is a matched monocentric cohort analysis investigating the prevalence of an adrenal incidentaloma among oncological patients diagnosed either before the diagnosis of malignancy or at the staging of the malignancy before any therapeutic regimen. The medical files of a total of 370 patients followed at the Units of Oncology and Endocrinology of the First Department of Internal Medicine at Laikon General Hospital were analysed from 2016 to 2024.
Methods
Patients with adrenal metastatic lesions were excluded based on routine imaging criteria (MRI or CT), functional imaging (18FDG-PET) or biopsies. A complete hormonal profile was performed including the baseline plasma and urine measurements as well as hormonal functional tests. All measurements were performed before any oncological therapeutic regimen. Forty subjects with no active malignancy or history of cancer and no adrenal lesion were included as controls. All controls were age, sex, and body mass index-matched with the oncological patients.
Results
A total of 48 (12.9%) oncological patients with a median age of 66 (25-75%: 59-72) years old out of a total of 370 oncological patients (41,7% with melanoma, 18,8% with breast cancer and the remaining with renal, lung, colon, and bladder cancer) had a diagnosis of a benign adrenal tumor found either incidentally at staging or based on their medical history. The 56.3% of them presented a left unilateral adenoma whereas the 27.5% had bilateral lesions. The median size of the adrenal lesion was 16.5mm (25-75%: 11-28) and based on the endocrine functional tests (1 mg overnight dexamethasone secretion test), 66.7% had NFAI and 33.3% MACS. The 29% of these patients presented with diabetes mellitus, 25% with osteoporosis and 32.5% with hypertension compared with 23%, 17% and 23% respectively among controls. The mean time between diagnosis of cancer and AI diagnosis was 1.93 years.
Conclusion
Benign AI were diagnosed in 13% out of patients with a history of cancer. The vast majority included NFAI. However relevant comorbidities were more frequent in those patients compared to age and sex-matched controls. These findings underscore the need for further research to establish recommendations for cancer screening in patients with AI.

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EP36

JOINT3699

Aspects of diagnosing testosterone-producing tumours

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Introduction
Several endocrine disorders can lead to elevated testosterone levels in women. During the differential diagnosis, it is essential to consider conditions such as polycystic ovarian syndrome(PCOS), congenital adrenal hyperplasia(CAH), Cushing's syndrome, exogenous testosterone intake, or testosterone-producing tumours of the ovaries or adrenal glands. In addition to hormonal assessments, imaging methods can be useful for accurate diagnosis.
Case descriptions
A 29-year-old woman was diagnosed with non-classical 21-hidroxylase deficiency. Even with glucocorticoid supplementation, consistently elevated testosterone suggested the possibility of autonomous androgen production. CT of the adrenal glands revealed no abnormalities. Transvaginal ultrasound and pelvic MRI detected a 3 cm mixed-echogenic tumour in the left ovary. A left-sided adnexectomy was performed, and histological analysis confirmed Leydig-cell tumour. A 65-year-old woman was presented with hirsutism. Her testosterone were elevated, whith suppressed LH and FSH. A CT did not reveal any abnormalities in the adrenal gland, the pelvic MRI showed cysts in the right ovary, the left ovary could not be visualized. Exploratory laparoscopy was conducted, leading to a bilateral adnexectomy. The histopathology identified Leydig-cell tumour in the right ovary. A 50-year-old woman was examined because of virilism. Testosterone level was found to be 524ng/dl(ref:8-60ng/dl). Based on hormone levels Cushing-syndrome, PCOS and CAH was unlikely. CT of the adrenal glands suggested the possible presence of right-sided adenoma. Pelvic MRI and transvaginal ultrasound did not indicate tumour in the ovaries. To determine the source of the elevated testosterone, selective sampling of both the ovarian and adrenal veins was performed. The results revealed that the testosterone was produced by the right ovary. Consequently, an adnexectomy was performed, which identified Leydig-cell tumour in the right ovary. A 50-year-old woman presented with hirsutism and androgenic alopecia was diagnosed with hyperandrogenism. An abdominal ultrasound and CT did not describe any abnormalities. However, a transvaginal ultrasound failed to visualize the left ovary. On MRI, a heterogenous, contrast-enhancing tumour measuring 6.3x4.8x6.1 cm in the right ovary was seen. Subsequently, a bilateral adnexectomy was performed. Histology report identified the tumour as Sertoli-cell tumour.
Discussion
Determining the etiology of hyperandrogenism can be challenging. Collaboration with the radiologists and gynaecologists is essential to evaluate each case. The hormonal testing plays a crucial role in the differential diagnosis. However if there is a suspicion of a testosterone-producing tumour, abdominal and pelvic CT and MRI imaging, can provide valuable insights. Selective sampling of the adrenal and ovarian veins may also be helpful in such cases.

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EP37

JOINT1812

Primary adrenal lymphoma- 15years retrospective analysis from a tertiary care centre

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Introduction
Primary adrenal lymphoma (PAL) is a rare malignancy, accounting for $<1\%$ of extra-nodal lymphomas yet highly aggressive and invasive disease. Timely diagnosis is crucial for improved prognosis. We describe ten cases of PAL seen in our department who presented with diverse clinical presentations, posing challenges in both diagnosis and treatment.
Patients and Methods
Ten cases of PAL were confirmed by histopathology and immunohistochemistry from a retrospective cohort of 125 cases of primary adrenal insufficiency admitted in the Endocrinology ward over 15 years duration from 2010-2025. Data-analysis was performed using SPSS 27.
Results
The median age at presentation was 53 years (range: 22–70 years), 7 were males and had symptom duration of 1–4 months. Features of adrenal insufficiency like nausea, vomiting, hyperpigmentation weight loss, and loss of appetite were reported in 7 out of 10 cases and were confirmed in all 7. Fever and B symptoms were present in 8 out of 10 cases. Anemia was present in 9 out of 10 cases, while pancytopenia was observed in 1. Hyponatremia was noted in 8 out of 10 cases, and severe hypercalcemia occurred in 1 case. The mean LDH level was 1796 U/l (range: 703–3584 U/l) normal range (85-450). All patients had bilateral adrenal enlargement with lymphadenopathy in 8 out of 10 cases, hepatomegaly in 3, and splenomegaly in 2 out of 10 cases. The adrenal gland contour was oval in 5 out of 10 cases, irregular in 4 cases, and round in 1. All 10 cases were identified as B-cell non-Hodgkin lymphoma (NHL). Five patients received the R-CHOP regimen, and one received the R-CVP regimen. Chemotherapy was not initiated in four patients due to poor performance status. The median survival was 8 months (range: 4–30 months) in the chemotherapy group compared to 1 month (range: 1–4 months) in the non-chemotherapy group. Survival was 1–3 months in 3 cases, 3–6 months in 3 cases, 6–12 months in 1 case, and over 12 months in 1 case.
Conclusion
In India, tuberculosis and histoplasmosis are the leading causes of primary adrenal insufficiency with bilateral adrenal masses. PAL should be considered if

infectious causes are ruled out, as its treatment differs and carries a poor prognosis. PAL prognosis is generally unfavorable, with predictors of poor outcomes including older age, large tumor size, bilateral adrenal involvement, adrenal insufficiency at presentation, elevated LDH levels, and non-germinal B-cell lymphoma.

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EP38

JOINT3241

Nonsurgical management of pheochromocytoma in the very elderly – a case series and review of the literature

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Introduction
Pheochromocytoma (PCC) is a rare tumor with potentially fatal complications, namely cardiovascular events and PCC spells. Few cases of PCC treated non-surgically in the elderly have been described.
Methods
we collected data regarding three PCC patients that did not undergo adrenalectomy for various reasons on an average follow up of 5.69 years.
Results
Patient 1 was 75 years old (YO) at diagnosis, he had a tumor diameter of 3.2 cm and refused surgery. He had a stroke 6.6 years after presentation and survived for 14.1 years. His first available 24-h urinary metanephrines and normetanephrines were 5.91 and 1.98 times upper normal limit (UNL) respectively. Blood pressure (BP) treatment was with doxazosin, losartan and bisoprolol. Patient 2 was 86 YO when he had an adrenal mass of 4.9*6.2*4.5 cm found on CT, he wasn't referred to workup at that time and workup was complete only 7.31 years later, at age 94 when the adrenal mass was 7.4*8.1*8.8 cm and 24-h urinary metanephrines, normetanephrines and methoxytyramine were 12.73, 15.51 and 1.42 times the UNL respectively. He had no cardiovascular events at this time and refused further workup. BP and heart rate (HR) were controlled with doxazosin and metoprolol. Ehocardiography showed an ejection fraction of 45% with diffuse reduction of systolic function and a grade 2 diastolic dysfunction. Patient 3 was 85 YO at diagnosis, with tumor dimensions of 4.5*5.5, she had a positive F-DOPA scan, refused urinary metanephrines collection or any other workup. On a follow up of 0.54 years BP was slightly elevated and was controlled with doxazosin, lercanidipine and bisoprolol. She remained alive with no cardiovascular events. Our average age at diagnosis was 82 years, and average follow up time was 5.69 years. During follow up one patient passed away after 14.1 years of follow up, the same patient experienced a stroke at 6.61 years and a syncope at 2.4 years. No other cardiovascular events were recorded in the other two patients. The average age at end of follow up was 88 years.
Conclusion
in this series of three elderly patients with PCC that did not have an adrenalectomy we found one occurrence of a stroke and one death in the same patient on an average follow up of 5.69 years. It thus seems that medical management may allow satisfactory disease control in select cases in which surgery is not possible or refused by very elderly patients.

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EP39

JOINT964

The necessity for new criteria for overnight dexamethasone suppression test to diagnosis of cushing's syndrome

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Introduction
The overnight 1 mg dexamethasone suppression test (ODST) is used to screen and diagnose Cushing's syndrome, suspected when plasma cortisol levels exceed 1.8 μg/dl after dexamethasone administration. However, factors such as stress, illness, obesity, pregnancy, oral contraceptives, alcohol abuse, depression, and medications affecting dexamethasone metabolism can lead to false-positive results, requiring careful interpretation. This study aims to propose new criteria for ODST cortisol levels in diagnosing Cushing's syndrome by confirming whether patients with positive ODST results were diagnosed with Cushing's syndrome through further testing.
Methods
This study was conducted on subjects who showed positive results from ODST for the evaluation of adrenal adenoma or adrenal hyperplasia and subsequently underwent the low dose dexamethasone suppression test (LDDST) between January 2021 and October 2024 at Kangbuk Samusng Hospital. Patients with CKD grade 3b (estimated glomerular filtration rate [eGFR] < 45 ml/min/1.73m^2), those on medications affecting dexamethasone metabolism, and those undergoing cancer treatment were excluded. Diagnosis of Cushing's syndrome required two or more positive results from the ODST, LDDST, or late-night serum cortisol test (> 7.5 μg/dl).
Results
A total of 154 patients with positive ODST results underwent the LDDST. The mean age of the subjects was 55.9 $\pm$ 14.2 years, 58 (37.7%) were male, and the median body mass index (BMI) was 24.7 [22.7, 27.3] kg/m^2. 73 (47.4%) had hypertension, 37 (24.0%) had diabetes, and 46 (29.9%) had dyslipidemia. The median eGFR was 101.1 ml/min/1.73m^2. The basal, ODST, LDDST, and late-night cortisol levels were 11.4, 3.5, 2.8, and 4.6 μg/dl, respectively. Among the patients, 42 were not diagnosed with Cushing's syndrome, while 112 were. There were no significant differences in age, BMI, sex, or comorbidities between those diagnosed and those not diagnosed with Cushing's syndrome. The eGFR was significantly lower in patients without Cushing's syndrome (97.0 [87.9, 104.6] ml/min/1.73m^2) compared to those with Cushing's syndrome (102.5 [94.3, 110.9] ml/min/1.73m^2) ($P = 0.039$). ODST, LDDST, and late-night cortisol levels were significantly lower in patients without Cushing's syndrome ($P < 0.001$). The ODST cortisol level for diagnosing Cushing's syndrome was 3.15 μg/dl (AUC 0.818).
Conclusion
Despite positive ODST results, many patients were not diagnosed with Cushing's syndrome. Considering the high prevalence of obesity and stress in modern society, further research is needed to establish new criteria for ODST cortisol levels in diagnosing Cushing's syndrome.

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EP40

JOINT1178

From venipuncture to self-sampling DBS: a shift in monitoring testosterone levels

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Background
Dried Blood Spot (DBS) sampling offers the convenience of at-home blood sampling, making it an advantageous solution for patients requiring regular check-ups of their hormone levels, such as testosterone. It eliminates the need for venipunctures, which require additional or longer hospital visits, resulting in significant advantages for patients, physicians, laboratory staff and hospitals. DBS samples can be sent by regular mail to the laboratory for analysis, ensuring that results are available during outpatient clinic visits. The aim of this study is to evaluate the feasibility and reliability of using DBS samples for monitoring testosterone levels in patients receiving testosterone replacement therapy (trt).
Methods
A total of 59 males from the andrology outpatient clinic receiving trt (via deeply intramuscular injection of testosteroneundecanoate or dermal application of testosterone gel) were included in this study. Blood was collected parallel by venipuncture (reference value) and finger prick (DBS sample) performed by the patient self after reading the instruction material to guide them and additional instruction from the andrology consultant. Testosterone concentrations in both serum and DBS were quantified using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Pearson correlation coefficient was calculated.
Results
39 DBS samples were suitable for analysis, while the remaining 20 samples were unreliable due to contamination from testosterone gel (12), improper sampling

technique such as finger stamping, blood stacking, or collection of too small droplets (6) or analytical difficulties (large duplicate variation) (2). The correlation coefficient between testosterone concentrations in self-sampled DBS and serum was $r = 0.87$.

Conclusions

For patients receiving trt via deeply intramuscular testosteroneundecanoate injection, monitoring testosterone levels via DBS sampling at home is feasible, enhancing patient comfort and convenience. Patient education is needed to ensure proper collection of DBS samples, leading to high quality DBS and accurate testosterone quantification.

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EP41

JOINT1580

Targeted proteomics reveals novel biomarkers of disease activity and cardiometabolic risk in acromegaly

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Objectives

Acromegaly is linked to metabolic complications such as diabetes and an elevated risk of cardiovascular disease, even though patients often exhibit a favorable body composition with reduced fat and increased muscle mass. This paradox highlights a gap in understanding the underlying metabolic consequences of disease activity [1]. Current diagnostic approach relies heavily on serum levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), which are dynamically influenced by various factors, thereby highlighting the need for more precise biomarkers for disease activity monitoring. We hypothesized that dysfunctional adipose tissue drives increased cardiometabolic risk in acromegaly through adipocytokine release and subsequent systemic insulin resistance. Moreover, we aimed to identify potential biomarkers for disease activity and cardiometabolic risk.

Methods

Clinical and biochemical data, including glucose, HbA1c, GH and IGF-1 levels, and body composition measured by dual-energy X-ray absorptiometry (DXA), were recorded in a cohort of patients with acromegaly ($n = 32$) at diagnosis and after successful disease remission by transsphenoidal surgery (mean $\pm$ 1SD, 18.3 $\pm$ 5.8 months). Expression of 92 proteins was measured on Olink Target 96 Cardiovascular III, in first-time-thawed EDTA plasma samples at baseline and after surgery. Statistical analysis was conducted in R using R Studio, and SPSS.

Results

Mean age at diagnosis was 49.8 $\pm$ 14.1 years, and 18 (56 %) were men. At diagnosis, GH correlated negatively with all fat depots and plasma MMP-3, and positively with MEPE and COL1A1. The correlations were not preserved after treatment. Following treatment, GH, IGF-1, glucose, and HbA1c decreased significantly ($P < 0.05$). Plasma MMP-3, IGFBP-2, and EGFR increased, whereas COL1A1, MEPE, OPN, MMP-2, and CNTN1 significantly declined (adjusted P-value < 0.05). Table 1 presents the statistically significant correlations between changes in GH and IGF-1 and glucose, total body fat and proteins.

Table 1. Spearman correlation coefficients (R) between changes (%) in GH, IGF-1, glucose, total body fat and selected proteins (p-values < 0.05 for all).

% change	Glucose	Total Body Fat	MEPE	MMP-3	IGFBP-2	MMP-2	EGFR
GH	0.39	-0.42	-	-	-	0.44	-0.39
IGF-1	0.42	-	0.36	-0.52	-0.60	-	-

Conclusion

Our results reveal close association between several proteins related to metabolic and cardiovascular dysregulation and disease activity in acromegaly. These findings point to COL1A1 and IGFBP-2 as potential biomarkers to assess disease activity and cardiometabolic risk.

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EP42

JOINT2418

Vitamin D receptor mRNA expression in adrenal medulla and pheochromocytoma cells

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Objective

The expression of vitamin D receptor (VDR) and the role of 1,25-dihydroxyvitamin D3 (1,25(OH)D3) in human adrenal medulla is not well investigated. Previous reports showed that 1,25(OH)D3 accumulates in the nuclei of adrenal medullary cells in mice and increases expression of tyrosine hydroxylase gene in cultured bovine adrenal medullary cells. No genomic data regarding VDR mRNA expression in human pheochromocytoma or normal adrenal medulla has been reported. The aim of this study was to elucidate the expression of VDR in healthy human adrenal medulla and human pheochromocytoma cells, and to investigate the potential association between VDR presence and the clinicopathological characteristics of pheochromocytoma.

Design and Methods

A total of 31 pheochromocytoma cases with available tissue samples from surgical resection, 4 samples of healthy adrenal cortex and 4 samples of unaltered adrenal medulla as control group were analysed. The expression of VDR at the mRNA level was assessed by digital PCR in all pheochromocytoma cases and the control group. For pheochromocytoma patients, clinical manifestation, hormonal status and histopathological results were retrospectively assessed.

Results

VDR mRNA expression in adrenal medulla and pheochromocytoma cells was compared to the expression in the control adrenal cortex, set at 1.0. The median VDR mRNA expression in pheochromocytoma specimens was the lowest when compared to unaltered adrenal medulla and adrenal cortex (median expression = 0.05; range: minimum = 0.0, maximum = 0.56). Unaltered adrenal medulla specimens demonstrated higher VDR expression than pheochromocytomas, but lower than that observed in the normal adrenal cortex (median = 0.49; range: minimum = 0.32, maximum = 0.58). No statistically significant correlations were observed between VDR mRNA expression levels in pheochromocytomas and most clinical parameters evaluated in this study. However, VDR expression in tumour tissues was negatively associated with somatostatin receptor 2 (SSTR2) expression, taking into account the confounding factors of sex and the interaction with elevated 3-methoxytyramine concentration.

Conclusions

In our study, we present, for the first time, the expression of the vitamin D receptor (VDR) in human adrenal medulla and pheochromocytoma tissue. VDR expression at the mRNA level was detected in unaltered adrenal cortex, adrenal medulla, and pheochromocytoma cells, with quantification achieved through digital PCR. The highest median expression was observed in the adrenal cortex, followed by an intermediate median expression in the adrenal medulla, and the lowest one in pheochromocytoma cells. No correlation between VDR mRNA expression levels and the primary clinical features of the disease was identified.

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EP43

JOINT1229

Long-term metabolic comorbidities in patients with adrenal incidentalomas - a single center experience

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Introduction

Current guidelines for managing adrenal incidentalomas (AI) do not recommend long-term follow-up for patients with non-functioning adrenal incidentalomas (NAI) unless in case of significant changes in comorbidities potentially attributed to mild autonomous cortisol secretion (MACS).

Aim

This study aimed to assess the long-term development of cardiometabolic risk factors in patients with AI and evaluate the need for follow-up.

Methods
In this single-center prospective cohort study, 88 patients with AI (70 females [79.5%], 18 males [20.5%]) underwent clinical, biochemical, and imaging evaluations at baseline and final follow-up (median 55 months, IQR 47–80). Based on the result of 1 mg dexamethasone suppression test at baseline, patients were stratified into NAI (1 mg dexamethasone suppression test [1 mg DST] cortisol $\leq$50 nmol/l) or MACS (1 mg DST cortisol $>$50 nmol/l).
Results
At the final follow-up, patients with MACS demonstrated a significant increase in body mass index (BMI) (27.1 vs. 27.8 kg/m^2, $P = 0.03$), a higher incidence of bilateral tumors (51.2% vs. 34%, $P = 0.016$), increase in antihypertensive medication count ($P < 0.001$), and a nonsignificant trend toward higher dyslipidemia rates (66% vs. 41%, $P = 0.06$). In contrast, NAI patients exhibited a significant increase only in antihypertensive medication count ($P < 0.001$). In the univariate linear regression model, significant predictors for antihypertensive medication count in NAI were baseline BMI (B = 0.08, 95% CI [0.005–0.166], $P = 0.04$), follow-up duration (B = 0.01, 95% CI [0.004–0.026], $P = 0.01$), and baseline antihypertensive medication count (B = 0.85, 95% CI [0.548–1.146], $P < 0.001$). In multivariate regression, follow-up duration (B = 0.01, 95% CI [0.001–0.018], $P = 0.04$), and baseline antihypertensive medication count (B = 0.73, 95% CI [0.406–1.056], $P = 0.01$) remained significant. Notably, 19.1% (9/47) of NAI patients progressed to MACS during follow-up.
Conclusions
Although NAI patients did not exhibit significant cardiometabolic risk progression over a median follow-up of 4.6 years, nearly 20% developed MACS. These findings suggest that patients with NAI should undergo at least one reassessment for MACS within a 4-year period to guide clinical management.

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EP44

JOINT1653

Analysis of clinical characteristics and pharmacological treatment to achieve adequate plasma renin activity levels in primary hyperaldosteronism

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Introduction
In primary hyperaldosteronism (PH), achieving a plasma renin activity (PRA) $\geq$ 1 ng/ml/h is associated with a lower cardiovascular risk. This study aims to analyze how many patients achieve this target and evaluate the number (nº) and type of medications used.
Materials and Methods
A retrospective observational study of a cohort of PH patients undergoing medical treatment for: lack of biochemical success after surgery; preference for medical treatment; or being unsuitable for surgery. Based on the PRA value at the last follow-up, patients were divided into two groups (21 patients with PRA $<$1 and 11 with PRA $\geq$1). Clinical and analytical data were collected, including the total nº and combinations of antihypertensive drugs used, focusing on the following combinations: mineralocorticoid receptor antagonists (MRAs) with ACE inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), and MRAs with hydrochlorothiazide (HCT), to determine their effectiveness in achieving the PRA target.
Results
During a mean follow-up of 45 months, only 33% of patients achieved the PRA target of $\geq$1. Clinical and analytical characteristics were similar in both groups, although the number of smokers tended to be higher in the PRA $<$1 group ($P = 0.06$). The number of antihypertensive medications (up to 7 drugs) used was similar in both groups ($P = 0.61$). In the PRA $<$1 group, the use of eplerenone was higher than that of spironolactone ($P = 0.038$). No significant differences were found regarding the combination of antihypertensive medications studied and PRA inhibition, although a trend toward significance was observed in patients treated with MRA and HCT ($P = 0.068$).
Conclusions
Achieving PRA levels $\geq$1 is difficult with medical treatment, and clinical and analytical characteristics do not help to identify which patients will achieve this target. Eplerenone is the least effective of the MRAs, and the combination of MRA and HCT may be a promising alternative.

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EP45

JOINT3269

3 cases with different clinical features due to adrenal insufficiency after adrenal hemorrhage in newborns

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Introduction
Adrenal hemorrhage is a rare condition in the neonatal period (0.2%-0.55%) and rarely causes adrenal insufficiency. Here, we present 3 cases that developed adrenal insufficiency in the neonatal period due to different reasons and then had different clinical courses.
Case 1
The patient was admitted to the neonatal intensive care unit due to urinary tract infection(UTI). During the investigation of the etiology of UTI, an ultrasound scan was performed to observe adrenal hemorrhage measuring 33x24mm on the right and 40x22mm on the left in both adrenal gland locations. After the 250 mg ACTH stimulation test, peak cortisol was determined 12.6 mg/dl and 6 mg/m^2/day hydrocortisone treatment was started. The patient was born term and 3800gr, had no birth trauma. The patient continued to use hydrocortisone for 6 months. In the 7th month 1 mg ACTH stimulation test, the peak cortisol response was observed as 16.2 and the medication was stopped. He has been followed up without medication for 6 years.
Case 2
A male patient born term, 4000gr and 52 cm, had a 43x16x33mm hemorrhage area in the right adrenal gland and a 35x20x33mm hemorrhage area in the left adrenal gland during the abdominal USG performed due to traumatic birth. The patient's cortisol was 11 mg/dl and ACTH was 202, and due to insufficient cortisol response to the standard dose ACTH stimulation test, hydrocortisone treatment was started. Hydrocortisone treatment is being continued at 12 mg/m^2/day.
Case 3
A female patient who was examined for sepsis as a newborn had a 23x13mm hematoma on the right adrenal gland and a 18x15mm hematoma on the left. She was born at term, vaginally, and weighed 3800grams. There was no hypoglycemia in the patient, but blood sodium was measured as 132 mg/dl and potassium as 6 mg/dl. When a standard dose ACTH stimulation test was performed, peak cortisol levels were determined as 12.6 mg/dl. The patient was started on 54 mg/m^2/day hydrocortisone treatment. When she was 15 months old, the treatment was discontinued because peak cortisol was sufficient in a standard dose ACTH stimulation test.
Discussion
Adrenal hemorrhage may be caused by different clinical reasons and may progress with different clinics. Our study has shown that the clinical course of adrenal insufficiency secondary to adrenal hemorrhage may be very variable, and it is important that the clinical follow-up of these patients must be personalized and frequent.

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EP46

JOINT278

Thematic analysis of quality of life in a community-based sample of adults living with congenital adrenal hyperplasia reveals a significant unmet medical need

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Introduction
Congenital adrenal hyperplasia (CAH) is a genetic disorder most commonly arising due to partial or total deficiency of the 21-hydroxylase enzyme, leading to decreased cortisol production and increased androgen secretion. The physical manifestations of CAH are well recognised but the effects on quality of life are unclear.
Aim
To explore the impact of CAH on quality of life.
Methods
In-depth, semi-structed interviews were undertaken virtually with a purposive sample of adults (>18 years) with CAH. Participants were recruited via the Living with CAH patient support group. Interviews were audio-recorded, transcribed verbatim and analysed inductively using reflexive thematic analysis. Ethical approval was obtained for the study.
Results
Twenty-one interviews were conducted with 4 men and 17 women living with CAH (median age = 41; age range: 20-62 years). Twenty had classical CAH and 1 had non-classical CAH. CAH was considered part of a participant's identity. The impact on quality of life was variable with significant effect at transitions of life (e.g. adolescence, family planning, menopause). The experiences of males and females were different, with females reporting greatest negative impact. Adrenal crises were physical effects noted by all participants. Females reported significant distress from precocious puberty, hirsutism and acne. Thirteen women had undergone genital surgery with a few participants reporting complications such as painful intercourse, urinary tract infections and incontinence. Medication side-effects (osteoporosis, diabetes, weight gain) were of particular concern to older participants but life-dependent need for steroid treatment outweighed the risks. Participants reported psychological symptoms including anxiety and depression. Female participants experienced childhood trauma from exhibiting genitalia during medical examinations and lack of agency in treatment decision, leading to mistrust of the medical profession. Complex family dynamics were also noted. Feelings of shame were often instilled in childhood with a reluctance to disclose the name of the condition to relatives and friends. Consequently, participants reported isolation and loneliness with difficulty forming friendships and intimate partner relationships. Maladaptive coping strategies including disordered eating, alcohol and substance misuse were also reported by a minority of individuals.
Discussion
CAH has a profound physical, psychological and psychosocial impact on individuals with loss of adjustment significant at transitions of life. Adopting a trauma-informed approach to care has the potential to improve patient health outcomes and quality of life. The study findings are limited to a self-selecting sample of predominantly females with CAH. Further work will explore the generalisability of the results to the wider CAH community.

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EP47

JOINT2159

Two different clinical presentations, one rare diagnosis: adrenocortical tumor

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Introduction
Adrenocortical tumors (ACTs) are rare in childhood, and most are functional, leading to endocrine symptoms. ACT should be considered in the differential diagnosis of children presenting with precocious puberty and/or Cushing syndrome. This report describes the diagnosis and treatment of two pediatric cases.
Case 1
A 3-year-old male patient with a history of left hemihypertrophy was referred due to the rapid (14-day) development of moon face and acanthosis nigricans(AN). On physical examination, weight:17 kg(0.5 SD), height:100 cm(-0.1 SD) with cushingoid face, AN on the neck and left hemihypertrophy. Laboratory investigations revealed hypercortisolism. A 40×38 mm heterogeneous mass in the left adrenal gland, with no invasion, poor fat content, and no calcifications reported on MRI. Following a multidisciplinary team discussion, the etiology of hypercortisolism was ACT, and the patient underwent left adrenalectomy. Histopathological examination confirmed a solid neoplasm with a Ki-67 index of 10%, without metastasis or invasion. During follow-up, the patient's physical examination was unremarkable, except for persistent left hemihypertrophy. Genetic analysis for Beckwith-Wiedemann syndrome yielded normal results, and further investigations are ongoing.
Case 2
A 2-year-old girl was referred to the oncology clinic due to an abdominal mass detected during examination for abdominal pain. MRI showed a heterogeneous 82×87×107 mm mass in the right adrenal gland, with hemorrhage, calcifications, and liver compression, reported as neuroblastoma. Tru-cut-biopsy revealed an ACT (Ki-67: 7-8%), and the mass was deemed inoperable due to compression of the IVC and portal vein. The patient developed hypertension after biopsy, managed with amlodipine. The case was referred to our clinic for further evaluation. History revealed genital hair development at 6 months, intermittent vaginal discharge, increased hair growth, and breast development over the past month. Family history included pancreatic and colon cancer. On examination: weight:10.6 kg (-0.92 SD), height:85 cm (-0.51 SD), BP 140/90 (>99th percentile), Tanner stage 3 breast/pubic hair, and distended abdomen with palpable liver (8 cm) with no clitoromegaly. Surgery was deemed unsuitable and chemotherapy was initiated per the multidisciplinary team's decision. Genetic analysis for *TP53* variant is ongoing.
Conclusion
Although rare, ACTs must be considered in the differential diagnosis ofchildren presenting with hormonal excess. Importantly, biopsy is contraindicated due to the risk of tumor cell dissemination, which worsens the prognosis. Thus, a multidisciplinary approach to ensure accurate diagnosis and optimal management is important. Early recognition is critical, as timely diagnosis and intervention can significantly impact prognosis.

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EP48

JOINT1921

A case of glucocorticoid deficiency due to MC2R mutation

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Background
A mutation in the adrenocorticotropic hormone (ACTH) receptor gene, also known as MC2R, causes familial glucocorticoid deficiency (FGD) type 1, a rare autosomal recessive disorder. This condition is characterized by resistance to ACTH action on the adrenal cortex, leading to isolated glucocorticoid deficiency with normal mineralocorticoid activity. It typically presents in infancy or early childhood with episodes of hypoglycemia, hyperpigmentation, recurrent infections, and convulsions, which can result in coma or death if left untreated. We report the case of a 2-year-old boy with isolated hypocortisolism due to MC2R mutation.
Clinical Case
Our patient was born at 39 weeks of gestation. His growth parameters at birth were within normal limits according to INeS Charts. From first day of life he presented recurrent severe hypoglycemic episodes, so he was held in neonatal intensive care unit. Neonatal physical examination revealed areas of hyperpigmentation on the limbs, trunk, and scrotum. Diagnostic investigations, including endocrinological and metabolic blood tests, showed elevated ACTH levels (>3000 ng/l), low cortisol, and normal 17-hydroxyprogesterone, ruling out congenital adrenal hyperplasia (CAH). Given the adrenal insufficiency, continuous intravenous hydrocortisone therapy was started to prevent adrenal crisis and later switched to an oral formulation after stabilization of blood glucose levels and improvement in laboratory tests. Subsequently, an abdominal ultrasound revealed bilateral adrenal hypoplasia. To further investigate the etiology of primary adrenal insufficiency, genetic testing was performed. Whole-exome sequencing identified the c.[634delA] variant in homozygosity in the MC2R gene, which was inherited from both parents and represents a rare cause of FGD. The patient was therefore referred to our endocrinology unit. During follow-up, oral hydrocortisone therapy was maintained at a dose of 10 mg/m^2/day, with regular progression in both height (-0.51 SDS) and weight (0.48 SDS), adequate height growth rate (4.41 SDS) and without any side effects.
Conclusions
Glucocorticoid deficiency is an endocrinological emergency and potentially life-threatening condition. Despite being the most common cause of primary adrenal insufficiency in pediatric patients, CAH is not the only condition that can lead to it. During the neonatal period, less common conditions should also be

investigated, such as familial glucocorticoid deficiency. Beyond the correct diagnostic approach, another challenge for the pediatrician is the appropriate therapeutic management of glucocorticoid deficiency, which involves adjusting the hydrocortisone dosage over time. This aims to avoid both excess and deficiency of cortisol, while keeping the patient asymptomatic with stable biochemical parameters, ensuring regular growth and enabling normal pubertal progression.

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EP49

JOINT3746

"Adrenal insufficiency with low 17-hydroxyprogresterone: lesson learned from a developing country"

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Background
Congenital Adrenal Hyperplasia due to 21 hydroxylase deficiency (21 OHD) is the primary cause of adrenal insufficiency in Indonesia, as limited resources of hormonal and genetic laboratories can pose challenges in diagnosing rare adrenal conditions leading to missed diagnosis with high mortality. Here, we present two exceptionally rare cases of congenital adrenal insufficiency other than 21OHD.
Case presentation
Case 1: A-seven-years-old boy was admitted to the hospital due to recurrent seizures, vomiting, dehydration, and repeated severe hyponatremia without hyperkalemia. There was no consanguinity. The older sibling had a similar history and died due to seizures at the age of 4.5 yo. Physical examination showed normal neurology examination, hyperpigmentation, and dark spots on the tongue, normal penis and testicles. Laboratory examination revealed a low 17-Hydroxyprogesterone (17-OHP) level (the hallmark of 21OHD), low cortisol level, and hyponatremia. This patient was treated as an adrenal insufficiency patient with hydrocortisone and fludrocortisone, and the response to treatment was good. Exome sequencing showed a hemizygous pathogenic variant in NR0B1 ChrX(GRCh37):g.30327091dup NM_000475.5:c.391dup p.(Arg131fs) which is not reported in previous studies. Pathogenic variants of the NR0B1 gene had been described previously as causative for X-linked recessive congenital adrenal hypoplasia. Case 2: A-18-days-old female baby was admitted to the hospital because of recurrent hypoglycemia and hyperpigmentation, recurrent vomiting, and hyperpigmentation. There was no consanguinity; the older sister died at the age of 3 months with a similar condition. Physical examination showed skin hyperpigmentation, no clitoromegaly, no palpable testis, presence vagina and labia minora. Laboratory results showed low 17-OHP level, hyponatremia, hyperkalemia, hypoglycemia, and a 46,XY karyotype. This patient was treated as an adrenal insufficiency patient with hydrocortisone and fludrocortisone. Exome sequencing showed a homozygous variant in the Steroidogenic Acute Regulatory Protein (StAR) gene as the causative for autosomal recessive lipoid adrenal hyperplasia, and this is the first reported case in Indonesia.
Conclusions
Adrenal insufficiency often presents with aspecific features leading to delayed or missed diagnosis. Low 17-OHP levels should prompt clinicians to consider alternative etiologies beyond 21-OHD,
Keywords
Adrenal insufficiency, developing country, Indonesia, Steroidogenic Acute Regulatory Protein (StAR), Congenital adrenal hypoplasia
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EP50

JOINT1365

How to discover non-functioning adrenal cortical adenomas

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Background
Non-functioning adrenal cortical adenomas (NFAA) represent 70-90% of non-functioning adrenal incidentalomas. Despite being non-secretory, these tumors may exhibit minimal, inapparent, yet prolonged cortisol secretion, which can predispose individuals to components of the metabolic syndrome. This underscores the importance of screening for NFAA and the need for continuous monitoring to ensure optimal management and early detection of potential metabolic complications.
Methods
The study was retrospective and included patients followed for non-functioning adrenal cortical adenomas associated with metabolic disorders. These patients were enrolled from the Endocrinology-Diabetology Department of Hedi-Chaker University Hospital in Sfax.
Results
Our cohort consisted of 31 patients with non-functioning adrenal cortical adenomas, aged between 34 and 80 years. A female predominance was observed in 60% of cases. The adrenal adenomas were diagnosed incidentally in 90.6% of patients, with a hypertensive peak in 6%, and refractory hypertension as the reason for diagnosis in 3%. Features such as truncal obesity, with or without hypertension, facial erythema, rapid weight gain, melanoderma, and hypokalemia were not identified as presenting symptoms. Abdominal ultrasound was performed for an unrelated indication and incidentally led to the discovery of an adrenal incidentaloma in 58% of the sample.
Conclusion
Early detection of NFAA through screening and continuous follow-up is essential for optimizing patient management and preventing long-term complications.

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EP51

JOINT890

A rare case of iatrogenic cushing's syndrome

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The complex pharmacological interaction between ritonavir, a protease inhibitor frequently used in HIV infection that acts through the inhibition of the cytochrome P450, and fluticasone produced a significant increase in the systemic concentrations of the latter, consequently generating iatrogenic Cushing's syndrome.
Clinical case
In 2022 a 42-year-old male with a history of chronic persistent asthma and HIV on ritonavir treatment was referred to by Pulmonology for presenting weight gain with truncal obesity, severe skin pain predominantly in recent and acute reddish stretch marks, edema in the lower limbs, asthenia and severe low back pain.
Personal history
In 2018 the patient was diagnosed with HIV, starting treatment with darunavir/ritonavir 800/160 mg and dolutegravir 50 mg/day evolving to undetectable viral load; he had grade II obesity and severe and persistent asthma. In July 2022 he presented worsening asthma and was treated with meprednisone 40 mg for 7 days, budesonide/formoterol 100 mg 2 puffs twice a day, montelukast 1 tablet/day at night, salmeterol/fluticasone 500/500 (Seretide diskus) 3 times a day and tiotropium 18 mg/day. The physical examination showed arterial hypertension (160/100 mmHg), heart rate: 100/bpm, rounded face, fatty hump, fat in the supraclavicular spaces, bilateral rhonchi, severe abdominal obesity, painful wide dark red striae. Although the findings were suggestive of Cushing's syndrome, the discontinuation of inhaled fluticasone was complicated due to the severity of the respiratory condition. Diagnostic studies confirmed suppression of the adrenal axis, MRI showed lumbodorsal vertebral compression fractures: T7-T10 and L4 and evidence of osteoporosis in the bone mineral density. After stabilizing the asthmatic condition, the dose of corticosteroids was reduced: salmeterol/fluticasone 25/250 mg 1 puff twice a day, budesonide was discontinued and hydrocortisone 10 mg/day was indicated. The antiretroviral medication had to be changed for Dolutegravir/ Tenofovir/ Lamivudine; the patient improved Cushing syndrome symptoms; zoledronic acid was prescribed for the secondary osteoporosis.
Conclusions
Cushing syndrome triggered by inhaled corticosteroids is very rare, that is why we started to investigate the possible interaction between fluticasone and HIV medication. We found that ritonavir was the drug which produced a severe increase of fluticasone half-life causing a dramatic syndrome. This case highlights the need for effective communication between health professionals, multidisciplinary management, and knowledge of drug interactions in unique clinical situations.

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EP52

JOINT13

A case of concurrent RET and FH GENE mutations in a patient with metastatic pheochromocytoma

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Introduction
Pheochromocytomas are rare tumours arising from the adrenal medulla. Numerous genetic defects have been identified either as a part of inherited syndromes or in sporadic forms.
Objective
We present the case of a 64-year-old female patient diagnosed with bilateral pheochromocytomas in 2009 treated surgically with bilateral adrenalectomy (R0, ki67 < 1%). She presented 14 years later with hypertension and important weight loss. Imaging showed multiple lesions in the retroperitoneal area, pulmonary and liver metastasis. Hormonal workup revealed plasma metanephrines and normetanephrines > 400 times the upper normal limit. Fine needle biopsy (FNB) of the hepatic lesion was compatible with metastatic pheochromocytoma (ki67 < 2%.)
Methods
Germline testing was pursued through a 67-cancer gene panel following genetic counselling.
Results
Genetic testing revealed a *RET* pathogenic variant, i.e.c.2370G > T p.(Leu790Phe) which is strong predisposing factor for pheochromocytoma diagnosis. A concurrently present variant in the fumarate hydratase (*FH*) gene was also identified; our patient was heterozygous for the c.1127A > C p.(Gin376Pro) (cluster 1b), 1127A > C, p.(Gin376Pro) which is classified as pathogenic and is associated with hereditary leiomyomatosis and renal clear cell carcinoma (HLRCC). Further familial genetic testing is expected to provide crucial information about the penetrance of the aforementioned predisposing variants.
Conclusions
Genetic analysis plays a critical role in the diagnosis and management of patients with pheochromocytomas. We presented an individual who had not just one but two clinically important germline variants, accounting perhaps for the aggressiveness of her tumour. The presence of clinically relevant variants may contribute to define not only genotype-phenotype correlations but are also important for cascade testing of asymptomatic individuals within the family.

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EP53

JOINT593

Two decades of ectopic ACTH cushing syndrome: retrospective analysis from a tertiary care centre in north India

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Introduction
Ectopic ACTH Cushing syndrome (EAS) is a rare yet significant cause of endogenous hypercortisolism. Differentiating EAS from pituitary Cushing syndrome (CD) poses a diagnostic challenge due to overlapping clinical and biochemical features. While inferior petrosal sinus sampling (BIPSS) is the gold standard and newer nuclear imaging modalities hold promise, these are not widely available. This study presents 2 decades of experience with EAS from a tertiary care center in India; comparing it's clinical, biochemical and radiological characteristics with those of CD. Additionally, it evaluates the diagnostic utility of the overnight high-dose dexamethasone suppression test (ONHDST) in this population.
Methods
This retrospective study analyzed 113 adults (30% male, age 18-72 years) diagnosed with ACTH-dependent Cushing syndrome (CS) (plasma ACTH > 20.0 pg/ml). The diagnosis of EAS was made by histologic confirmation of tumor on histopathology, finding an ectopic tumor on radiology/imaging, or a central: peripheral gradient of < 2 on BIPSS. Parameters differentiating EAS and CD were analyzed, and the diagnostic performance of ONHDST was evaluated.
Results
Among 113 patients with ACTH-dependent CS, 27(24%) had EAS while 86(76%) had CD. The most common source of EAS was the lung in 14(52%) patients [10 pathologically confirmed pulmonary neuroendocrine tumors (NET), 4 did not undergo surgery]. 4 patients had thymic NET, 2 had medullary thyroid carcinoma, 1 had a gall bladder NET and 6 had occult EAS. Multivariable logistic regression identified male gender, hypokalemia, and < 50% suppression on ONHDST as significant predictors of EAS. In a receiver-operating characteristic (ROC) curve analysis, < 50% suppression following ONHDST had 77% sensitivity, 62% specificity, 40% positive predictive value (PPV) and 89% negative predictive value (NPV) in diagnosing EAS vs CD (AUC 0.70; 95% CI 0.59-0.81; $P = 0.002$). The major diagnostic dilemma usually occurs when the MRI is normal or shows a small microadenoma. In this situation the ONHDST using the same cut-off performed better (sensitivity 77%, specificity 71%, PPV 54% and NPV 87%) (AUC 0.77; 95% CI 0.66-0.88; $P = 0.00009$). Among 10 patients with histopathologically confirmed pulmonary NET, 9 were in remission at last contact, while one patient was lost to follow-up. Other forms of EAS ($n = 17$) had poorer outcomes: 9 lost to follow-up, 7 died, and 1 in remission after bilateral adrenalectomy.
Conclusion
EAS accounted for 24% of ACTH-dependent CS in our institution and was mostly due to pulmonary NETs, which had good prognosis. The ONHDST is a valuable test in differentiating CD from EAS, especially in resource limited settings.

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EP54

JOINT1021

Assessment of atherosclerotic cardiovascular disease (ASCVD) risk using ASCVD risk estimator plus in indian patients with type 2 diabetes – a subgroup analysis from real-world, retrospective study

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Background
T2D is associated with increased cardiovascular (CV) morbidity and mortality. ASCVD risk assessment can help to identify individuals with higher risk and optimizing treatment. This subgroup analysis of a retrospective, observational, multicentre, electronic medical record (EMR) based study (HEART STRONG STUDY) aimed to assess ASCVD risk in patients with T2D.
Methods
Aggregated and anonymised EMRs of patients aged 20-79 years, with total cholesterol (TC) 130-320 mg/dl, HDL 20-100 mg/dl and data available on T2D and smoking status and hypertension treatment were used to calculate ASCVD Risk Scores by American College of Cardiology Risk Estimator+. EMRs of patients with current or history of ASCVD were excluded. Primary endpoint was mean 10-year ASCVD risk. Here we present subgroup analysis of patients with T2D.
Results
Of total patients on EMR from 2017-2023, 4114 patients met eligibility criteria of which 3423 had T2D. Mean age was 55.8 years, BMI 26.89 kg/m^2 and 80% were males. Mean 10-year ASCVD risk score ($n = 2777$) was 17.8% vs 16.6% in overall study population. Risk was high, intermediate, borderline and low in 35.9 vs 32.6%, 34.9 vs 34.1%, 11.2 vs 11.9%, and 18 vs 21.3% in T2D vs overall study population. Mean Lifetime risk ($n = 2115$) was 54.6% and mean Optimal risk ($n = 3112$) was 5.4%. Mean values of TC, LDL-C, HDL, VLDL, TG were 182.5 ($n = 3423$), 103.7 ($n = 3331$), 42.6 ($n = 3423$), 28.4 ($n = 2143$), and 180.1 ($n = 3242$) mg/dl respectively. Mean HbA1c was 9% ($n = 2836$), FBG was 168 mg/dl ($n = 2868$), PPBG was 248.65 mg/dl ($n = 2703$). Metformin (91%), Sulphonylurea (59%), DPP4i (53%), SGLT2i (19%) were most frequently prescribed antidiabetic drugs. Patient receiving > 4, 4, 3, 2, 1 antidiabetic drugs were 18.9, 22.5, 24.0, 24.4, 9.9% respectively. Lipid lowering agents were prescribed to 56% patients.
Conclusion
In this T2D subgroup, almost every third patient had either high or intermediate ASCVD risk. Diabetes was poorly controlled despite multiple drugs which is likely to lead to poor CV outcomes. About half patients received lipid lowering agents and 19% received SGLT2i despite guideline recommendations. Adherence to guidelines and aggressive T2D treatment is urgently needed to reduce CV disease burden in Indian patients.

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EP55

JOINT1368

Treatment of MACS with low doses of metyrapone - a preliminary report

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The justification of the elective surgery in a patient with mild autonomous cortisol secretion (MACS) is debatable, as adrenalectomy does not result in clinical improvement in every patient, especially in cases without lateralization of hormone secretion. So why not try to treat these patients pharmacologically, avoiding irreversible surgery? We would like to present the preliminary findings of the study we are conducting in Poland, in the first 9 MACS patients out of 50 planned as per protocol, treated with low-dose metyrapone. 6 patients have completed 6-month treatment, 3 others are so far at 3 months, and 5 more have been enrolled to date. Presented group consists of 8 women and 1 man, mean age 63.44 $\pm$ 7.41 years. 5 out of 9 presented bilateral adrenal lesions. Hypertension has been diagnosed in 8 subjects, hyperlipidaemia in all 9, 8 were overweight or obese, 4 had impaired glucose tolerance, and 5 presented osteopenia or osteoporosis. 500 mg of metyrapone (two caps of Metopirone® 250 mg) have been administered once daily at circa 7pm with a light meal. The drug was well tolerated by all patients. The following tests have been performed prior to treatment and at 3 and/or 6 months: - metabolic profile including HbA1C and oral glucose tolerance test (OGTT) measuring both glucose and insulin concentrations in patients without diabetes; morning and midnight serum cortisol, ACTH plasma concentration and 24-h urinary free cortisol (UFC), body composition and bone mineral density assessment. During treatment with metyrapone, we observed a reduction in morning and midnight serum cortisol levels, as well as in 24-h urinary cortisol excretion. No disinhibition of ACTH secretion was noted. After 3 months of treatment already, the effect of metyrapone upon blood pressure made possible in almost half of the patients (4/9) discontinuation of one of the anti-hypertensive drugs they were taking. In patients who completed the full 6-month course of treatment, we found considerable decrease in body weight (2/6), body fat (3/6), waist circumference (6/6), insulin (2/6) and uric acid (5/6) levels. Further patients are being enrolled in the study. The final statistical analysis is planned upon completion of the study on a set of 50 patients. Preliminary observations are encouraging with regard to the anticipated effects of the proposed treatment in MACS patients. As part of this presentation, we prepared a case report on our first MACS patient who completed the study.

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EP56

JOINT3347

The role of a multidisciplinary team in the management of phaeochromocytomas

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Introduction
Phaeochromocytomas, Paragangliomas, Glomus jugulare are rare neuroendocrine tumours arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia. Most of them produce catecholamines. They cause variable symptoms like headache, hyperhidrosis, tachycardia, and hypertension.
Case
A thirty seven year old window cleaner, was referred to Cardiology with a six months history of worsening random dizziness, impacting on his work. He reported one to five minutes episodes of feeling faint, chest tightness, breathlessness, closing of his throat, tingling sensation of the face, grey face and hands. Symptoms occurred up-to five times per day. He has a ten year history of random palpitations, dizziness and non-cardiac chest pain, which was evaluated by Cardiology. Six months previously, he was commenced on a diet for hypercholesterolemia. He takes no medications or supplements. He binge drinks, smokes nicotine, uses cocaine once or twice per week and used cannabis previously. No family history of note, except father dying at age of forty six from a heart attack. Clinic blood pressure was one hundred and thirty one over ninety three mmHg. He had two symptomatic episodes of his blood pressure raising to two hundred and forty one over one hundred and seventeen mmHg for two and then three minutes. His physical examination was unremarkable. ECG and Holter were normal. Echocardiogram revealed mild concentric LVH, preserved LVEF. Renal function, electrolytes, cortisol, TSH, CK, aldosterone/renin ratio were normal. Urine metanephrines were raised. Doxazosin initiated. He underwent adrenal MRI revealing a large left adrenal tumour suggestive of phaeochromocytoma. Contrast CT adrenal, abdomen, NM MIBG whole body were consistent with beta-adrenergic receptor positive tumour tissue of neural crest in origin in the left adrenal gland, most probably due to a solitary phaeochromocytoma. He was referred to Endocrine MDT and admitted for a laparoscopic left adrenalectomy. The histology result was consistent with benign pathology and a follow-up was arranged for a repeat metanephrine +/- MIBG or MRI if positive metanephrines.
Discussion
Thorough evaluation led to treating this patient's symptoms and preventing cardiovascular, respiratory, metabolic or neurological complications including death.
Conclusion
Phaeochromocytomas, Paragangliomas, Glomus jugulare tumours cause less than zero point one percent of the hypertension cases. It is extremely important to exclude these conditions as a cause for hypertension in male and female patients in their third and forth decade because of a high risk of death. The post-mortem diagnosis is as high as fifty percent. Managing phaeochromocytomas require multidisciplinary approach.

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EP57

JOINT2585

Pheochromocytoma and pregnancy: diagnostic challenges and multi-disciplinary management

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Introduction
Pheochromocytomas are rare neuroendocrine tumors, typically located in the adrenal medulla, but they can also affect sympathetic paraganglia, where they are referred to as paragangliomas. Rare but serious during pregnancy, pheochromocytoma poses a high risk of maternal and fetal mortality, highlighting the importance of early diagnosis and treatment to improve prognosis.
Observation
A 31-year-old patient was admitted for severe preeclampsia at 31 weeks of gestation, with a history of untreated hypertension prior to pregnancy. Given the suspicion of secondary hypertension and the presence of the Menard triad, an abdominal MRI was requested, which revealed a left adrenal mass measuring 5.8 $\times$ 4.7 $\times$ 7.6 cm, with a cystic fleshy component in the center (necrosis?), associated with centimeter-sized juxta-lesional lymphadenopathy, suggestive of pheochromocytoma; however, an adrenal corticoid tumor could not be ruled out, necessitating confrontation with clinical, biological, and histological data.
Methoxy derivatives
Normetanephrine 18.45 µmol/24h (0.40-2.10 µmol/24h) Metanephrine 0.17 µmol/24h (0.20-1.00 µmol/24h). After a multidisciplinary team meeting: Decision for fetal extraction via cesarean section followed by left adrenalectomy 10 days later. The newborn died on day 3 due to respiratory distress.
Discussion
The symptoms of pheochromocytoma during pregnancy are often nonspecific and can mimic common conditions such as preeclampsia or gestational hypertension. The biological diagnosis relies on measuring plasma or urinary metanephrines, which remain reliable during pregnancy (Gruber *et al*., 2022). A significant elevation of these markers confirms the diagnosis. MRI imaging without gadolinium is the preferred examination to locate the tumor during pregnancy, as it is non-radiating and very sensitive. Initial management involves medical treatment aimed at stabilizing blood pressure and preventing hypertensive crises. Alpha-blockers, such as phenoxybenzamine or doxazosin, are used to block the effects of catecholamines. Surgical excision of the tumor is the curative treatment for pheochromocytoma. The timing of the intervention depends on the stage of pregnancy: Before 24 weeks of amenorrhea, laparoscopic surgery is recommended after medical stabilization. After 24 weeks, surgery is generally deferred until after delivery, except in life-threatening situations.
Conclusion
Pheochromocytoma during pregnancy is a rare but potentially fatal condition. Its diagnosis requires heightened vigilance in the face of atypical hypertension or paroxysmal symptoms. Management relies on rigorous medical stabilization, followed by surgical excision at the appropriate time.

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EP58

JOINT3982

Incidentaloma: pathological and biochemical analysis management in the disorders of the adrenal medulla in albania popullation

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Background & Aim
The adrenal incidentaloma is an adrenal tumor discovered by an imaging test that is being done for a control by that is not related to adrenal disease. Pheochromocytoma is a rare tumor that develops in the adrenal medulla, the inner part of the adrenal glands. This tumor leads to the excessive release of catecholamines, resulting in symptoms such as rapid heart rate, high blood pressure, anxiety, intense headaches, excessive sweating, and unintentional weight loss.
Methodology
This study studied Incidentaloma patient with the pheochromocytoma. Levels of catecholamines and their byproducts in the blood and urine are measured. The analysis includes measuring plasma-free metanephrines or fractionated metanephrines in urine. Additional tests, such as measuring total urinary metanephrines, plasma or urinary catecholamines, or urinary vanillylmandelic acid (VMA), will be used to confirm the presence of the tumor.
Results
The study was conducted on patients aged 15-98 years old. In this study, the pathological pathologies and imaging images of the patients are going to be analyzed. We detect elevated levels of catecholamines or their byproducts in the blood and urine of patients with pheochromocytoma. The most accurate tests include measuring plasma-free metanephrines or fractionated metanephrines in urine. Additional tests, such as measuring total urinary metanephrines, plasma or urinary catecholamines, or urinary vanillylmandelic acid (VMA), will be used in future steps to confirm the presence of the tumor.
Conclusion & Future Research
This study highlights the diagnostic value of plasma-free metanephrines and fractionated urinary metanephrines as the most accurate tests for detecting the tumor. Elevated levels of catecholamines and their byproducts provide critical evidence for diagnosis, while additional confirmatory tests, including urinary vanillylmandelic acid and total catecholamine measurements, can strengthen diagnostic accuracy. Early and precise diagnosis is essential to prevent life-threatening complications such as hypertensive crises, arrhythmias, or stroke. Future research should focus on refining diagnostic algorithms, and incorporating novel biomarkers.
Keywords
Adrenal Tumors, Catecholamines, Metadrenalines, Phaeochromocytoma, Hypertension
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EP59

JOINT2404

Stratification of total cardiovascular risk in young patients with type 1 diabetes mellitus

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Background
Cardiovascular disease (CVD) is a common macrovascular complication of type 1 diabetes (T1D) which still remains the leading cause of death even in well-controlled T1D. Over the last decades young patients with T1D have not shared in the overall reduction of cardiovascular morbidity and mortality but instead according to data from recent epidemiological studies showed a striking increase. Therefore, to improve the prognosis of young patients with T1D targeted primary prevention of CVD is crucial e.g., total cardiovascular risk assessment.
Objectives
Assessment and stratification of total CV risk in young patients with T1D living in Minsk.
Methods
The study was based on a retrospective review of young patients with T1D without previous CVD attending the outpatient clinic "Minsk City Clinical Endocrinological Center". The stratification of CV risk was performed using the Steno T1 Risk Engine (ST1RE). Control group included patients without T1D, for CV risk stratification Framingham risk score was used.
Results
Eighty-eight patients were enrolled (43F, 45M), median age 36 years [IQR 28-41] with onset of T1D 16 [11-25]. Of these, 20,5% (18 patients) had an early onset of T1D 6,5 [5-8,5]. Glycemic control of our young patients with T1D was suboptimal HbA1c – 7,65% [6,7-8,65]. Using the ST1RE algorithm: 23,9% (21 patients) were at high CV risk, 76,1% (67 patients) had moderate and none had low risk. In the control group ($n = 88$): 95% of patients had low CV risk, 5% had moderate CV risk. The frequency of occurrence of moderate risk was statistically higher in patients with T1D when compared to the control group (76,1% vs 5%, $p < 0.01$).
Conclusions
Our study suggests that further preventive interventions based on accurate CVD risk prediction algorithm is required for primary prevention of CVD in young patients with T1D.
Key words
type 1 diabetes, cardiovascular risk, young patients, prevention, Steno-calculator
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EP60

JOINT2165

Pituitary adenomas in adult bulgarian CAH patients

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Background
The prevalence of asymptomatic pituitary adenomas varies between 10% and 22%, while clinically relevant pituitary adenomas occur in 1 of 1000 individuals (1). The prevalence of pituitary lesions in patients with congenital adrenal hyperplasia (CAH) is unknown. Therefore, the study aims to present pituitary findings in CAH patients from a single Expert Center for Rare Endocrine Diseases.
Methods
The present retrospective study includes all patients (18-57 years old) with CAH who have been followed-up in the last 15 years. Imaging studies have reported the prevalence and characteristics of the established pituitary formations.
Results
The data of 72 CAH patients (60 women and 12 men) were studied. Ten pituitary lesions (13.9 %) were found, including one Rathke cyst (1.4%), three prolactinomas (4.2%), and six nonfunctioning adenomas (8.3%) in 8 CAH women and 2 CAH men. Additionally, three female cases of "empty sella" were revealed by imaging studies (4.2%). The main indications for MRI in CAH patients were headache, mildly or moderately increased prolactin levels, and increased ACTH levels with suspicion of reactive adenomas. All pituitary adenomas were microadenomas varying between 3 and 7.8 mm. Most pituitary microadenomas (66.7 % [6/9]) were found in women with a late CAH form. No age (27.5 vs. 28 years, $P = 0.530$) or ACTH differences (16.61 vs. 15.05 pmol/l, $P = 0.491$) were found between patients with pituitary lesions and other CAH patients;
Conclusions
Pituitary microadenomas are commonly found in female patients with a late CAH form. Further studies are needed to evaluate the prevalence of different pituitary lesions and their evolution in CAH individuals.
Keywords
CAH, pituitary adenoma, prolactinoma.
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EP61

JOINT1740

Multiple recurrent cerebral and coronary vasospasms as an unusual initial presentation of pheochromocytoma: a case report and literature review

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Introduction
Pheochromocytomas (PHEOs) are rare tumors arising from chromaffin cells and secreting catecholamines. Arterial vasospasm is an organ and life-threatening condition. We present a rare case of recurrent coronary and cerebral vasospasms as an initial presentation of PHEO.
Case presentation
A 65 y-o female, known for type 2 diabetes, first presented for thunderclap headache that lasted 4 minutes. Cerebral CT-scan was normal. Two weeks later, she returned with recurrent symptoms plus retrosternal pain. Cerebral angio-CT scan demonstrated arterial vasospasms. She was diagnosed with reversible cerebral vasospastic syndrome (RCVS) plus vasospastic angina and started on calcium channel blockers (CCB). Three months later, she returned with retrosternal pain and non-ST-segment elevation myocardial infarction (high-sensibility troponins 279 ng/l, N 0-34), but normal coronary angiography and transthoracic cardiac ultrasound. In the following months, she experienced multiple paroxysmic episodes of headache and retrosternal pain, with palpitations and diaphoresis, but normal blood pressure. After multiple visits to the emergency room, PHEO was diagnosed with elevated plasma metanephrines (2.52 nmol/l, $n < 0.48$) and normetanephrines (4.46 nmol/l, $n < 1.20$), as well as 24h urinary catecholamines (noradrenaline: 832 nmol/d, $n < 472$; adrenaline: 402 nmol/d, $n < 108$; normetanephrines: 1524 nmol/d, $n < 235$; metanephrines: 1298 nmol/l, $n < 269$). Adrenal MRI showed a 4.7 × 4.8 cm right adrenal mass, with DOTATATE-PET CT SUVmax of 14. Alpha-blocker was started. Peri-operative management included CCB maintenance and crystalloids administration. The patient underwent right laparoscopic adrenalectomy without significant hemodynamic instability. Pathology confirmed a PHEO, with PASS score of 4 and Ki-67 of 1.63%. All medication was stopped afterwards. Four months later, the patient is in clinical and biochemical remission.
Genetic analysis
Multigene panel of 19 PHEO susceptibility genes performed on leucocyte DNA (INVITEA) identified a rare missense variant of uncertain significance in the gene *TMEM127* (c.427G>A (p.Val143Ile), gnomAD exomes allele frequency: 2.531160e-05).
Discussion
PHEO diagnosis is often overlooked in this context. In our cohort of 465 patients with PHEO and paragangliomas, no other patient was diagnosed with arterial vasospasm. However, coronary and cerebral vasospasms were individually previously described as very rare complications of PHEOs in four and ten patients respectively, but never simultaneously. Some authors suggest that PHEO should be excluded in RCVS, but we did not find such recommendation for coronary vasospasm.
Conclusions
To our knowledge, this is the first case of a patient with PHEO presenting with both multiple recurrent coronary and cerebral vasospasms. This atypical presentation should be known of medical teams to avoid potential delay in PHEO diagnosis.

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EP62

JOINT1020

A Chinese case of familial progressive hyperpigmentation and hypopigmentation misdiagnosed as primary adrenal insufficiency

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Objective
We report the clinical characteristics, diagnosis, and genetic analysis of a case of familial progressive hyperpigmentation and hypopigmentation (FHPP).
Methods
The clinical information of a 2-year-old girl with "hyperpigmentation since birth" was retrospectively reported. Whole exome sequencing analysis was performed on DNA extracted from peripheral blood and skin tissue. Candidate variant was verified by Sanger sequencing of her parents.
Results
A Chinese girl with uniform hyperpigmentation was noted since birth. She was born to healthy nonconsanguineous parents, following an uneventful pregnancy. At 2-month-old, blood tests revealed potassium levels of 6.06 mmol/l, sodium levels of 134.6 mmol/l, ACTH levels of 73.85 pg/ml, cortisol levels of 17.78 ug/dl, 17α-hydroxyprogesterone <0.2 ng/ml, and progesterone <0.05 ng/ml. Adrenal ultrasound and CT scans showed normal and the chromosome karyotyping showed 46, XX. She was initially diagnosed with primary adrenal insufficiency and started on hydrocortisone replacement therapy at a dose of 40 mg/m^2.d. Subsequently regular follow-up showed normal electrolyte levels, with ACTH level fluctuating between 1.5-12.4 pg/ml. The hydrocortisone dose was gradually reduced to 1.5 mg/day (2.6 mg/m^2.d). The child did not experience any salt-losing crises, but the hyperpigmentation gradually progressed. At 2-year-old, she was re-evaluated in our endocrinology department. Physical examination revealed a height of 90 cm (P25-50), weight of 12 kg (P25). Her trunk showed general hyperpigmentation, especially in the areolas and skin folds, with some superimposed irregular café –au–lait spots. Hypopigmented macules were also seen on the trunk. The level of ACTH, electrolyte and blood gas analysis were rechecked and showed normal after discontinuing hydrocortisone. The ACTH stimulation test indicated normal adrenal cortical function, then hydrocortisone treatment was continuous discontinued. Whole exome sequencing of peripheral blood and skin tissue revealed a heterozygous c.100A>C (p.Thr34Pro) variant of the KITLG gene, which was not present in her unaffected parents. The latest follow-up, conducted 1.5 years after discontinuing hydrocortisone (when she was 4-year-old), showed no salt loss crises. Her height and weight were both at average levels, and the hyperpigmentation became more noticeable with age.
Conclusion
Hyperpigmentation is a characteristic of many clinical diseases and can be challenging to diagnose. For infants with progressive skin pigmentation and hypopigmentation spots, FPHH caused by KITLG gene heterozygous variants should be considered.

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EP63

JOINT3859

Evaluation of cardiovascular complications of primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism is a common condition associated with various complications, particularly cardiovascular ones. These complications are not widely studied, and further research is needed to better determine their prevalence. The objective of this study is to assess the cardiovascular impact of primary hyperparathyroidism in our series.
Objective
The aim of our study was to assess cardiovascular complications in patients with primary hyperparathyroidism.
Materials and Methods
A retrospective descriptive study including 40 patients followed for primary hyperparathyroidism over a 6-year period from 2018 to 2024.
Results
The mean age was 50 ± 10 years, with a male-to-female ratio of 0.05, and 95% of the patients were women. The evaluation of cardiovascular impact in primary hyperparathyroidism revealed electrocardiographic signs of hypercalcemia in 12.5% of patients, as well as newly diagnosed hypertension with a normal echocardiography, without valvular or myocardial calcifications, in 22.5% of patients. Notably, no cases of pulmonary embolism or peripheral venous thrombosis were observed in our study population.
Conclusion
Primary hyperparathyroidism is known for its cardiovascular complications, which are linked both to the direct effects of parathyroid hormone (PTH) as a hormone with cardiovascular properties and to the impact of hypercalcemia. Consequently, PHPT contributes to the worsening of cardiovascular risk factors or their de novo occurrence, highlighting the importance of early screening and appropriate management.

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EP64

JOINT1114

Clinical and paraclinical monitoring of pediatric patients with congenital adrenal hyperplasia: challenges and outcomes

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Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by mutations in the CYP21A2 gene, leading to 21-hydroxylase deficiency, the most common form of CAH. Classic CAH presents as either virilizing or salt-wasting forms. This study evaluates the clinical and paraclinical evolution of 11 pediatric patients with classical CAH, focusing on treatment response and management challenges.

Methods

A retrospective analysis was conducted on clinical, paraclinical, and genetic data from 11 children diagnosed with CAH, aged between 1 month and 12 years. Parameters such as growth, bone age, androgen axis control (17-hydroxyprogesterone [17-OHP], testosterone, androstenedione, dehydroepiandrosterone sulfate [DHEA-S]), renin levels, and blood pressure were analyzed. All patients were treated with hydrocortisone and fludrocortisone, with doses adjusted based on weight and body surface area.

Results

1. Genetic Profile: The most frequent mutations identified were I2 splice, P30L, and Del 8bp E3. Rare combinations of severe mutations were observed, associated with virilizing and salt-wasting forms.
2. Growth: Most patients exhibited accelerated bone age compared to chronological age, necessitating regular adjustments of hydrocortisone doses to prevent early puberty.
3. Complications: Three patients developed obesity (BMI >95th percentile). Two patients presented with Grade I hypertension, likely due to fludrocortisone overtreatment, which was managed by dose adjustment. Four patients had genital ambiguity, with surgical interventions (e.g., feminizing genitoplasty) planned or performed.
4. Paraclinical Response: Most patients had 17-OHP and renin levels outside the target therapeutic range (17-OHP >10 ng/mL, renin >30 pg/ml), requiring treatment optimization. Elevated androstenedione levels correlated with signs of virilization.

Discussion

The results underscore the challenges in managing CAH in pediatric patients, including the high prevalence of metabolic complications, the need for continuous treatment adjustments, and the importance of multidisciplinary monitoring. Androgen axis control in our cohort was moderate, consistent with findings in the literature. These findings highlight the need for dose adjustment guidelines based on body surface area and growth rates.

Conclusions

Individualized monitoring is essential to optimize CAH treatment and prevent long-term complications. This study advocates for stricter dosing protocols and closer collaboration among endocrinology, genetics, and pediatric surgery teams.

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EP65

JOINT2308

Effects of cushing's Syndrome remission on glycemic control: does remission always lead to improvement

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Introduction

The remission of Cushing's syndrome (CS) is known to improve glycemic control, but the extent and statistical significance of these improvements remain poorly documented. This study aims to quantitatively assess the effect of CS remission on glycemic parameters.

Methods

A cohort of **22 patients with CS** was followed from diagnosis to remission. The primary glycemic parameters analyzed were **fasting blood glucose (FBG) and glycated hemoglobin (HbA1c)**, measured before and after treatment. A **paired t-test** was used to compare pre- and post-remission values. Additional analyses were performed based on **baseline glycemic status and the type of treatment received** before remission.

Results

The analysis demonstrated a significant improvement in glycemic control following CS remission. On average, **fasting blood glucose decreased by 23% ($P = 0.001$), and HbA1c dropped by 0.9% ($P = 0.008$)**. Among **diabetic patients ($n = 10$)**, fasting blood glucose decreased from **142.6 ± 18.4 mg/dl to 109.2 ± 14.7 mg/dl ($P = 0.001$)**, while HbA1c declined from **7.8 ± 1.1% to 6.9 ± 0.9% ($P = 0.005$)**. Notably, **50% of these patients achieved normoglycemia post-remission**, whereas the remaining half continued to exhibit impaired glucose metabolism. In contrast, **non-diabetic patients ($n = 12$)** also experienced significant reductions in glycemic markers. Their fasting blood glucose decreased from **98.7 ± 10.3 mg/dl to 89.4 ± 7.8 mg/dl ($P = 0.02$)**. Patients who required **insulin therapy before remission ($n = 6$, 27.3%)** exhibited variable responses post-remission. While **four patients (66.7%) continued to require pharmacological treatment**, those initially managed with oral antidiabetic drugs or lifestyle modifications were more likely to achieve complete glucose normalization. Furthermore, an analysis of **baseline cortisol levels** revealed a significant correlation with post-remission glycemic outcomes. Patients with persistent hyperglycemia had significantly **higher baseline cortisol levels (562.3 ± 91.4 nmol/l vs. 398.1 ± 76.2 nmol/l, $P = 0.02$)** compared to those who achieved normoglycemia.

Discussion

This statistical analysis confirms that **CS remission leads to significant improvements in glycemic control**, particularly in diabetic patients. However, the degree of improvement appears to be influenced by **baseline cortisol levels and disease duration**, highlighting the impact of prolonged hypercortisolism on **insulin resistance and pancreatic beta-cell dysfunction**. Despite overall improvements, some patients **remain hyperglycemic post-remission**, emphasizing the need for ongoing metabolic follow-up.

Conclusion

Our findings demonstrate that **Cushing's syndrome remission significantly improves glycemic parameters**, particularly in diabetic patients. However, **persistent hyperglycemia post-remission is associated with higher baseline cortisol levels and pre-existing insulin dependence**, suggesting a potential irreversible impact on pancreatic function. **Long-term monitoring remains essential to optimize metabolic outcomes in these patients.**

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EP66

JOINT2086

Infant with pubarche and suppressed serum cortisol. what is the diagnosis?

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Introduction

Pubarche is a rare encounter during infancy that needs to be thoroughly investigated. Etiology ranges from normal variant to adrenal tumors.

Methods

An 8-month-old girl with pubarche was referred by her pediatrician after initial evaluation that revealed suppressed levels of cortisol and adrenal androgens. Parents noticed pubic hair onset about one week before referral. Her past medical history was remarkable for recurrent respiratory infections during the previous trimester and bronchiolitis for which she was treated with inhaled corticosteroids in high doses (250 micrograms of fluticasone propionate twice daily), with short intervals without treatment. The review of the growth chart revealed impaired growth velocity from the age of 6 months, as the infant's length deviated from the 50th to the 10th percentile, while her weight followed the 50th percentile. On physical examination her length was 66 cm (10th %ile), her body weight (BW) 8.35 kg (50th %ile), Tanner stage: Axillary I, pubic hair II, breast II. Facial plethora was appreciated, while clitoral size was normal.

Results

Diagnostic work-up confirmed suppressed cortisol, adrenal androgens and inappropriately low ACTH (serum Cortisol 0.36μg/dl, ACTH 11.52pg/ml, DHEA-S 0.003μg/dl, 17-OH PRG 0.95ng/ml, FSH 3.88mIU/ml, LH<0.3mIU /ml, prolactin 473mIU/ml, estradiol 9.9 pg/ml). Tumor markers (βHCG, aFP) were negative. Abdominal sonogram was normal. The diagnosis of iatrogenic Cushing syndrome was established, based on the above medical history, physical examination and laboratory results. Inhaled corticosteroids were discontinued and hydrocortisone was administered at a replacement dose until the adrenal axis recovered. During follow up, two months later, her height velocity accelerated and laboratory results were normalized (serum Cortisol 11.3 μg/dl, ACTH 52.5pg/ml, DHEA-S 5.1μg/dl, 17-OH PRG 1.2ng/ml, FSH 4.92mIU/ml, LH< 0.2mIU/ml, estradiol<6pg/ml). Hydrocortisone was discontinued. At the age of 12 months, the infant had complete regression of pubic hair and normal growth,

(length 76 cm, 75th %ile, BW 10.8 kg, 50th-75th %ile), while premature thelarche persisted.
Conclusions
Inhaled steroids are commonly used in treatment of asthma and respiratory pediatric infections. They are considered safer compared to systemic steroids, however iatrogenic Cushing syndrome can be caused by high-dose inhaled regimens. That's why children on steroid treatment should be followed up closely to prevent iatrogenic Cushing syndrome. The differential diagnosis of the syndrome includes malignant tumors, adenoma, and nodular hyperplasia of the adrenal glands, which are very rare in infants.

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EP67

JOINT488

Hypovitaminosis D and its association with the incidence and severity of major adverse cardiovascular events

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Background
traditionally associated with bone metabolism, hypovitaminosis D has emerged as a potential cardiovascular risk factor. Although it is a global issue, few studies in Colombia have evaluated its local impact. This study addresses that gap by examining its role as a potentially modifiable cardiovascular risk factor.
Objective
to determine the association between hypovitaminosis D and the development of major adverse cardiovascular events (MACE), as well as the relationship between the severity of hypovitaminosis D and mortality associated with these events in a Colombian population.
Methods
we conducted a retrospective cohort study with 254 patients aged $\geq$50 years treated between January 2021 and April 2022. Patients were categorized as having insufficient ($<$30 ng/mL) or sufficient ($\geq$30 ng/mL) vitamin D levels. Demographic, clinical, and paraclinical variables were analyzed alongside MACE occurrence using descriptive statistics and logistic regression models.
Results
fifty percent of patients had vitamin D insufficiency, and 10.2% had severe deficiency ($<$15 ng/mL), predominantly in women $>$65 years. Patients with hypovitaminosis D showed a higher incidence of MACE and a 57.1% mortality rate compared to 0% in the sufficient group. In multivariate analysis, chronic kidney disease was the main risk factor for MACE (OR: 6.84; 95% CI: 1.14–40.9), and vitamin D levels $<$15 ng/mL were associated with increased cardiovascular risk (OR: 4.1; 95% CI: 0.99–17.02).
Conclusion
hypovitaminosis D increases the risk of MACE and mortality, particularly in patients with chronic kidney disease.

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EP68

JOINT2402

Significant metabolic syndrome improvement in a patient with adrenal Cushing's syndrome treated preoperatively with osilodrostat

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Background
Cushing syndrome (CS) is associated with high morbidity and mortality, due to its metabolic consequences. The treatment of choice is surgical resection of the causative tumor. Data on the preoperative use of osilodrostat, an inhibitor of 11β-hydroxylase, in patients with adrenal CS (ACS) are scarce. We present a rare case of ACS treated preoperatively with osilodrostat with significant metabolic syndrome improvement.
Case presentation
A 47-year-old woman, with a previous history of cervical cancer, presented to the outpatient clinic with a 3,6 cm left adrenal mass discovered incidentally, 4 years prior to presentation. She suffered from poorly-controlled diabetes mellitus (DM) (HbA1c 9,5%), dyslipidemia, chronic obstructive pulmonary disease (COPD) and significant weight gain (25 kgr, BMI 46) over the last 8 years. Clinical examination revealed facial plethora, posterior cervicothoracic fat pad and severe truncal obesity. Laboratory tests were indicative of adrenal Cushing syndrome (morning serum cortisol 20,7 μg/dl after low dose oral dexamethasone suppression, adrenocorticotropin (ACTH)5,32 pg/ml and urinary free cortisol 384 μg/24hr (normal values 20,9-292 μg/24hr). Adrenalectomy was postponed twice due to her severe obesity and poorly-controlled DM and COPD. The patient was lost to follow-up. She returned a year later with deterioration of her clinical symptoms. Her urinary free cortisol levels were further increased ($>$1000 μg/24hr). Treatment with osilodrostat was decided at a dose of 4 mg daily. However, a week later she presented with symptoms suggestive of adrenal insufficiency (nausea, fatigue and low blood pressure). Osilodrostat was reduced to 1 mg daily, while oral hydrocortisone 20 mg daily was added with symptom resolution. Two weeks later, hydrocortisone was stopped and osilodrostat was continued with a slow titration initially to 2 mg for 6 months and subsequently to 3 mg. Ten months after her 1st osilodrostat dose, the patient achieved a significant weight loss (20 kg, BMI:38), while her DM and dyslipidemia were well controlled (HbA1c 6,1%) without treatment modification. Her last urinary free cortisol measurement was within normal range (147 μg/24hr). She has been scheduled for adrenalectomy next month.
Discussion
Treatment of ACS with osilodrostat, has been rarely reported in the literature. In our patient, a 10-month treatment with low osilodrostat dose resulted in significantly reduced cortisol levels concomitantly with important weight loss and improvement of all metabolic parameters prior to curative adrenalectomy. Further studies are warranted to evaluate preoperatively osilodrostat use on surgery-related morbidities and outcomes in such patients.

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EP69

JOINT1188

Mild autonomous cortisol secretion (MACS): data from a romanian tertiary centre

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Introduction
Mild autonomous cortisol secretion (MACS) is diagnosed, based on an abnormal overnight 1 mg dexamethasone suppression test, in 20-50% of patients with adrenal adenomas without signs of Cushing syndrome. MACS is associated with cardiovascular morbidity, fragility fractures, decreased quality of life and increased mortality. Management of MACS should be individualized based on patient characteristics and include adrenalectomy or conservative follow-up with treatment of associated comorbidities.
Aim
To retrospectively compare the comorbidities and the management between a cohort of cases with MACS and non-functional adenomas (NFA) admitted at least yearly in a tertiary institution, between 2019-2023.
Patients and Methods
229 patients (170 women, 59 men) were evaluated for adrenal lesions. 135 patients were included in the study after exclusion of other adrenal functional lesions. Adrenal function was assessed by basal and dynamic cortisol (suppression tests) and ACTH, testosterone, DHEA-S, aldosterone and renin, urinary and plasma metanephrines and normetanephrines.
Results
In the MACS group 34 patients were included with a ratio of almost 1:3 for the non-functional adenoma group (n = 101 patients). 11 patients (7 left nodules + 4 right nodules) in the MACS group underwent surgery vs 4 patients in the NFA group. The criteria for surgery were the radiological features [Hounsfield units, biggest nodule or the easiest surgical approach (if bilateral)]. There were 2 cases of post-operatory transient adrenal insufficiency (evaluated with 1 ug short Synacthene testing), 1 case of residual cortisol secretion after surgery (surveillance decided). The mean follow-up duration was 4.8 years ($\pm$3.06). All the other patients had normal hormonal work-up after surgery. When discussing comorbidities: the MACS group had a higher rate of dyslipidemia of 85.3% vs 67.3% in the NFA group (P = 0.049), a higher prevalence of hypertension: 82.4% vs 59.4% in the NFA group (P = 0.021) and a higher prevalence of diabetes mellitus: 32.4% vs 13.9% (P = 0.022). Interestingly, the MACS group showed greater dimensions of the adrenal lesions than the NFA group in transverse and antero-posterior computed tomography measurements ($p<0.023$).

Conclusion
The detailed continuous clinical and biochemical follow-up every 6-12 months of patients with MACS is necessarily for proper and individualized management, especially for evaluating and modifying the treatment of comorbidities.

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EP70

JOINT1940

ESPE caucasus&central asia school (C&CAS) sharing knowledge for saving patients' lives:organizing newborn-screening and pediatric endocrinology care for patients with adrenal insufficiency in armenia

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Introduction
Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder associated with congenital errors of steroid biosynthesis in the adrenal glands. A delayed diagnosis is associated with an increased risk of neonatal morbidity/mortality, whereas early diagnosis reduces mortality rates. Newborn screening of CAH is a cost-effective method to identify affected neonates early. Treatment is lifelong, and access to necessary medication, which is affordable and lifesaving, is unfortunately still low in Armenia. The ESPE C&CA School took place in Yerevan in 2023. During this event teachers shared knowledge and experience regarding CAH. Armenian doctors received support from the ESPE in developing and implementing a strategic plan to address unmet needs in the area of CAH, which was a great opportunity for a country with limited resources.
Aim
To initiate research into CAH, implement standardized systematic education for both patients and families with CAH and healthcare providers, to continue the evaluation and monitoring of the implemented program.
Methods
Identifying the pediatric population with CAH, creating and organizing standard educational program for healthcare staff, implementing of educational programming for parents and families and translating and distributing the CAH emergency cards and providing access to the online version at the www.a-drenals.eu, starting the CAH newborn screening in the Capital of Armenia and regions.
Results
A newborn-screening program was started from 11 April 2024 including the capital city of Armenia. 16 168 newborns were screened, 4 cases of CAH from which were conformed. It is planned to involve into the newborn-screening program all the Armenian regions starting from April 2025. Two medical centers are involved in the process: in one center the screening is done, and these data is referred to the pediatric endocrinology center where the next investigations, management and follow-up are done. One of the challenges we meet is the lack of Synacten, less availability of hydrocortisone, as well as some financial issues. The European CAH emergency cards have been already translated into Armenian. An individual treatment plan has been created and adapted to local practices.
Conclusion
A newborn-screening for the all Armenian regions and the educational approach for pediatric endocrinologists will significantly improve the quality of CAH patient revelation and care. This approach ensures that patients and their families receive consistent and high-quality medical care and education. Now we can "speak the language" of European Pediatric Endocrinologists! More long-term follow up is needed to endure sustained benefits for CAH patients in Armenia.

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EP71

JOINT1002

Primary adrenal insufficiency secondary to bilateral adrenal metastases: can extreme hyponatremia be compatible with life?

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Introduction
Severe hyponatremia is associated with high mortality, with severity linked to its etiology and the speed of onset. Primary adrenal insufficiency should be considered, bearing in mind that, although rare, bilateral adrenal metastases can be a potential cause.
Clinical case
A 53-year-old male was admitted at emergency room with confusion and diarrhea. His medical history included plurimetastatic lung adenocarcinoma. On examination, he presented with hemodynamic instability and hyperpigmentation of the skin and mucosae. Blood gas analysis revealed metabolic acidosis compensated by respiratory alkalosis and unmeasurable sodium level. Analytical workup showed $Na^+ < 100$ mmol/l (RR 136-146), K^+ 5.5 mmol/l (3.5-5.1), serum osmolality 214 mOsm/Kg (260-302), ACTH 615 pg/ml (9-52), urinary Na^+ 43 mmol/l and urinary osmolality 423 mOsm/Kg (300-900). Based on clinical presentation, medical history and laboratory findings, a diagnosis of symptomatic hypovolemic hypoosmolar hyponatremia secondary to primary adrenal insufficiency due to bilateral adrenal metastases was made. The patient started treatment with intravenous hydrocortisone and fluid therapy, leading to clinical improvement and was subsequently admitted for continued care. One year after this acute event, the patient remains stable under clinical follow-up in Endocrinology and Medical Oncology, on hydrocortisone (20 mg) and fludrocortisone (0.1 mg) treatment, with stable neoplastic disease under systemic palliative therapy.
Conclusions
Extreme hyponatremia (< 100 mmol/l) is rare and potentially fatal. In oncology patients, it requires clinical suspicion due to nonspecific symptoms often attributed to progressive neoplastic disease or antineoplastic therapy. Its etiology must be determined along with ensuring a safe correction. Severe hyponatremia caused by primary adrenal insufficiency is extremely rare in the literature. Although adrenal metastases are not uncommon in oncology patients, the prevalence of resulting primary adrenal insufficiency is notably low. The prognosis for these patients is generally very poor. However, as this case illustrates, advancements in oncological treatments have significantly improved outcomes.

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EP72

JOINT3790

Evaluation of bilateral adrenal incidentaloma at an endocrine department in Tunisia

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Introduction
Bilateral incidental adrenal incidentaloma represent 10–23% of all incidental adrenal nodules. The general approach to these nodules follows the same premise as for unilateral incidental adrenal nodules however there are features unique to bilateral nodules including the differential diagnosis, the diagnostic approach as well as the management. The aim of our study is to describe the clinical and biological profile of bilateral AIs.
Methods
This was a retrospective, descriptive study carried out in an Endocrinology department, on records of patients in whom a bilateral AI has been discovered. The following parameters were identified: Clinical and biological presentation, etiological profile, diagnosis and therapeutic means.
Results
A total of 29 records were studied, 18 women and 11 men with a mean age of 57,2 years [26-80 years]. Of these patients, 10 were hypertensive, 8 were diabetic and 5 six had dyslipidemia. Metabolic syndrome was present in 11 patients and 4 patients had history of extra-adrenal neoplasma. Adrenal CT scans were performed in 26 patients and MRI in tox others. AIs in Size was greater than 4 cm in 2 cases. Adrenal insufficiency was found in 6 patients with bilateral AIs. Hormonal exploration revealed a secreting mass in 7 cases concluding to MACS in 5 patients and primary hyperaldosteronism in tow cases. in a single case, the presence of large bilateral masses was associated with 11 beta hydroxylase deficiency in a 27-year-old patient in whom the diagnosis has been confirmed genetically. Myelolipomas were diagnosed in two cases and a bilateral acute adrenal hemmoragia during covid 19 infection in another case. hydrocortisone has been prescribed in patients with adrenal insufficiency as a replacement therapy and as a suppressant treatment in patients with congenital adrenal hyperplasia. Aldactone treatment has been prescribed for the case of primary

hyperaldosteronism. Therapeutic monitoring or abstention have been decided in other patients
Conclusion
Hormonal exploration and radiologic imaging generally makes it possible to link AIs to its etiology and to establish the therapeutic strategies adapted for each patients. investigation of adrenal insufficiency is the rule in order to avoid acute decompensation.

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EP73

JOINT3288

An adolescent-onset case of X-linked adrenoleukodystrophy with diagnostic challenges

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Introduction
X-linked adrenoleukodystrophy (X-ALD) is a rare peroxisomal disorder caused by mutations in the ABCD1 gene, leading to impaired beta-oxidation of very-long-chain fatty acids (VLCFAs) and their accumulation in the brain, spinal cord, gonads, and adrenal glands. It should always be considered in the etiology of primary adrenal insufficiency in males. Here, we present a case of X-ALD with diagnostic challenges.
Case
A 17-year-old male presented with fatigue, exhaustion, diarrhea after an active day, followed by confusion and syncope the next morning. He was evaluated at a center in Rome, Italy, where hypoglycemia, hyponatremia, metabolic acidosis, and hypocalcemia were detected. Low serum cortisol and markedly elevated ACTH levels suggested primary adrenal insufficiency, hypocalcemia was considered to be due to hypoparathyroidism, which led to a diagnosis of autoimmune polyglandular syndrome. Intravenous hydrocortisone infusion, oral fludrocortisone, calcium, and calcitriol was initiated. The patient was subsequently transferred to our hospital via air ambulance. In the history the patient reported fatigue, difficulty during physical exertion or severe illnesses, and significant skin darkening over the course of 2 years. Parents were first-degree cousins. On physical examination, height, weight SDS were normal. There was hyperpigmentation on extensor surfaces. Puberty was consistent with Tanner stage 5. Autoimmune markers for celiac disease and thyroid autoantibodies were negative. The treatment initiated in Italy was continued. Over the course of his treatment serum phosphate levels were within normal limits, suggesting that hypocalcemia might be linked to critical illness rather than hypoparathyroidism, and original diagnosis was reconsidered. Etiological evaluation for primary adrenal insufficiency revealed elevated plasma VLCFA levels. Calcitriol was discontinued, and hypocalcemia did not recur. Genetic analysis (hemizygous *ABCD1* c.1876G>A (p.Ala626Thr mutation) proved a diagnosis of X-ALD. There were no cognitive abnormalities, behavior changes, handwriting issues, or neurological symptoms. MRI findings of the brain and spinal cord were unremarkable. During the last follow-up, mild sensory loss was noted on physical.
Conclusion
Clinical course of hypocalcemia in critical illness may lead to a misdiagnosis of hypoparathyroidism. Reassessment is important during follow-up.
Key Words
Critical illness hypoparathyroidism, primary adrenal insufficiency, primary hypothyroidism, X-linked adrenoleukodystrophy

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EP74

JOINT2953

Pheochromocytomas and paragangliomas: clinical presentation, management, and outcomes in a tunisian cohort

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Introduction
Pheochromocytomas and paragangliomas are rare neuroendocrine tumors that develop from chromaffin cells located in the adrenal medulla and neural ganglia. The incidence of these tumors ranges from 0.04 to 0.95 per 100,000 individuals annually, with an increase in diagnoses attributed to advancements in imaging technologies. Both the clinical presentation and management of these tumors are highly variable, posing challenges in early detection, biochemical assessment, and treatment.
Subjects and methods
This retrospective descriptive study was conducted on 17 patients diagnosed with pheochromocytomas or paragangliomas at the Endocrinology and Diabetology Department of Tunis Military Hospital from 2013 to 2024. The study analyzed various parameters, including demographic features, clinical findings, biological aspects, radiological assessments, and post-operative follow-up.
Results
The study involved 17 patients, consisting of 10 females (58.8%) and 7 males (41.2%). The median age at diagnosis was 49 years, ranging from 33 to 62 years. The main circumstances leading to the diagnosis included paroxysmal symptoms in 41.2% of patients and incidental findings in 58.8%. Sixteen patients had pheochromocytomas (94.1%) while one had a paraganglioma (5.9%). Hypertension was prevalent among participants; 64.7% experienced permanent hypertension, while 23.5% had resistant hypertension. Other common symptoms included headaches (76.5%), sweating (76.5%), palpitations (70.6%), and abdominal pain (29.4%). Biologically, normetanephrine secretion was predominant in 50% of cases, while 33.3% of patients exhibited exclusive metanephrine secretion. Functional imaging revealed single hyperfixation in 88.9% of cases. The median tumor size was 52.5 mm, ranging from 46.25 mm to 65.25 mm, and the median absolute washout was 35%, ranging from 23% to 49.45%. Additionally, no patient presented with metastatic tumors. Surgical treatments were performed through laparotomy in 82.4% of cases and laparoscopy in 17.6%. Postoperatively, blood pressure normalized in 44.4% of patients, while 33.3% experienced recurrent hypertension. Metabolically, diabetes worsened in 28.6% of patients. Three months later, 14 participants had normalization of methoxylated derivatives, while the remaining were lost to follow-up. Our findings align with the existing literature on demographic trends, clinical presentations, and biochemical profiles. There is variability in the management of hypertension, surgical techniques, and metabolic outcomes.
Conclusion
Pheochromocytomas and paragangliomas have diverse clinical and biochemical profiles, complicating their diagnosis and treatment. While surgery is the main treatment of these tumors, outcomes can vary, particularly for hypertension and diabetes. Long-term follow-up is crucial to monitor recurrence and manage metabolic complications.

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EP75

JOINT912

Prevalence, clinical and laboratory features of pheochromocytoma in minsk residents: analysis of data for 2023

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Introduction
According to official statistics, the prevalence rate of the pheochromocytoma (PHC) at the beginning of 2022 in the Republic of Belarus was 0.74 per 100 thousand population, which may indicate insufficient timely diagnosis of this disease. **The aim was** to assess the prevalence and clinical and laboratory features of PHC in residents of the city of Minsk, referred to confirm this diagnosis at the Minsk City Clinical Endocrinology Center.
Materials and methods
A one-time retrospective study was performed, which included 50 patients, residents of the city of Minsk (12 men and 38 women; 1: 3.2), referred for additional diagnostics of PHC during 2023.
Results and their discussion
In total, data from 59 patients with clinical manifestations of secondary arterial hypertension and/or adrenal formations were analyzed. The average age of patients was 69(56-74) years. Adrenal masses were detected in 78%($n = 39$), arterial hypertension was confirmed in 88%($n = 44$). Comorbid conditions include thyroid pathology (60%, $n = 30$), parathyroid glands (2%, $n = 1$), diabetes mellitus (12%, $n = 6$), psychoemotional disorders (panic attacks in4%, $n=2$). The results of laboratory diagnostics showed the level of free metanephrine in blood plasma - 60.83(19.29-103.1) pg/ml, an increase in the indicator is typical for 28%($n = 14$), an increase in the upper limit of the reference by 3 or more times - 4%($n = 2$). The concentration of normetanephrine was 189.45(59.5-275.7) pg/ml, above the reference interval in 48%($n = 24$), an increase by 3 or more times - 4%($n = 2$). Taking into account the clinical, anamnestic and laboratory-instrumental data, a subgroup of patients with confirmed diagnosis of PHC was formed, including 5 people, which is 10%. Average age was 70 (60-71) years, the ratio of men ($n = 3$)

to women ($n = 2$) was 1.5:1, adrenal masses were detected in 60% ($n = 3$), with a native density of more than 10 UHin 40% ($n = 2$), and a size of more than 4 cm in 40% ($n = 2$). A history of surgical treatment of adrenal masses was reported in 20% ($n = 1$). Antihypertensive therapy is received by 60% ($n = 3$), two drugs – 40%($n = 2$), three drugs, including digoxin – 20%($n = 1$). The median metanephrine was 135.1 (15.6-299.8)pg/ml, increased in 60%($n = 3$), more than 3 times–40%($n = 2$), normetanephrine - 570.1(417.8-2219)pg/ml, increased in all patients, more than 3 times–60%($n = 3$), aldosterone – 132.4(94.21-172.45)pg/ml, renin – 0.15(0.09-0.49)μIU/ml.
Conclusions
Confirmation of PHC was noted in 10% of patients, which confirms the clinical significance of the study of free plasma metanephrines and substantiates the importance of this study in patients with adrenal tumors and the presence of arterial hypertension.

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EP76

JOINT2139

21-hydroxilase autoantibodies positivity in Bulgarian patients with addison's disease and premature ovarian failure

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Background
Autoimmunity plays a fundamental role in the development of Addison's disease (AD), and the presence of 21-hydroxylase autoantibodies (21OH-Abs) has been widely used as a highly specific diagnostic marker for proper diagnosis, considering that up to 90% of AD patients remain positive for 21OH-Abs up to 30 years post-diagnosis of AD (1). Moreover, 21OH-Abs could predict autoimmune adrenalitis in patients with premature ovarian failure (POI) making their measurement a recommended diagnostic tool (2). Therefore, the present study aims to establish the prevalence of 21OH-Abs positivity in Bulgarian patients with AD and POI.
Methods
A total of 43 AD (35 women and eight men [18-75 years]), 15 female non-genetic POI patients [18-39 years], and a control group of 31 healthy individuals (23 women and eight men [25-73 years]) were included in the study. 21OH-Abs were measured by ELISA (ElisaRSR™ 21-OH Ab) in all participants.
Results
21OH-Abs were positive in 72.1% [31] of AD patients (50% [4] of AD men and 77.1% [27] of AD women, $P = 0.227$), while no one of the POI patients or healthy controls showed positive results. Six (17.1%) of the AD women had also POI with four of them (66.7%) being 21OH-Abs positive. Negative for 21OH-Abs AD patients were slightly older than positive AD patients (55.5 vs. 50 years, $P = 0.063$) , However, no significant association between 21OH-Abs positivity and the disease duration was observed.
Conclusions
21OH-Abs were highly positive in AD patients, proving the autoimmune etiology of the disease. Nevertheless, nearly 30 percent of patients were antibody-negative, suggesting decreased antibody production associated with aging or different underlying AD causes that need to be explored. In Bulgarian POI patients, 21OH-Abs positivity appears to be uncommon.
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EP77

JOINT3460

Reversion of impaired glucose tolerance and diabetes in patient with primary hyperaldosteronism –case report

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A 65-year-old patient was referred to an endocrinologist due to hypokalemia and arterial hypertension. He had been taking medication for arterial hypertension for more than 30 years and had normal values with amlodipine and perindopril. Hypokalemia was constant in laboratory findings over the years, with potassium levels usually 3.0–3.9 mmol/l. He also had episodes of supraventricular tachycardia a few months ago. Laboratory findings two years ago showed impaired glucose tolerance with FGP 6.7 mmol/l and HbA1c 6.4% then. These findings were checked and now showed that the patient had overt diabetes mellitus with HbA1c 7.1%. Aldosterone level was measured and came convincingly high with suppressed renin angiotensin plasma activity (0.1 ug/l/h) and aldosterone 2131 pmol/l and 1978 pmol/l, respectively, so a confirming test was not needed. Further, an abdominal CT scan was done and showed an adenoma in the right suprarenal gland. The patient refused adrenal vein sampling since he was not interested in surgical treatment, so spironolactone 50 mg was initiated. The patient was not obese, with an ITM of 24 kg/m^2 and no changes in body weight during the years. Also, there was no family history of diabetes. Since the initiation of spironolactone treatment, hypokalemia withdrew, and the patient noticed normal glucose levels during SMBG with FBG constantly below 7 mmol/l and postprandial BG below 8 mmol/l. After six months, he had definite remission of diabetes with HbA1c 5.7% without any medication. It is known that primary hyperaldosteronism leads to many cardiovascular consequences, but it can be seen in a broad range of phenotypes. It is important to remember that primary hyperaldosteronism is one of the possible endocrine causes of glucose metabolism impairment, which was the case with the patient we presented. Also, although the use of MRA as spirinolactone is connected with development of glucose metabolism impairment the opposite happened in this case.

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EP78

JOINT1072

Uncharted territory: a novel SDHC mutation in a young patient with paraganglioma

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Introduction
Paragangliomas are rare neuroendocrine tumours of the sympathetic or parasympathetic ganglia that have a strong genetic predisposition. Mutations of the succinate dehydrogenase (SDHx) genes are most commonly involved and transmitted in an autosomal dominant manner.
Objective
We present the case of a 23-year-old female patient who was referred to our department for hoarseness and a palpable mass in the neck. Magnetic resonance imaging (MRI) revealed a 37x17x36 mm lesion involving the right carotid space, while the 68-Gallium-DOTATATE scan that followed unveiled a strong enhancement of the described mass (SUVmax = 18, SUVliver = 7). Urine and plasma metanephrines/normetanephrines levels were negative for catecholamine excess. The lesion was removed surgically, and the histology report confirmed the presence of a right carotid body paraganglioma.
Methods
Germline testing was pursued through a 50-cancer gene panel following genetic counselling.
Results
Genetic testing revealed a SDHC likely pathogenic variant (c.2T > G p.Met1?)in a heterozygous state, causing a substitution in exon 1 of the SDHC gene, which disrupts the initiation (start) site of the coding for the SDHC RNA that probably leads to not expressing the corresponding protein from the mutant allele, consistent with SDHC haploinsufficiency. This specific variation (chr1:161284197) has not been referred before in the gnomAD database, however, five other variants in the same coding area are listed in the CliVar database as pathogenic and related to paragangliomas. This patient was also a carrier of an SPG11 gene mutation (c.1471-1472delCT) which is associated with hereditary spastic paraplegia (HSP) in the homozygous states. Currently, no direct link has been found between these two gene mutations, as the first involves disruption of central to mitochondrial energy metabolism and the latter disorders in axonal maintenance and endosomal-lysosomal transport of neurons. The genetic analysis of the parents is pending.

Conclusion
Genetic analysis plays a vital role in the diagnosis and management of patients with paragangliomas. Clinically relevant variants can not only help establish genotype-phenotype correlations but also may identify asymptomatic family members.

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EP79

JOINT1974

Cyclical cushing's syndrome secondary to ectopic ACTH-secreting neuroendocrine tumor: a diagnostic and therapeutic challenge

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Introduction
Cyclical Cushing's Syndrome (CCS) involves alternating episodes of hypercortisolism and eucortisolism, with an annual incidence of 0.2-5.0 cases per million. Ectopic ACTH secretion accounts for 26% of CCS cases. Diagnosing and treating CCS is challenging due to its episodic nature. We present a case of CCS caused by ectopic ACTH secretion from a neuroendocrine tumor (NET).
Case Report
A 45-year-old male was diagnosed with a NET at age 39, following a transthoracic biopsy of a 127x96mm anterior mediastinal mass, incidentally, found on a CT scan. Retrospectively, the patient reported symptoms including edema, fatigue and myopathy. New-onset hypertension and hypokalemia raised suspicion for Cushing's syndrome (CS). Laboratory tests confirmed ACTH-dependent CS, with urinary cortisol of 3510µg/24h (167–827) and ACTH of 246pg/ml (7–63). Elevated chromogranin A (1875ng/mL, <102), calcium (11.3 mg/dl, 8.6–10.2), and PTH (96.9pg/ml, <72) were also noted, with normal remaining pituitary function. The concurrent diagnosis of primary hyperparathyroidism prompted genetic testing, which ruled out multiple endocrine neoplasia type 1 (MEN-1). Resection of the mediastinal mass confirmed a NET G2 (Ki-67 of 10%) with ACTH-positive immunoreactivity, validating ectopic CS. Despite surgery, persistent local disease required treatment with somatostatin analogues, chemotherapy, and radiotherapy, though tumor progression continued. The patient also started bisphosphonate therapy for hyperparathyroidism. Postoperatively, transient reduction of hypercortisolism was observed (cortisol 215µg/24h, ACTH 40.3pg/ml). Over the following years, the patient experienced three episodes of severe hypercortisolism (peak urinary cortisol of 7365µg/24h, ACTH 154pg/ml), linked to the initiation of NET-targeted treatments (radiotherapy, chemotherapy). Management include metyrapone (up to 1600 mg/day), antihypertensives, and antidiabetics. These phases alternated with periods of eucortisolism that required no treatment. In september 2023, bilateral adrenalectomy was performed to address cyclical hypercortisolism. Postoperatively, the patient started glucocorticoid and mineralocorticoid replacement therapy, with no further treatment needed for cortisol-related comorbidities.
Conclusion
This case highlights the complexity of managing CCS, particularly due to ectopic ACTH from a NET. Bilateral adrenalectomy, though a last-resort option, resolved hypercortisolism and related comorbidities, improving quality of life. However, further management of the NET remained essential, highlighting the need for individualized therapeutic strategies in complex CCS cases.

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EP80

JOINT3530

Incidental adrenal mass leading to diagnosis of a rare composite pheochromocytoma

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Introduction
Composite pheochromocytoma (CP) is an exceptionally rare tumor (3% of the cases of pheochromocytomas) derived from neural crest cells. It is characterized by the coexistence of a chromaffin cell tumor and another tumor of neuronal origin, most commonly a ganglioneuroma, which arises from autonomic ganglion cells of the nervous system. The majority of diagnoses occur between the third and fifth decades.
Case Report
A 53-year-old woman, medicated with a combined oral contraceptive, presented with an incidental left adrenal mass identified on abdominal magnetic resonance imaging (MRI) performed for study of Hepatic focal nodular hyperplasia. Her family history was positive for melanoma (mother) and prostate cancer (father). The patient was referred to the endocrinology department for further investigation. She reported episodic palpitations and excessive sweating. Arterial hypertension was not observed. MRI demonstrated an expansive lesion at the left adrenal limb junction, measuring 28x24 mm, with necrotic areas and solid components, displaying T2 hyperintensity displayed, T1 hypointensity and progressive contrast uptake, particularly avid at the periphery during the arterial phase, suggestive of pheochromocytoma. Biochemical evaluation revealed elevated plasma metanephrines (163 pg/ml normal <90 pg/ml), elevated urinary total metanephrines (1154 µg/day; normal <320), including urinary metanephrines (646 µg/day; normal <320), urinary normetanephrines (392 µg/day; normal <390) and normal chromogranin (2.6 ng/mL, normal <100ng/mL). Staging with 123I-MIBG scintigraphy showed intense radiopharmaceutical uptake at the lesion site, with no evidence of distant lesions. The patient underwent laparoscopic left adrenalectomy with perioperative alpha-blockade (doxazosin), without complications. Histopathological analysis revealed a composite pheochromocytoma with ganglioneuroma, with complete surgical excision. Genetic testing did not identify any mutations associated with pheochromocytoma-related syndromes. The patient showed improvement in symptoms, with normalization of metanephrines 4 weeks after surgery.
Discussion/conclusion
CPs are rare entities requiring multidisciplinary management. Adrenalectomy is the gold standard treatment. There are cases of CPs with a malignant neurogenic component, however, CPs with ganglioneuroma component usually have an indolent behavior. Careful histopathological examination is essential. Genetic testing may provide insights into potential hereditary syndromes linked to composite adrenal tumors.

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EP81

JOINT2902

ACTH-independent cushing's disease due to macronodular hyperplasia with a late diagnosis of klinefelter's syndrome

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Klinefelter's syndrome is the most common genetic form of male hypogonadism. However, the overt phenotype does not become apparent until after puberty. During childhood and even early puberty, pituitary-gonadal function is relatively normal in 47XXY subjects. Clinical manifestations of androgens deficiency may vary and it's related to the degree of decreased testosterone production and androgens alterations. Thus there are patients with no secondary sexual development; others cannot be distinguished from healthy individuals. Even though many of the undiagnosed causes are due to failure to recognize Klinefelter syndrome, the majority of missed diagnoses are due to minimally abnormal phenotype of Klinefelter syndrome.
Case Report
A 65-year-old male was diagnosed in May 2023 with multinodular goiter and bilateral macronodular adrenal hyperplasia based on CT findings, later on confirmed with ACTH-independent Cushing's syndrome (basal cortisol = 16.10 ug/dl, ACTH = 1.50 pg/ml, cortisol after 2x2DXM = 18.18 ug/dl), with secondary diabetes mellitus HbA1c = 6.9% and hypertension. At that time primary hypogonadism was diagnosed: testosterone = 1.08 ng/ml, FSH = 31.54 mIU/ml, LH = 25.26 mIU/ml. He underwent laparoscopic left adrenalectomy on November 2023 with significant clinical improvement, normalization of blood pressure and remission of diabetes (Hba1c = 5.7%). Although post-operatively patient had an apparent normalization of adrenocortical function, he presented adrenocortical insufficiency (ACTH = 4 pg/ml, cortisol 8AM = 4.87ug/dl) requiring initiation of low-dose hydrocortisone replacement therapy. He was also found with primary hypogonadism, (testosterone = 1.05 ng/ml, FSH = 36.81mUI/ml, LH = 40.27mUI/ml). He reported a history of surgical single testis, but had never undergone further investigation for gonadal dysfunction. Karyotyping was performed given the biochemical findings and clinical

suspicion, confirmed the result-47XXY, diagnostic of Klinefelter syndrome. The patient's long undiagnosed hypogonadism together with Cushing's syndrome had likely contributed to his osteoporosis (DXA L_1-L_4T score = -4.0 DS). Management was done by administration of ibandronate and transdermic testosterone.
Conclusions
This case illustrates the complications that can arise from the association between Cushing's disease and delayed diagnosis of hypogonadism. One reason for the delayed diagnosis of Klinefelter's syndrome was that hypogonadism, is a feature common to both Klinefelter's and Cushing's syndrome, which masked it's recognition. The overlapping metabolic and hormonal clutter in Cushing's syndrome can hide clinical presentation of Klinefelter's syndrome, leading to delayed recognition and treatment of osteoporosis, but in the absence of fractures, most likely to have a positive outcome and improvement in bone mineral density. Rapid approach of Klinefelter in older patients may improve long-term results by addressing associated metabolic, cardiovascular and bone complications.

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EP82

JOINT3924

Age-related differences and machine learning- based insights in patients with non-functioning adrenal adenomas

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Background
Non-functioning adrenal adenomas (NFAs) are considered benign incidental findings, yet their potential metabolic impact remains uncertain. Emerging evidence suggests that NFAs may be associated with metabolic disturbances and an increased prevalence of comorbidities, such as hypertension, type 2 diabetes, depression, osteoporosis and hepatic steatosis. It remains unclear whether these clinical and biological alterations are age-dependent or if obesity acts as a mediator in this association.
Methods
We analyzed a cohort of 150 patients with NFAs, stratified into 2 age groups(below50 and over 50 years). This cutoff was chosen based on physiological transitions associated with aging, including a higher prevalence of insulin resistance, altered immune function and increased cardiometabolic risk. Each of these subgroups is further divided based on the presence or absence of obesity. Clinical analyzed features are: arterial hypertension, osteopenia/osteoporosis, clinical depression, hepatic steatosis, type 2 diabetes. Biological parameters included total, LDL and HDL-cholesterol, serum triglycerides, fasting serum glucose, serum uric acid, serum phosphate, lymphocyte, eosinophil and basophil percentage and C-reactive protein levels. Machine learning (ML) techniques, including Permutation Feature Importance and attention mechanisms, were applied to identify the most relevant predictors of metabolic alterations and evaluate whether obesity mediates these associations. To enhance the accuracy and interpretability of our results, we applied the Permutation Feature Importance method which evaluates the relevance of each feature by measuring its impact on model performance when its values are randomly permuted.
Results
This study aimed to:assess differences in clinical, metabolic, and biochemical features between younger and older patients with NFAs, evaluate the prevalence of associated comorbidities and apply ML techniques to identify key metabolic risk patterns. Additionally, we investigated whether obesity mediates the relationship between NFAs and metabolic alterations, providing new insights into the potential interplay between NFAs, metabolic dysfunction and systemic disease. We selected the Permutation Feature Importance method due to its ability to provide a direct and intuitive measure of feature importance without requiring access to the model's internal structure. Additionally, we utilized an attention mechanism to assess the importance of these features in predicting metabolic risk. This approach led to a significant increase in model accuracy- approximately 17% higher compared to traditional ML models-demonstrating the benefits of explainability and attention mechanisms in optimizing predictive algorithms.
Conclusion
Our findings suggest that while obesity is common in patients with NFAs, it does not fully explain the observed metabolic alterations. Instead, obesity may act as an aggravating factor, amplifying the metabolic impact of NFAs. Future studies should explore the potential role of insulin resistance and chronic inflammation in the NFA-obesity-metabolism axis.

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EP83

JOINT1528

Exploring the role of bilateral adrenalectomy in pediatric cushing's syndrome: case series and literature review

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Introduction
Cushing Syndrome (CS) is an endocrine disorder caused by prolonged exposure to elevated cortisol. Distinctive clinical features of the disease termed "cushingoid features" include facial plethora, obesity, and growth failure in children. In pediatric patients, diagnosis and treatment is scarcely documented, particularly for ACTH-independent forms where bilateral adrenalectomy (BLA) is currently the only available curative treatment.
Objectives
To present two cases of neonatal ACTH-independent Cushing Syndrome managed with BLA. These cases are analyzed for surgical outcomes and pre- and post-operative cortisol trends, in aims to reach a conclusion for management of CS in pediatric patients aged 0-14. Additionally, this review examines existing literature on BLA in pediatric ACTH-independent CS to provide a comprehensive understanding of its efficacy and safety.
Methods
This case series details clinical presentation, laboratory findings, imaging results, and surgical management of two pediatric patients with ACTH-independent CS. A review of literature on pediatric BLA was conducted to contextualize these findings within broader clinical practice.
Results
A total of 7 cases of pediatric CS treated with BLA were analyzed, including 2 from our center and 5 previously reported in the literature. Of these cases, 6 (85.7%) favored BLA after reporting resolution of symptoms. 5 cases (57%) described a decrease in cortisol levels, and 1 case (14%) succumbed to chronic sequelae of CS.
Conclusion
These cases support the role of BLA as a viable treatment for pediatric ACTH-independent CS to target refractory disease activity. While BLA effectively normalizes cortisol and improves clinical symptoms, postoperative management of potential complications and lifelong glucocorticoid replacement therapy remains essential. Our review highlights the need for further research on pediatric BLA outcomes to enhance decision-making and optimize care for pediatric patients with CS.
Keywords
Cushing Syndrome, pediatric, adrenalectomy, ACTH-independent hypercortisolism.

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EP84

JOINT58

Aldosteronproducing adrenal oncocytoma

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Introduction.
The usual location of oncocytic cell tumors is in kidney, salivary gland, thyroid gland, parathyroid, and pituitary gland, although they have also been reported in other locations. Adrenal oncocytomas (AO) are extremely rare, mostly benign and non-functional, however they can be hormonally overproduced and potentially malignant. We present a case of resistant hypertension resulting from aldosterone-producing AO.
Case presentation
A 63-year-old male hospitalized in the emergency department for hypertensive encephalopathy, with high blood pressure levels resistant to medication. The patient was known to be hypertensive for 15 years with current antihypertensive therapy of Olmesartan plus 40/12.5 mg daily, Lercanicipine 20 mg daily and Moxonidine 1 mg daily. Routine laboratory examinations showed K + 3.2 mmol/l and other laboratory parameters within the norm. Echocardiography showed severe concentric hypertrophy of the left ventricle with other echographic indices within the norm. According to the criteria of the European Society of Endocrinology for the exploration of secondary hypertension (Resistant HTN with unexplained hypokalemia and severe concentric hypertrophy of the left ventricle) plasma renin activity, aldosterone and their ratio were measured, which

resulted in compatibility for primary hyperaldosteronism. Adrenal CT identified a solid mass in the left adrenal gland which was 15 × 10 mm in size, consistent with adenoma. The patient underwent surgical intervention of the adrenal mass, which was followed by stabilization of blood pressure values. The histopathologic study showed cortical adenomas with oncocytic cells.
Discussion
About 1.8% of adrenal tumors are oncocytic tumors, which are discovered incidentally and present as benign, nonfunctioning tumors. According to recent data, about 20% of adrenal oncocytomas are malignant and 30% of them are functional, causing symptoms related to hormonal overproduction. Histological diagnosis differentiates these tumors from adrenal adenomas.

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EP85

JOINT709

Adult onset of X-linked adrenoleukodystrophy: insights from a unique case

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Introduction
Adrenoleukodystrophy (ALD) is a rare X-linked disorder caused by mutations in the *ABCD1* gene, leading to an abnormal metabolism of very long-chain fatty acids (VLCFAs). As a result, VLCFAs accumulate in the adrenal cortex, testes, white matter of the brain and spinal cord.
Case presentation
A 27-year-old male, with a history of alopecia areata, presented to the emergency department complaining of abdominal cramps, nausea, and vomiting that started approximately one week prior to presentation, along with increased cravings for salty foods, daytime sleepiness, and dizziness over the past six months. He had also recently sustained a severe ankle sprain resulting in a calcaneus fracture and an avulsion fracture of the lateral malleolus tip, requiring immobilization in a cast. The physical examination revealed hyperpigmentation of the skin on the mammary areolas and scrotum, low blood pressure (100/70 mmHg) and tachycardia (110 bpm). Laboratory evaluation showed hyponatremia and hyperkalemia. Adrenal crisis was suspected and treatment with Hydrocortisone hemisuccinate and isotonic saline solution were initiated, with a favorable outcome. The diagnosis of primary adrenal insufficiency (PAI) was established based on hormonal test results showing low cortisol levels (4.1 µg/dl) and elevated ACTH levels (1906 pg/ml). The patient was discharged on Hydrocortisone (20 mg/ day) and Fludrocortisone (0.1 mg/ day) therapy. Despite adequate physical therapy for the ankle sprain, the patient experienced progressive walking difficulties, weakness, and pain in the legs, prompting a neurology referral. He was diagnosed with spastic paraparesis, ataxia, and bipyramidal syndrome. Given the combination of neurological symptoms and PAI, adrenoleukodystrophy was suspected. Evaluation of VLCFAs revealed elevated levels of hexacosanoic acid (1.15 mg/l), along with increased C24/C22 (2) and C26/C22 (0.07) ratios. Genetic testing identified a hemizygous missense variant in the *ABCD1* gene, c.1833G>C, p.(Gln611His), classified as likely pathogenic, which was inherited from the patient's mother who is heterozygous for the same mutation.
Conclusions
ALD is a disorder with variable clinical manifestations, usually including signs and symptoms of PAI and progressive neurological dysfunction. To the best of our knowledge the mutation found in our patient has not been described in the literature, although another missense variant in the same codon, p.(Gln611Arg), was reported in individuals with *ABCD1*-related phenotypes, emphasizing the importance of the affected amino acid. [1]
References
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EP86

JOINT348

Adrenergic crises simulating severe cardiac pathology

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Introduction
Pheochromocytomas can present serious cardiac complications that simulate acute pulmonary edema, arrhythmias, myocarditis, acute coronary syndrome, dilated/hypertrophic cardiomyopathy and takotsubo syndrome. They can also cause neurological complications (PRESS syndrome). The management of adrenergic crises is complicated: intravenous antihypertensives, alpha-antagonists and beta-blockers and in unstable patients, vasopressors.
Objectives
To identify rare cases of pheochromocytoma with severe cardiac pathology diagnosed in our hospital.
Material and Methods
We collected 2 cases of adrenergic crises induced by pheochromocytoma seen in the emergency room, one with a fatal outcome and a postmortem autopsy diagnosis and the other with a satisfactory evolution after adequate diagnosis and treatment.
Results
1) 53-year-old woman admitted for respiratory distress, chest pain, seizure episode and sudden decrease in level of consciousness. Hypotension, tachycardia and tachypnea. D-dimer 46335, Troponin I 2922.30 and metabolic acidosis. ECG: ST depression on the lower face. Chest X-ray: acute pulmonary edema. Urgent coronary angiography: normal coronary arteries and pattern compatible with stress cardiomyopathy/myocarditis. Echocardiogram: non-dilated LV, mild-moderately depressed systolic function, marked hypokinesia of the basal septum (Takotsubo). Chest CT angiography: cardiac failure, renal infarcts and 46 mm left adrenal mass (adrenal hemorrhage/-pheochromocytoma). Hormonal study: Elevated metanephrines.
   - Evolution: High doses of norepinephrine and dobutamine are required to maintain blood pressure with severe systolic dysfunction, so levosimendan is started. Pulmonary edema and cardiac function improve, but neurological evolution is poor (head CT - ischemic lesions/vasogenic edema), resulting in death.
   - Autopsy: myointimal hyperplasia of coronary arteries. Generalized alveolar edema. Bilateral adrenal hemorrhage, with pheochromocytoma in the left adrenal gland. Heart: changes in the heart muscle typical of infarction, with cardiomyopathy and myointimal hyperplasia of coronary vessels, which could lead to arrhythmogenic changes.
2) 60-year-old male admitted for cardiorespiratory arrest. General malaise, tachycardia, profuse sweating. metabolic acidosis, troponin I 40. ECG: sinus tachycardia and peaked T waves. Chest CT: rules out PE, bilateral pleural effusion and heart failure, left adrenal mass 6 cm. Urgent catheterization: normal coronary arteries. Severely dilated left ventricle (dilated cardiomyopathy), severe hypokinesia (LVEF 15%). Hormonal analysis (urine 24h): elevated metanephrines. Scintigraphy: left adrenal pathological deposit compatible with pheochromocytoma. Cardiac MRI: Non-ischemic dilated cardiomyopathy with severe biventricular systolic dysfunction. Evolution: need for vasoactive drugs with arterial hypertension, alpha and beta blockade is started. After completing the study, surgical resection showed improvement in ventricular function.

Conclusions
Pheochromocytoma may resemble acute coronary syndrome/cardiogenic shock with high mortality, and should be suspected in patients with normal catheterization.

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EP87

JOINT2107

Preparation for adrenal cortical carcinoma surgery with injectable fluconazole, a second successful experience (case report)

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Background
The malignant adrenocortical carcinoma is an aggressive tumor of the adrenal cortex, with an incidence of between 1 and 2 cases per million population and a peak between the ages of 40 and 50. Rapid management of hypercorticism is essential to prepare for surgical intervention. As Ketoconazole is not available, Fluconazole, another azole antifungal, is a suitable alternative that has been successfully used in our department for another patient with paraneoplastic Cushing's syndrome, with no adverse effects.
Case presentation
The patient was 31 years old and presented with hypertension complicated by heart failure and a clinical Cushing's syndrome consisting of truncal obesity, buffalo neck, and purple stretch marks; the hormonal work-up confirmed

endogenous hypercorticism. A CT angio scan identified a large left adrenal mass measuring 205 × 191 × 156 mm, with infiltration of the perilesional fat. Further staging via thoraco-abdomino-pelvic CT revealed the presence of pulmonary metastases. Following the successful emergency surgery on injectable Fluconazole for a patient with paraneoplastic Cushing's syndrome, we opted for fluconazole 400 mg injectable daily, with 24-h urinary free cortisol (UFC) monitoring and liver function tests every 48 hs. After 12 days of treatment, the patient's UFC levels decreased from 632.5 nmol/24 h to 60 nmol/24 h without any signs of liver damage. Following adrenalectomy, the patient experienced a postoperative adrenal insufficiency with a postoperative UFC of 16.73 nmol/24 h at 7 days after surgery.
Conclusion
This is the second case in our department of successful management of hypercorticism by injectable fluconazole in preparation for surgery. These findings suggest that Fluconazole is a safe and effective alternative to ketoconazole. Further studies involving larger patient populations are needed to fully evaluate its potential as a synthetic anti-cortisolic agent.

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EP88

JOINT1177

Diagnosis of pheochromocytoma in a patient with recurrent reverse takotsubo cardiomyopathy

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Background
Pheochromocytomas (PHEO) are rare neuroendocrine tumors that secrete excess catecholamines, leading to severe cardiovascular complications. While their typical symptoms include episodes of hypertension and tachycardia, their association with Takotsubo syndrome (TTS) is less commonly recognized, especially with reverse TTS, which is an even more rare clinical presentation of PHEO. TTS often resolves with supportive care, however when related to catecholamine excess from pheochromocytomas, can lead to recurrent episodes and long-term cardiovascular risks.
Objectives
This case report aims to increase awareness among clinicians regarding the causal association between Takotsubo cardiomyopathy and catecholamine secreting pheochromocytoma.
Case Presentation
A 40-year-old female patient with a history of reverse Takotsubo cardiomyopathy two years ago, currently on ongoing antihypertensive treatment, was admitted to the emergency department due to palpitations, chest pain, headache, and vomiting. Clinical evaluation revealed a hypertensive crisis (B*P* = 220/110 mmHg), sinus tachycardia (HR = 120 bpm) and ischemic changes on the ECG. Biochemical tests revealed elevated troponin levels, severe hyperglycemia and increased lactate in the blood gases without acidosis. Echocardiography showed hypokinesia of the left ventricle, leading to urgent coronary angiography, which was normal. The patient was admitted to the ICU and treated with a non-selective beta-blocker (labetalol) and intravenous nitrate, leading to significant improvement in the left ventricular echocardiographic findings, suggesting a possible reverse Takotsubo syndrome. Due to the clinical picture, the patient's young age and medical history, pheochromocytoma was suspected.
Results
A computed tomography (CT) scan revealed a nodular mass in the left adrenal gland (3.1 x 2.7 cm) with heterogeneous contrast uptake. Hormonal screening confirmed elevated plasma catecholamines levels: metanephrine: 330 ng/l (normal <88), free normetanephrine: 1030 ng/l (normal <115), and free 3-methoxytyramine: 37 ng/l (normal <17.4). Staging with whole-body CT and Tecrotyde scan did not show secondary lesions or paragangiomas. The patient was prepared with alpha-blocker (doxasocin) for 15 days and underwent laparoscopic left adrenalectomy. Histopathological diagnosis confirmed pheochromocytoma (size =3 cm, PASS score= 1, Ki67 <1%, PT1NxMx). Genetic testing was negative. Postoperatively, hormonal screening was negative and imaging showed no recurrence. The patient remains asymptomatic without anthihypertensive medication.
Conclusion
The association between pheochromocytomas and Takotsubo syndrome underscores the importance of recognizing catecholamine-induced myocardial dysfunction in patients with acute chest pain and ECG abnormalities. Clinicians should suspect pheochromocytoma in unexplained TTS cases as early diagnosis and treatment are essential to prevent long-term cardiac damage. Further research is needed for optimal management of this potentially life-threatening complication.

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EP89

JOINT1452

The combination of afternoon and midnight salivary cortisol improves the diagnosis of cushing's syndrome

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The diagnosis of Cushing's syndrome is based on the inhibition test with 1 mg dexamethasone (1 mg DST), 24-h urine free cortisol, and serum and salivary cortisol measurements at midnight. Nevertheless, the diagnosis is challenging and often fraught with many pitfalls depending on several factors, such as taking drugs that interfere with the hypothalamic-pituitary-adrenal axis (HPA axis), the presence of molecules active on CYP3A4 enzyme and many other factors such as age, sex, and body mass index. In addition, some diseases such as renal and liver failure, or psychiatric disorders, reduce the diagnostic power of the tests commonly used in the diagnosis of hypercortisolism. We propose a new diagnostic strategy, simple to perform, easy to reproduce and with a high diagnostic performance. It consists of measurements of salivary cortisol by LC-MS/MS method, at three different times of the day: the first in the morning (0800 h), the second around 1400 h and the third between 2300 h and 2400 h. The reproducibility and specificity of the test identify patients with hypercortisolism in 95% of cases at midnight. Interestingly, when considering two specific points on the salivary cortisol curve, the success rate rises to 100%. Furthermore, the method allows diagnosis even in patients who cannot perform the commonly used diagnostic tests.

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EP90

JOINT3684

Adrenal tuberculosis has not revealed all its secrets:an unusual case

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Introduction
Adrenal tuberculosis is rare, accounting for between 3% and 9% of the etiologies of adrenal insufficiency (AI). It is responsible of acute or chronic adrenal insufficiency. Our case illustrates an unusual presentation of adrenal tuberculosis whose ultimate aim is to make our medical community aware of the various aspects of this widespread condition in the Moroccan context.
Case
A 43-year-old patient with a history of chronic smoking and cured hepatitis B presented with diffuse abdominal pain. presented with diffuse abdominal pain with no other associated digestive signs. Questioning revealed weight loss of 8 kg in 2 months, associated with progressive melanoderma. Abdominal computed tomography revealed a necrotic pseudo adrenal mass measuring approximately 63x35x75 mm. Chronic adrenal insufficiency was based on a low cortisol level of 5.2ng/dl. The patient was started on hydrocortisone replacement therapy and referred for surgery due to the "suspicious" nature of the adrenal mass. The patient was referred to us from the pre-anaesthesia consultation for preoperative endocrinological evaluation. The clinico-biological data were in favour of a peripheral AI. The etiological investigation, notably the Quantiferon test, was very positive at 10 UI/ml. X-ray was normal. The diagnosis of adrenal tuberculosis was in consultation with the pneumo-phtisiologists, was based on a combination of radiological (appearance suggestive of a bacillary cause), clinical (signs of tuberculosis of tuberculosis impregnation) and biological (very positive quantiferon). The patient was put hormone replacement therapy with hydrocortisone, combined with antituberculosis antituberculosis treatment.
Discussion
The adrenal localization of tuberculosis occurs via the hematogenous route from the CT scan and biopsy play a vital role in the diagnosis. Adrenal tuberculosis, a rare cause of AI in the literature, is discovered late in the course of infection, with pathognomonic signs are adrenal calcifications, testifying to the chronicity of the

condition. Anti-tuberculosis treatment can lead to partial recovery of steroidogenesis. Our patient's clinical course looks very satisfactory, pending sufficient time for radiological control.

Our case

- Reports an AI during the active, progressive phase of adrenal tuberculosis, in contrast to cases often reported in the chronic phase.
- Unusual tumor-like radiological findings, which may lead to surgical intervention.
- Underlines the importance of multidisciplinary care and the need to respect the sphere of specialized skills.

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EP91

JOINT1355

Post operative hypoaldosteronism after unilateral adrenalectomy. a case report and review of the literature

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Primary Aldosteronism (PA) is the most common cause of secondary hypertension and is associated with long term morbidity and organ dysfunction including chronic kidney disease (CKD). Optimal management for unilateral PA is adrenalectomy however development of post-operative hypoaldosteronism with resultant hyperkalaemia is increasingly being recognised as a complication. We present a patient with delayed diagnosis PA, established CKD and recovery complicated by hypoaldosteronism. We review the literature regarding the risk factors for and management of post-operative hypoaldosteronism, and present local data on post-operative hyperkalaemia rates. We describe a 60-year-old man who underwent unilateral adrenalectomy after 10 years of refractory hypertension. At time of surgery, he had established stage G3aA2 CKD, type 2 diabetes mellitus and ischaemic heart disease. Two weeks after surgery, the patient was admitted to hospital with severe hyperkalaemia, that was initially resistant to standard treatment measures. His hyperkalaemia resolved after initiation of Fludrocortisone and Sodium Bicarbonate. Post operative hyperkalaemia has been described in between 3-48% of patients undergoing unilateral adrenalectomy and attributed to transient, but sometimes prolonged, hypoaldosteronism. Most cases of hyperkalaemia are reported to occur within one to three weeks of surgery, however reports of up to 6 months post operatively have been described. This is likely a consequence of prolonged renal exposure to aldosterone excess, resulting in chronic suppression of renin with subsequent atrophy and suppression of the contralateral zona glomerulosa cells. In our hospital, between 2010 - 2020, 23 patients underwent unilateral adrenalectomy. Eight patients (34.8%) experienced transient hyperkalaemia; however, no cases of prolonged hyperkalaemia were recorded. Only 39.1% of patients had potassium levels monitored beyond 28 days, and 21.7% has levels monitored for less than 14 days. Hyperkalaemia can be severe and associated with life threatening cardiac arrhythmias. Despite this, there are not clear consensus guidelines on strategies to predict, prevent or monitor for this. Suggested risk factors include age >50 years, duration of hypertension >10 years, established CKD, adrenal adenoma >2 cm and male gender. As patients with established complications of hypertension may be both more at risk of complications, and less likely to derive benefit from surgery, this case highlights some considerations and complexities of patient selection for surgical management of PA. This case provides strength to recommendations to recognise and treat PA early, and to develop robust protocols for post-operative electrolyte surveillance, treatment and management of anti-hypertensives in the peri-operative setting.

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EP92

JOINT1333

Congenital adrenal hyperplasia and addison's disease: coincidence or consequence?

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Case description

In 2014, a 25-year-old patient was referred with unfulfilled desire to conceive, oligomenorrhoea, pronounced hirsutism since age 17, and clitoromegaly. A transvaginal ultrasound revealed bilateral ovarian lesions (left 4x2x1.5 cm; right 2x2 cm) later confirmed through MRI, as well as enlarged adrenal glands. Diastolic blood pressure was elevated and laboratory testing showed normal electrolytes and low cortisol (82 nmol/l[80-638]), however the patient had no signs of hypocortisolism. Further evaluation showed: testosterone 12.1 nmol/l[0.3-1.7], DHEA-sulfate 3.99 µmol/l[1.7-9.7], androstendione° >35.0 nmol/l[2.0-9.0], aldosterone 47 pmol/l[32-654], renin 0.6 ng/l[1.7-23.9], 17-OH-progesterone (stimulated) 19.4 nmol/l[<43], 11-desoxycortisol° >180 nmol/l[<12], ACTH 2008.0 pg/ml[<46.0]. We diagnosed congenital adrenal hyperplasia (CAH) with 11-β-hydroxylase deficiency and ovarian adrenal rest tumors (OARTs). Whole exome sequencing did not reveal a pathogenic variant. Due to active mineralocorticoid and glucocorticoid precursors, no substitution was required. Treatment with glucocorticoids was initiated to control androgen excess and restore menstruation. Subsequently she became pregnant spontaneously in 2017. After delivery, glucocorticoids were discontinued; nevertheless she became pregnant a second time and now has two healthy sons. In 2021, the patient presented with severe fatigue and low blood pressure of 92/61 mmHg (heart rate 69/min). Androgens were almost unmeasurable and cortisol very low: cortisol 20 nmol/l, ACTH 1107.0 ng/l, DHEA-sulfate 0.14 µmol/l, androstendione° <1.05 nmol/l, 17-OH-progesterone 1.6 nmol/l, 11-desoxycortisol° 10.2 nmol/l, sodium 140 mmol/l, potassium 3.9 mmol/l. She was diagnosed with an Addisonian crisis and substituted with hydrocortisone. 21-hydroxylase antibodies were positive (1.2 U/ml[<0.4]), suggesting autoimmune Addison's disease, however further autoimmunological testing (ANA, IgG, IgM, IgA, complement CH50, C3/C4, B-cell and T-cell-subpopulations) was negative. In 2022, aged 32 years, the patient presented with premature ovarian failure (cessation of menstruation, hot flashes, estradiol 26.5 pmol/l[114-1959], LH 48.1 IU/l[<95.6], FSH 21.8 IU/l[1.7-21.5]) and hormone replacement was started. Surprisingly, the OARTs regressed and had not been detectable in imaging since 2019.

Discussion

This case raises the question of whether the concurrence of CAH, Addison's disease, and premature ovarian failure in this patient is coincidental or indicative of a potential underlying connection. A case report (Sigrid Aslaksen *et al*., 2019) documented a patient with CAH with mutation in 3β-hydroxysteroid dehydrogenase and subsequent Addison's disease and premature ovarian failure. We hypothesize that prolonged ACTH stimulation could have led to progressive depletion or dysfunction of ACTH-dependent tissue. This is supported by the finding that the mineralocorticoid steroid synthesis, regulated by the Renin-Angiotensin-Aldosterone system rather than ACTH, remained intact.

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EP93

JOINT3461

How early should screening be performed in patients with congenital adrenal hyperplasia?

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Introduction

Testicular adrenal rest tumor (TART) is a rare type of benign tumor of the testis. However, TARTs have been described in rarer forms of congenital adrenal hyperplasia(CAH) such as CYP11B1, 3β-hydroxysteroid dehydrogenase type 2 deficiency (3βHSD2D) as it occurs in 21-hydroxylase deficiencydeficiency, although no clear association between hormonal control of all cells and the development of TART has been shown. TART may be missed on physical examination when it is deeply located and less than 2 cm in size. Ultrasound as a first-line examination method provides important information for the recognition of TART. Accurate and timely recognition of TART in cases of infertility or progression and deterioration is important, especially in the absence of adequate and continuous hormonal control.

Methods

Pediatric patients who were followed up in pediatric endocrine outpatient clinic between 2022 and 2024 with the diagnosis of adrenal insufficiency and screened for TART with routine testicular ultrasonography were included in the study. We included10 cases of TART with CAH (7 cases of 21-hydroxylase deficiency, 2 cases of 11β-hydroxylase deficiency, 1 case of 3βHSD2D-related TART).

Virilization and under-masculinization were assessed using Prader staging and pubertal development sttaged according to the system of Tanner. Steroids higher than the target range supported by high ACTH levels during follow-up were classified as poor control.
Results
The age of the patients was 13.07 ± 3.68 years. 3 patients (30%) were well controlled. All patients had advanced bone age and 1 patient was receiving GnRH analog therapy due to precocious puberty. The youngest affected patient was 5 years old. 2 (20%) patients were of Syriac nationality and had no regular follow-up with poor control.2 patients were interpreted as REST in the first USG and were diagnosed as Leyding cell tumor (LCT) with biopsies performed due to clinical progression. One of the two patients had no genetic diagnosis but was considered to have 21-hydroxylase deficiency based on laboratory and clinical findings.
Conclusion
Early diagnosis and treatment of TART is important for the preservation of gonadal function in children with CAD. Timely detection of the disease is important to prevent irreversible gonadal dysfunction and infertility. Abnormal serum ACTH levels are not seen in some cases and are also seen in patients younger than 6 years of age, so we recommend screening with early US scanning. Rarely, it can be caused by LCT and should be kept in mind in this respect.

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EP94

JOINT751

Non-arteritic anterior ischemic optic neuropathy and addison's disease

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Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common cause of acute optic neuropathy in adults presenting as sudden, painless vision loss due to ischemia of the optic nerve head. Risk factors that have been strongly associated with NAION include hypertension, hypercholesterolemia, diabetes mellitus, cardio- and cerebrovascular disease, and obstructive sleep apnoea. Addison's disease which is a rare autoimmune condition leading to adrenal insufficiency, is not commonly linked to NAION. However, chronic hypotension and vascular dysregulation in Addison's disease may contribute to ischemic complications, including NAION.
Case Presentation
We report on a 46-year-old female with known Addison's disease who presented with acute, painless blurry vision in the right eye upon waking up. On examination at eye casualty, visual acuity was 6/18 in the right eye and 6/6 in the left eye. Fundoscopy revealed optic disc swelling. Inflammatory markers were within the normal range with a very low GCA probability score and given the young age, Giant cell arteritis was considered highly unlikely. MRI of the brain showed white matter foci in keeping with small vessel disease and empty Sella syndrome. The neurologist reviewed her, and multiple sclerosis was excluded. She had a long-standing history of Addison's disease and autoimmune hypothyroidism. She was being treated with fludrocortisone and prednisolone and had previously experienced subjective hypotensive episodes. Lying and standing blood pressure checks in the clinic did not document postural hypotension. Adherence to corticosteroid and mineralocorticoid replacement therapy was monitored with serum prednisolone levels within the therapeutic range and plasma renin activity levels indicating sufficient fludrocortisone dosing. 24-h ambulatory blood pressure monitoring was arranged which could have detected nocturnal hypotension, however, our patient was unable to attend this. Chronic hypotension secondary to adrenal insufficiency was suspected as the precipitating factor for optic nerve head ischemia during presumed nocturnal hypotensive episodes, however, we could not conclude this due to lack of evidence of documented nocturnal hypotension. The patient did report subjective symptoms of dizzy spells, especially at night though with no other associated symptoms. Other vascular risk factors were absent, however, suggesting Addison's disease as a possible cause.
Conclusion
This case highlights a rare but significant association between Addison's disease and NAION. Clinicians should consider adrenal insufficiency in atypical presentations of NAION, particularly in younger patients or those without traditional vascular risk factors. Early recognition of Addison's disease and appropriate hormonal therapy may reduce the risk of ischemic events, including NAION.

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EP95

JOINT2546

Skin lightening cream causing hypoadrenalism

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Introduction
Skin lightening creams contain steroids and are easily accessible from over the internet and shops which are not regulated. Topical corticosteroids have important anti-inflammatory and immunosuppressive activity and are often prescribed for the treatment of dermatological disorders such as eczema and psoriasis. Adrenal insufficiency has been known to be a side effect for using topical steroid creams for long period of time and are therefore prescribed and monitored by the dermatologist.
Case Presentation
35-year-old female presented with 1-year history of lethargy, fatigue and muscle cramps which had got worse in the last one week. No infective signs. She was haemodynamically stable and apyrexic. She has a past medical history of depression and anxiety and was taking mirtazapine medication. Her menstrual cycle is regular and has two children. Her 9am Cortisol was found to be 7 nmmol/l and the pH, lactate and glucose was within normal range. She denied taking oral or inhaled steroids but on further questioning it was found she has been taking a skin lightening cream call 'Fashion fair cream' which contains clobetasol propionate. She had been using this cream all over her body for many years. On examination her skin had different pigmentation, thinner with more prominent veins. She had multiple striae on her arms, thighs and abdomen. She also looked cushingoid with moon face, central obesity, buffalo hump of neck, and striae all over the body significantly on the abdomen. Short synacthen test showed cortisol levels of 8nmol/l(0mins), 106 nmol/l(30mins) and 73 nmol/l(60mins). She was reviewed in the endocrine clinic where she was advised to stop her topical cream and started on hydrocortisone 10 mg/5 mg/5 mg with aim to wean down slowly
Conclusion
Many skin lightening creams contain steroids which patients may not be aware of. Long-term use of topical steroid cream can cause side effects and most importantly secondary adrenal insufficiency. Although commonly prescribed for dermatological conditions such as eczema and psoriasis they are monitored closely. However, skin lightening creams are not monitored and are easily available without prescription or monitoring from shops and online. This could lead to adrenal insufficiency if used for longer period of times. It is important to take a full history to check if patients are taking topical cream, eye drops, etc that may contain steroids. It is also important to have an MDT approach with the dermatologist and endocrinologist to help wean patient off the steroids and treat appropriately.

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EP96

JOINT1638

Thyroid hormone resistance syndrome de novo in a patient with THR mutation c.749T > C. a case report

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Background
Thyroid function test discrepancies often cause diagnostic delays and sometimes lead to unnecessary treatments. Thyroid hormone resistance syndrome is rare (1/40,000 births), affecting both sexes equally, with autosomal dominant inheritance. Diagnosis relies on excluding other causes of hyperthyroxinemia and genetic analysis of the thyroid hormone receptor (THR) beta subunit. Clinical symptoms are usually minimal. The primary differential diagnosis is with TSH-producing tumors and analytical laboratory system discrepancies.
Methods
A 22-year-old woman presented with discordant thyroid function tests since 2023, showing elevated or normal TSH and elevated free T4 and free T3 levels. No family history of thyroid dysfunction. Diagnosed with polycystic ovary syndrome, grade 1 obesity, and mild hyperprolactinemia. Previous tests from another hospital and ours (with a different system) revealed subclinical hypothyroidism with normal free T4 levels (2022 and earlier). No clear symptoms of hyperthyroidism or hypothyroidism. Treated with progesterone only and no supplements. Physical examination

showed no goiter, tachycardia, or ophthalmopathy. Anti-thyroid antibodies (anti-peroxidase and anti-thyroglobulin) were positive, TSI negative. Free alpha subunit and SHBG levels were normal. Pituitary MRI was normal. Thyroid ultrasound showed no nodules. Blood samples on other platforms (Vitros ECiQ and Architect i2000SR) showed similar results to our hospital (Cobas e801 Roche). Other studies were negative, including antibodies (antinuclear, heterophile, anti-thyroxine), rheumatoid factor, and no macro TSH or macro free T4. Genetic study for familial dysalbuminemic hyperthyroxinemia was negative. Serum selenium levels were normal. T3 suppression test (100 mg for 8 days) showed TSH 0.094 mIU/ml on day 8 (normal response). Octreotide LAR test (20 mg/28 days) showed no TSH decrease after one month. Genetic study for thyroid hormone resistance syndrome identified missense variant of the THRB gene c.749T>C (p.Ile250Thr) variant associated with OMIM #188570, autosomal dominant inheritance from her mother, with her two siblings also affected.
Conclusions
A previously normal phenotype did not raise suspicion for thyroid hormone resistance syndrome. Routine tests (TSH only) can overlook family history of thyroid discordant study. Genetic testing was key to diagnosis in this case. It is relevant that this case involves a woman of childbearing age, due to the therapeutic considerations for a future pregnancy.

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EP97

JOINT2534

Ectopic ACTH syndrome in a patient with pheochromocytoma

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Introduction
Pheochromocytoma is a rare catecholamine-secreting tumor that arises from chromaffin cells in the adrenal medulla. Pheochromocytomas may rarely secrete adrenocorticotropic hormone (ACTH) or CRH (corticotropin-releasing hormone) and calcitonin in addition to catecholamines. Ectopic ACTH syndrome due to pheochromocytoma is a very rare disorder. These patients carry a significant risk of severe complications if not diagnosed and managed appropriately.
Case
A 53-year-old male was referred to our clinic with muscle weakness, weight loss, high blood pressure, headache, palpitations, and flushing. The patient had developed diabetes in the last month and was taking oral antidiabetic medication. The patient was normokalemic in her first evaluation and in her hormonal evaluation. The patient's hormone levels showed that ACTH was 19.8 pg/ml, cortisol was 15.4 µg/dl, DHEA-SO4 was 89.51 µg/dl (34.5-568.9), 24-h urine cortisol was 46.69 µg (10-100), 1 mg dexamethasone suppression test was 11.1, 24-h urine metanephrine was 2719 µg, normetanephrine was 2693 µg, plasma metanephrine was 303 pg/ml, and normetanephrine was 935 pg/ml. The CT imaging of the patient's abdomen revealed a 35x30 mm thick-walled, low-density, heterogeneous lesion in the right adrenal gland. During follow-up, the patient rapidly became hypokalemic, potassium replacement was administered, and spironolactone was started. Plasma cortisol level increased to 110 µg, ACTH level to 452 pg/ml and 24-h urine cortisol level increased to 3755 µg. We started the patient on 400 mg of fluconazole intravenously. During follow-up, the patient benefited somewhat from the treatment. The treatment brought the patient's blood pressure and blood sugar under control. The patient was operated after appropriate surgical preparation. After the removal of a right adrenal pheochromocytoma, the patient's elevated levels of serum and urine corticosteroids, plasma ACTH, plasma catecholamines, and urinary catecholamine metabolites decreased. Pathological examination revealed diffuse positive staining with ACTH in the pheochromocytoma area. The patient became normotensive after the operation. The patient, who was receiving basal-bolus insulin therapy, continued his diabetes treatment with oral antidiabetic.
Conclusion
Ectopic ACTH syndrome is very rare in patients with pheochromocytoma. These patients have a relatively rapid course, marked hypokalemia, diabetes mellitus or significant hypertension. The management of these patients is difficult, and there may be difficulties in obtaining therapeutic agents. Proper preoperative recognition and management can result in total cure.

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EP98

JOINT3800

Acute hypoglycemia after surgery – a clue for the diagnosis of adrenal insufficiency

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Introduction
Adrenal insufficiency (AI) is a rare but potentially life-threatening condition that often remains undiagnosed until an acute illness or other major physiologic stress, such as surgery, occurs. Cortisol deficiency leads to unopposed insulin action, resulting in increased peripheral glucose uptake and decreased hepatic glucose output, leading to hypoglycemia. This case report describes a patient who developed severe hypoglycemia after cholecystectomy, which eventually led to the diagnosis of AI.
Case presentation
A 42-year-old female patient with no known comorbidities underwent elective laparoscopic cholecystectomy for symptomatic gallstone disease. Preoperative assessment, including fasting glucose and routine laboratory tests, was unremarkable. The surgical procedure was uneventful, and no intraoperative complications were noted. However, on the first postoperative day, she developed severe hypoglycemia with a documented blood glucose level of 1.6 mmol/l (28.8 mg/dl), accompanied by neuroglycopenic symptoms. She was immediately treated with 10% intravenous glucose, which led to a rapid improvement in symptoms. After this episode, the patient remained hemodynamically stable and experienced no further hypoglycemic events during her hospitalization. Because the initial hypoglycemic episode was unexplained and neither exogenous insulin, an oral hypoglycemic agent, nor an anesthetic known to induce hypoglycemia was used, an endocrinological consultation was requested. At discharge, she was provided with a continuous glucose monitor (CGM) and a glucometer to detect possible recurrent hypoglycemic episodes. At her first endocrinological follow-up with CGM, early morning hypoglycemic episodes were noticed. Morning cortisol levels (measured at 8:00 am) were low (160 nmol/l), with an inadequate rise in cortisol levels during the Synacthen stimulation test. In addition, elevated ACTH levels of 64 pmol/l and positive anti-21-hydroxylase antibodies confirmed an autoimmune cause of primary adrenal insufficiency. Screening for other autoimmune diseases, including celiac disease, autoimmune thyroiditis, primary ovarian insufficiency and pernicious anemia, was negative. The patient was started on hydrocortisone replacement therapy, with dose adjustments for physiologic stress such as infection, surgery, or trauma. A review of previous medical records revealed multiple emergency room visits for nausea, vomiting, hyponatremia, and renal acute insufficiency, suggesting preexisting adrenal dysfunction in acute illness.
Conclusion
While transient hypoglycemia due to fasting or anesthetics may occur in the postoperative period, severe hypoglycemic episodes should prompt further endocrinologic evaluation. Recognizing adrenal insufficiency as a potential underlying cause is crucial, as timely diagnosis and appropriate glucocorticoid replacement therapy can prevent life-threatening complications and improve the patient's prognosis.

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EP99

JOINT551

Composite adenomatoid tumor with myelolipoma of adrenal gland: case report

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Introduction
Adenomatoid tumor and myelolipoma are benign, hormonally inactive neoplasms of mesothelial origin, usually occurring in the male and female genital tracts. Rare extragenital adenomatoid tumors have been identified in the adrenal glands, heart, mesentery, pleura, and lymph nodes. That are often incidental findings in the adrenal glands. Myelolipoma is more common than adenomatoid tumor in this location but both are rare, yet the pathogenesis of both remains unclear
Case report
A 32 years old female gives a history of dragging left loin pain occurring in attacks for 2 years Examination revealed: Bp: 140/95, pulse: 84/Minute, Weight: 83 kgs Examination was normal apart from Left suprapubic anterior abdominal swelling about 2 to 3 cms with minimal tenderness Triphasic CT showed: A well circumscribed oval shaped right side hepatorenal pouch hypodense cystic lesion is seen insepraple from right adrenal gland is noted measuring 5.1*2.6 cms & indenting the liver surface. Mild hepatomegaly. A fairly defined isodense lesion is noted at the

left semilunar is being inseparable from left lateral aspect of the left rectus muscle measuring 2.3*2.2 cms.A left adnexal cyst is noted measuring 4.8*4.8 cms. MRI of the abdomen for further evaluation of the adrenal mass showed: Right adrenal multiloculated cystic lesion is seen measuring 2.5*4.5*5 cms, eliciting high T2 & low T1 signal with marginal septal postcontast enhacement yet no diffusion restriction. She was referred for the investigation of incidental adrenal mass. Serum cortisol and adrenaline metabolites were normal
Results of serum Cortisol am: 16.7 (5-25 mg/dl), ACTH am: 21.4(10-60 pg/dl) Cortisol pm: 5.2(3-10 mg/dl), Plasma renin: 12.68 (0.7-3.3 pg/dl), Aldosterone: <3.7 (<15 ng/dl)Plasma metanephrin: less than 14.9 (0.5 pg/dl), Plasma normetanephrin: 82 (<0.9 pg/dl)Urine metanephrin: 52(24-96 mg/24 hs), Urine normetanephrin: 88(75-375 mg/24 hs)The patient underwent surgery and removed both the adrenal swelling and the anterior abdominal wall swelling. The postsurgical recovery was uneventful. Microscopic examination revealed Right adrenal mass: adenomatoid tumor associated with myelolipoma. Free resection margins. Anterior abdominal swelling: endometriosis. No malignancy.
Conclusion
We report a rare case of primary Adenomatoid Tumor and Myelolipoma of Adrenal Gland treated with complete surgical resection of the tumor. A meticulous assessment of histological features pose a diagnostic challenge will aid in an accurate and effective diagnosis.. The differential diagnosis includes adrenocortical carcinoma and metastatic carcinoma, especially signet ring cell carcinoma.

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EP100

JOINT2965

Neurofibromatosis type 1 with pheochromocytoma with high potential for progression (clinical case)

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Neurofibromatosis type 1 (NF1) is one of the most common genodermatoses, and it can be associated with pheochromocytoma (PCC) in up to 14,6% of patients. PCC linked to *NF1* gene mutation belongs to the 2nd molecular cluster of genetic alterations that usually has low risk of tumor progression and metastasis. We present a clinical case of PCC in a female patient with NF1 and high potential for progression. Female patient P., 72 years old, has a medical history of multiple neurofibromas and skin spots since childhood, but no one paid attention to these signs. Over the last year, she noted episodes of rapid heartbeat and high blood pressure (BP) up to 190/90mmHg at the first time, so antihypertensive therapy was prescribed. Upon physical examination, BMI-18.9 kg/m^2, BP 124/78 mmHg, heart rate 68 bpm. She had multiple neurofibromas ranging in size from a few mm to 2 cm, "freckling" of the skin and multiple Lisch nodules on the iris of the eyes, which provided diagnosis of NF1. The tests showed an increase in metanephrines to 649 mg/day(18-277), normetanephrines to 3248 mg/day(42-423), testosterone to 8,16nmol/l (0,46-1,18). CT-scans demonstrated a formation of the right adrenal gland, 83x68x69mm with native illumination +38HU and areas of necrosis. After adrenalectomy histological and immunohistochemical examinations of the tumor verified PCC with a high potential for progression (average proliferation index Ki67 16.5%, PASS 9 points, GAPP 5 points). Six weeks after surgery, there was no any episodes of high BP, but there was a slightly elevated level of normetanephrines to 119 mg/day (5-77), after another 4,5 months to 363 mg/day. Testosterone levels also remained elevated up to 11,04nmol/l. This case demonstrates the lack of attention of doctors to NF1 diagnosis. Despite such a vivid clinical signs, the diagnosis was established during hospitalization at the age of 72. The development of arterial hypertension at this age may well be natural, which in turn can complicate the diagnosis of PCC. Despite the fact that *NF1*-associated PCC could have a low progression potential, in our clinical case high risk of malignance was detected. An increasing testosterone level is not characteristic of PCC, so the search for the source of hyperandrogenemia is needed. The patient is currently undergoing additional examination to exclude residual PCC tissue and a possible androgen-producing tumor.

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EP101

JOINT2041

Carotid paraganglioma: About 4 cases

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Introduction
Carotid paragangliomas are the most common cervicocephalic paragangliomas. They are neuroendocrine tumors developed from small neuroectodermal structures derived from the neural crest. Their non-secreting nature makes their diagnosis difficult. Imaging allows their characterization and provides a precise lesion assessment.
Aim
The aim of this work is to study the clinical and paraclinical particularities and the therapeutic management of carotid paragangliomas.
Material and methods
A retrospective study collecting 4 cases of patients with carotid paraganglioma.
Results
These are 4 patients (2 men and 2 women) with a mean age of 50 years, who presented with chronic latero-cervical swelling. Ultrasound was performed in 4 cases showing a hypervascularized hypoechoic mass. CT scan performed in 3 cases showed an intensely enhancing isodense mass widening the carotid bifurcation. MRI performed in 3 cases showed a typical paraganglioma appearance with flow void spots. The paraganglioma was bilateral in one case, for which radiotherapy was indicated. The other 3 cases were operated on without incident with a favorable subsequent evolution.
Conclusion
Carotid paragangliomas are rare neuroendocrine tumors, most often benign and non-secreting, with a slow progression (5-7 years) and a growth rate of approximately 5 cm/year and of genetic origin in 10% of cases. The reference examination remains the CT angiography. Management is multidisciplinary, only surgical treatment is curative. When it is not possible, radiotherapy to reduce tumor progression may be an alternative to treatment.

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EP102

JOINT1900

A rare case of codeine-induced secondary adrenal insufficiency with hyponatremia worsened by hydrochlorothiazide: a case report and review of literature

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Introduction
Adrenal insufficiency can result from a variety of causes, including primary adrenal disorders, secondary causes such as adrenocorticotropic hormone (ACTH) deficiency, or suppression of the Hypothalamic-Pituitary-Adrenal (HPA) axis by medications. Long-term use of codeine is a recognized but underdiagnosed cause of opioid-induced adrenal insufficiency (OIAI), resulting from HPA axis suppression. It is important to note that Hydrochlorothiazide, a thiazide diuretic, is well-documented to cause hyponatremia. We present a case of a 67-year-old woman with codeine-induced secondary adrenal insufficiency and moderate hyponatremia exacerbated by Hydrochlorothiazide, highlighting the diagnostic and therapeutic challenges in managing such a complex condition.
Case report
A 69-year-old female, with a history of hypertension and osteoporosis, presented in June 2024 to the emergency department with hypotension, hyponatremia, and normal kalemia. She had been undergoing long-term treatment with codeine and paracetamol for bone pain. Upon arrival, she showed signs of hypotension. Her laboratory findings revealed moderate hyponatremia, along with low cortisol and ACTH levels confirming secondary adrenal insufficiency (SAI). Kidney function and complete blood count were within normal ranges. Hydrocortisone therapy was initiated, leading to an improvement in cortisol levels. Head CT, abdominal and thyroid ultrasound were normal, excluding other causes of situation. She was prescribed hydrocortisone (20 mg morning, 5 mg at noon, 5 mg evening), fludrocortisones 0.1 mg in addition to the previous treatment with antihypertensive (Irbesartan, Hydrochlorothiazide, Amlodipine, Metoprolol). After two weeks, her sodium levels improved to normal, while potassium remained stable. She discharged in a stable situation but six months later, the patient presented again to the emergency department with a hypertensive crisis (200/110 mmHg), hyponatremia and a 12 kg weight gain. The cortisol and ACTH levels were low. After workup it was concluded as
Final Diagnosis
Secondary adrenal insufficiency due to long -term codeine use, with hyponatremia exacerbated by hydrochlorothiazide. The synacten stimulation test resulted positive. After that, it was stopped Fludrocortisones and Hydrochlorothiazide and decreased gradually the dose of Hydrocortisone and Codeine (with monitoring by the toxicologist to prevent withdrawal syndrome). Follow-up tests confirmed stable electrolytes and cortisol levels.
Conclusion
This case highlights the critical importance of accurate diagnosis and tailored treatment in patients with secondary adrenal insufficiency induced by medication. It underscores the need for awareness of the potential for opioid-induced adrenal insufficiency and the exacerbating effects of thiazide diuretics, necessitating careful management and timely intervention to prevent complications.

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EP103

JOINT2052

Unmasking the genetics: decoding the paternal code in pheochromocytomas

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Introduction
Pheochromocytomas and paragangliomas (PPGLs) have the highest heritability among endocrine tumors, with approximately 40% of patients carrying a germline mutation in one of about 20 related genes. Succinate dehydrogenase (SDH) complex gene mutations are a well-known cause of hereditary PPGLs. Interestingly, unlike other SDH subunit gene mutations, germline SDHD mutations exhibit a 'parent-of-origin' effect. Tumors typically develop only when the mutated allele is inherited paternally, consistent with maternal imprinting. However, rare cases of maternally inherited SDHD pathogenic variants causing disease have been reported, including our case.
Case Report
A 22-year-old man presented with a two-week history of right iliac fossa pain, which resolved spontaneously. He denied headaches or palpitations but reported generalized sweating. Hypertension was noted on examination. CT revealed an incidental finding of a 5.5 cm left adrenal mass. Notably, he had a strong family history of SDHD mutation, with all affected family members on the maternal side, primarily presenting with head and neck paragangliomas. Plasma metanephrines showed an elevated normetanephrine level of 5690 pmol/l (reference range <560 pmol/l), with normal metanephrine and 3-MT levels. A DOTATATE PET scan revealed an intensely avid left adrenal mass with no suspicious findings elsewhere, particularly in the head and neck region. He subsequently underwent a laparoscopic left adrenalectomy, and histology confirmed a 46 mm PPGL with clear margins, a GAPP score of 2 and negative SDHB staining. Genetic testing identified a heterozygous c.191_192delTC (Leu64Profs*4) mutation in the SDHD gene, along with a variant of uncertain significance in the PDGFRA gene. Upon reviewing his family' genetic test results, it was confirmed that he carried the same SDHD mutation as his mother and maternal grandfather. Postoperatively, his plasma metanephrines normalized. We plan to request tumor gene expression analysis to confirm loss of heterozygosity, further establishing the pathogenicity of the mutation. Additionally, we intend to screen his father to rule out any potential paternal inheritance.
Conclusion
An international consensus on the role of surveillance for maternally inherited SDHD pathogenic variants has not yet been established. Given the rarity of such cases, it is important to discuss genetic testing with the patient and his first-degree relatives, as well as to consider ongoing surveillance for the patient himself.

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EP104

JOINT340

Adrenal suppression secondary to intranasal corticosteroid use: a case report

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Background
Glucocorticoids are widely used anti-inflammatory drugs for various pediatric conditions. Adrenal suppression is a rare but serious complication, typically associated with systemic glucocorticoid administration: most commonly, oral, intravenous or intramuscular. While the association between inhaled glucocorticoids and hypothalamic-pituitary-adrenal axis suppression is well-established, the systemic absorption of nasal corticosteroids remains controversial. Current international guidelines for allergic rhinitis suggest that the risk of adrenal insufficiency associated with intranasal glucocorticoid use is minimal.
Case Presentation
A previously healthy 6-year-old girl presented to our pediatric endocrinology clinic for evaluation of Cushing syndrome. She had been referred by her pediatrician following multiple visits to family practice, given the family's concerns around changes in facial features and increased hair growth. Her medical history was significant for seasonal allergic rhinitis, treated with intranasal beclomethasone for over three months. This had been prescribed by her family physician, at usual doses, and discontinued two weeks prior to her clinic visit. There was no additional exposure to any other medications or supplements. On physical examination, the patient exhibited facial rounding and increased hair growth along the sideburns and back. Laboratory evaluation revealed an undetectable morning cortisol level (<28 nmol/l) and a low ACTH level (2 pmol/l). Further testing confirmed an insufficient cortisol response to ACTH stimulation (peak cortisol 172nmol/l). Other pituitary hormone levels were within reference range. A diagnosis of adrenal suppression secondary to high-dose intranasal steroid use was made. The patient was started on hydrocortisone replacement with gradual tapering. Her family received education on stress dosing during illness to prevent adrenal crisis.
Discussion
This case underscores the possible systemic effects of intranasal corticosteroids. Prolonged use, high doses, concomitant use of CYP3A4 inhibitors, and the presence of genetic variations that affect steroid metabolism, could increase the risk of adverse effects. Early recognition and intervention are critical to prevent life-threatening adrenal crises.
Conclusion
Awareness of adrenal suppression as a potential side effect of intranasal corticosteroids is essential. This case emphasizes the need for judicious use of any type of glucocorticoids. Patient and family education, along with routine monitoring of at-risk patients, are crucial for mitigating risks.

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EP105

JOINT1594

Giant bilateral myelolipomas in a female patient with untreated classic 21-hydroxylase deficiency: a case report

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Background
Chronically increased ACTH concentrations in poorly controlled patients with classic 21-hydroxylase deficiency (21-OHD) lead to adrenal hyperandrogenaemia and hyperplasia of the adrenal cortex. Markers of disease control correlate with the adrenal volume and poor disease control is associated with an increased incidence of adrenal tumours, in particular myelolipomas.
Clinical Case
We report the case of a 59-year-old female patient with classic 21-OHD (salt-wasting form). In childhood and adolescence, she had glucocorticoid (GC) and mineralocorticoid (MC) replacement therapy and had normal pubertal development. At the age of 25, she discontinued hormonal replacement therapy, which led to secondary amenorrhea, hair loss, hirsutism and deepening of the voice. She never experienced an adrenal crisis. As she suffered from severe alopecia at 56 years of age, GC and MC therapy was restarted, but the clinical and biochemically signs of hyperandrogenaemia persisted. At the age of 59 years an abdominal mass was palpated in a clinical routine check-up by the family practitioner, the patient was referred to the University Hospital and finally giant bilateral myelolipomas were diagnosed. The left-sided tumour measured 24.5 x 20.5 x 9.7 cm (2230 g), the right-sided measured 14.5 x 11.6 x 6.5 cm (501 g). Due to their massive size and the increased risk of rupture and haemorrhage, bilateral adrenalectomy was performed and the patient was educated for adrenal crisis prevention and sick day rules.
Conclusion
This case highlights the long-term consequences of untreated 21-OHD, as well as the importance of lifelong continuous therapy, good therapeutical management and adherence. In poor disease control in 21-OHD screening for adrenal tumours should be considered.

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EP106

JOINT2560

Achieving spontaneous pregnancy in a patient with classic congenital adrenal hyperplasia through modified-release hydrocortisone

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Background
Female patients with classic congenital adrenal hyperplasia (CAH) experience significantly reduced fertility due to hormonal dysregulation, psychosocial and psychosexual factors and anatomical changes following surgery for virilised external genitalia. Normal fecundity can be achieved with optimal hormonal management; however, achieving optimal hormonal control is challenging, leading to a prolonged time to pregnancy compared to the general population.
Clinical Case
We report the case of a 33-year-old woman with simple virilising CAH and infertility for over three years. CAH was diagnosed at the age of two; since then, she received glucocorticoid (GC) replacement therapy and had a normal pubertal development. On prednisolone substitution and antiandrogenic contraception, she maintained good hormonal control, showed no clinical signs of hyperandrogenism and had a regular menstrual cycle. At the age of 30, she stopped contraception in order to conceive. She experienced inadequate hormonal control, irregular menstrual cycles and no spontaneous pregnancies occurred. To optimise disease control her treatment was adjusted multiple times, including the use of prednisolone and dexamethasone, dose escalations and additional fludrocortisone. Assisted reproductive technologies, including two cycles of *in vitro* fertilization, were unsuccessful. While the concentrations of follicular 17OHP and androgens normalised with increased GC dosage, morning serum follicular progesterone concentrations remained elevated. The patient was then switched to the newly available modified-release hydrocortisone (MR-HC Efmody®) at a daily dose of 35 mg/day (10-0-0-25mg). A non-stimulated spontaneous dichorial twin pregnancy occurred within 9 weeks. The course of pregnancy was uneventful and the patient delivered two healthy girls via caesarean section. After delivery and breastfeeding hormonal parameters revealed morning serum follicular progesterone concentrations within the target range under MR-HC treatment.
Conclusion
The presented case of a female patient with classic CAH and infertility for over three years highlights the challenges of fertility treatment in CAH. The normalisation of morning follicular progesterone concentrations and the successful spontaneous pregnancy under MR-HC treatment, indicate that due to the circadian release MR-HC normalises adrenal steroid precursor synthesis in a more physiologic manner. Therefore, it could be a promising therapeutic option for fertility treatment in women with classic CAH.

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EP107

JOINT1916

Bilateral macronodular adrenal cortical disease: a case series

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Introduction
Bilateral macronodular adrenal cortical disease (BMACD) is a heterogeneous condition characterized by the presence of multiple nodules larger than a centimeter in diameter and is associated with mild autonomous cortisol secretion. Its prevalence has recently increased due to the wide use of imaging studies.
Purpose
This study aimed to describe the clinical and biochemical characteristics, as well as comorbidities and responses to dynamic tests aiming to investigate paradoxical adrenal cortical receptor expression, in a series of patients with BMACD monitored at our center.
Methods
This study included a series of patients referred for investigation of bilateral adrenal tumors. Patients were screened for pheochromocytoma, primary hyperaldosteronism, and autonomous cortisol secretion. The possibility of late-onset congenital adrenal hyperplasia was ruled out by measuring 17-OH progesterone. In order to detect paradoxical receptor expression patients underwent dynamic tests, including the Synacthen test, mixed meal test, posture test, LHRH assay, TRH test, glucagon test, desmopressin test, and metoclopramide test. The response to these tests was evaluated based on changes in cortisol values, with an increase of $<25\%$ considered a non-response, 25-49% a partial response, and $\geq 50\%$ a complete response.
Results
The study included 6 female patients with bilateral macronodular adrenal hyperplasia, with a mean age of 56.7 ± 6.6 years and BMI of 30.6 ± 9.8. Three patients had arterial hypertension, and four had dyslipidemia under treatment. Only one patient showed clinical features of Cushing's syndrome. Based on the overnight dexamethasone suppression test, 3 patients were diagnosed with autonomous cortisol secretion, while 2 others had probable autonomous cortisol secretion. During the various dynamic tests, two patients exhibited a response to the mixed meal, one responded to metoclopramide, one responded to both metoclopramide and desmopressin, and one responded to the LHRH test. Notably, one patient did not show a response to any of the tests performed.
Conclusion
The majority of BMACD patients exhibit a mild autonomous cortisol secretion. Identifying paradoxical receptor expression can enhance our understanding of adrenal steroidogenesis and potentially guide personalized treatment.

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EP108

JOINT2072

A patient with pheochromocytoma and MDH2 variant (c.478G > A)

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Introduction
Pheochromocytomas and paragangliomas (PPGLs) are rare catecholamine-producing tumours with metastatic potential. Approximately 40% of PPGLs are caused by germline variants. In this report, we present a patient with pheochromocytoma and a *MDH2* variant.
Case Presentation
A 66-year-old man was referred to the Endocrinology Department for investigation of a 5.4 cm right adrenal incidentaloma, detected in a chest CT scan performed due to COVID-19 infection, with imaging features not indicative of adenoma (CT density >20 HU, no signal suppression on out-of-phase T1-weighted MRI imaging). During admission, he presented daily episodes of paroxysmic hypertension, tachycardia, headache and pallor lasting approximately 10-20 minutes. Hormonal evaluation revealed markedly elevated 24h urine metanephrine [4149 μg/24h (52-341)] and normetanephrine [6703 μg/24h (88-444)] levels (measured by HPLC) and a diagnosis of pheochromocytoma was made. After two weeks of doxazocin preparation, an uncomplicated laparoscopic right adrenalectomy was performed. Histology revealed a pheochromocytoma (PASS score 7) with Ki-67 of 6%; intense edema and hemorrhagic infiltration in neoplastic cells was also observed. Whole exome sequencing identified the missense *MDH2* gene (NM_005918.4) variant, c.478G > A, resulting in replacement of valine by methionine at codon 160, p.Val160Met, of MDH2 protein. At the most recent clinical review, six months after adrenalectomy, the patient is asymptomatic with normal 24h urine metanephrine and normetanephrine levels and no evidence of disease recurrence.
Conclusion
MDH2 encodes the mitochondrial malate dehydrogenase which is essential for the conversion of malate to oxaloacetate as part of the proper functioning of the Krebs cycle and it has been, recently, added to the list of potential PPGL susceptibility genes. To our knowledge, this is the second report of a patient with a *MDH2* variant and pheochromocytoma. The p.Val160Met variant of *MDH2* is reported in 0.011% of alleles in European (Non-Finnish) individuals in gnomAD database. Although this specific variant is considered to be of uncertain significance according to ACMG criteria, a recent study showed that p.Val160Met variant causes protein 3D structure destabilization and impairment of MDH2 molecular function, classifying it as likely pathogenic. Further genetic studies are needed to determine the role of p.Val160Met *MDH2* gene variant in the pathogenesis of PPGLs.

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EP109

JOINT3379

Amiodarone-induced thyrotoxicosis type 2 and iatrogenic cushing syndrome in patient with advanced heart failure and left ventricular assist device

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Background
Amiodarone-induced thyrotoxicosis (AIT) is a complication of amiodarone therapy that can be difficult to diagnose and treat, especially in patients with advanced heart failure (HF), because of symptoms that mimic low cardiac output syndrome.
Patient findings
We describe a 19-year-old patient with advanced heart failure due to dilatative cardiomyopathy with surgically implanted left ventricular assist device (LVAD), awaiting heart transplantation. Due to the earlier manifestation of atrial fibrillation (AF), the patient was previously treated with amiodarone, during 18 months, which led to the development of amiodarone-induced thyrotoxicosis (AIT) type 2, as a result of destructive thyroiditis. Despite treatment with various modalities of corticosteroid therapy, AIT was highly resistant to treatment. Due to severe thyrotoxicosis, it was not possible to perform surgical treatment, total thyroidectomy. Prolonged treatment of thyrotoxicosis with various recommended treatment modalities, continuous corticosteroid therapy led to the development of iatrogenic Cushing's syndrome. Also, at that time, the diagnosis of thrombophilia was made, and heparin-induced thrombocytopenia (HIT) was confirmed.
Conclusion
Treatment of patients with severe HF and LVAD, associated with AIT and associated iatrogenic Cushing's syndrome, is an endocrinological emergency, with many challenges and requiring a multidisciplinary approach to treatment. AIT is associated with an increased risk of cardiovascular (CV) events, especially in patients with severe HF, so early diagnosis and adequate and timely treatment are very important.

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EP110

JOINT1969

Case report: trauma - induced adrenal hematoma and pseudopheochromocytoma phenomenon

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Introduction
Adrenal masses are a common finding during routine radiological procedures. While most are commonly benign, some may be malignant and/or have autonomous hormonal secretion. A rare pathology includes adrenal hemorrhage, leading to the subsequent organization of blood collections into hematomas. The most cases of adrenal hematomas are unilateral and traumatic in origin, though systemic infections and hemostatic disorders may affect both adrenal glands.
Case Presentation
A 57-year-old male patient was admitted to our hospital due to an incidentally discovered adrenal mass. A year before his admittance, he suffered a contusion of the right hemiabdomen, which was followed by persistent chronic chest pain, high blood pressure, headache, excessive sweating, and a rapid heartbeat. The chest CT showed pleural effusion and adrenal mass. Abdominal CT showed an altered morphology of the right adrenal gland, which was enlarged to 46x24x52 mm, suggestive of an adrenal hematoma. Surrounding fat tissue showed a characteristic periadrenal reactive change, typically seen in hematomas. Initial functional tests revealed primary hypocorticism (low morning cortisol: 73.9 nmol/l with compensatory elevated ACTH: 54 pmol/l) and normal electrolytes (Na: 135 mmol/l; K: 4.6 mmol/l). Urinary catecholamine levels were elevated (adrenaline: 18.02, noradrenaline: 803.4, dopamine: 3261.7 nmol/24h). Two months later, follow-up CT has detected a reduction in diameter of hypodense lesion in the right adrenal gland, measuring approximately 28x15 mm, suggesting a hematoma in the resorption phase. During hospitalization in our institution, the abdominal MRI showed a hypoplastic right adrenal gland, FDG PET-CT, performed due to elevated catecholamine levels, showed no evidence of increased metabolic activity suggestive of pheochromocytoma. Control catecholamine and their metabolite levels were normal (adrenaline 76.6; noradrenaline 332.3; dopamine 2492; metanephrine 0.21; normetanephrine 0.56; 3-methoxytyramine 0.92 nmol/24h). Evaluation of the HPA axis indicated the continued presence of hypocorticism (ACTH 15.1 pmol/l; Synacthen test: Cortisol: 152…239…120…38 nmol/l). Regarding the duration of hypocorticism in the presence of normal left adrenal gland additional tests, including immunology and virology, were conducted; the results were negative.
Conclusion
We concluded that hematoma formation resulted from trauma, leading to primary hypocoticism, and the increased catecholamine levels in these circumstances were likely due to adrenal medulla cell lysis. The case illustrates that adrenal hematoma can clinically and biochemically mimic pheochromocytoma. This phenomenon, known as**"pseudopheochromocytoma**," is typically characterized by symptoms of sweating, headaches, palpitations, and hypertension, all of which were observed in our patient.

Keywords
adrenal hematoma, primary hypocorticism, pseudopheochromocytoma.
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EP111

JOINT2399

Unfavorable metabolic outcomes in pediatric patients with classic congenital adrenal hyperplasia - study method proposal

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Background
Congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency is an autosomal recessive condition with a prevalence of approximately 1 in 15 000. Children with classic form of CAH (CCAH) experience an increased cardiometabolic risk compared to general population. We conducted a systematic review of published studies regarding the cardiometabolic phenotype in children with CCAH, identifying 25 studies on the subject. Qualitative analysis showed that children with CCAH have elevated multiple cardiometabolic risk factors. Findings concerning lipid metabolism are variable and limited in children with CCAH as well as in adults and there are no data regarding lipoprotein subclasses. Small, dense low-density lipoprotein (LDL) particles are highly susceptible to oxidation, while high-density lipoproteins (HDL) exhibit potent antioxidant properties. This research method was designed to explore the metabolic phenotype regarding alterations in lipoprotein size and subclasses distribution and redox status markers in children with CCAH.
Methods
after obtaining the consent of parents/guardians and children, 20 children with CCAH of both genders were included, with a control group consisting of 20 children without CAH who were assessed due to signs of premature puberty. Basic demographic data were collected on all subjects, as well as other anamnestic and clinical data of importance in the evaluation of CCAH (independent variables: age, gender, anthropometric features, CCAH type (SW or SV), serum androgen levels, total daily dose of hydrocortisone and the outcomes of interest: body mass index, waist and hip circumference, body composition, fasting glycaemia, HOMA IR, heart rate, blood pressure, lipoprotein subclasses and particles, inflammatory status). The size and subclass distribution of lipoprotein particles will be determined by gradient gel electrophoresis. Paraoxonase-1 (PON1) activity will be assessed as a biomarker of HDL's antioxidant properties. The redox status of study participants, including prooxidative markers (TOS, PAB), oxidative damage indicators (AOPP), and antioxidative defense biomarkers (SH-groups, SOD), will be evaluated using spectrophotometric methods.
Results
Comparisons between groups will be conducted using t-tests or Mann-Whitney U tests for continuous variables and Chi-square tests for categorical variables. Spearman correlation coefficients will assess associations between variables, followed by multiple linear regression to identify independent predictors. Binary logistic regression will evaluate associations between independent variables and metabolic outcomes, while ROC (Receiver Operating Characteristic) analysis will assess the diagnostic accuracy of selected biomarkers. Statistical analysis will be performed by SPSS v.18 (Chicago, IL, USA).
Conclusion
Further studies of cardiometabolic phenotype in CCAH are needed especially in children, where present data are scarce.

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EP112

JOINT3870

CAH care in a district general setting: care, safety and preferences

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Introduction
CAH is a heterogeneous collection of rare congenital diseases. Historically, numerous studies have highlighted suboptimal care for patients with these conditions, with guidelines aimed to improve physical health and quality of life, and reduce complications, and as with most rare diseases, suggestion that care is best provided at dedicated clinics and the transition process is a key feature.
Aim
To review the care of patients with CAH at our centre (a District General Hospital)
Methods
The biochemistry database was interrogated to find all patients who had a measurement of 17 OHP over the last 5 years. Patients records were then checked to identify all patients with confirmed CAH (excluding non-classical), and data including mode of referral, laboratory results, treatment, scans and mental health comorbidities collected for these patients.
Results
13 patients were identified, with one exclusion due to being under the paediatric team. Male:female ratio was 4:8. 5/12 had 21-hydroxylase deficiency, in all others the genotype was unknown. 8 patients were looked after historically for >10 years at the centre, 3 referred directly from tertiary paediatric clinics and 1 re-referred after being lost to the transition process. Treatment was with prednisolone in 7/12, hydrocortisone 3/12 and dexamethasone 2/12. None were treated with modified release hydrocortisone or combination therapy. All patients has annual checks for testosterone, 17-OHP, androstenedione, gonadotrophins, U+Es and aldosterone/renin ratio. 8/12 patients had elevated 17-OHP levels, with 4/12 within the reference range. All patients had measurement of lipids, glycaemic assessment and BP checked annually. BMI was checked in 11/12 patients. Only one of the male patients had US assessment for TARTS in the preceding 2 years. Emergency hydrocortisone kits were documented for 10/12 patients, 11/12 patients had the NHS Steroid Alert Card. No patients had been admitted in a hypoadrenal crisis in the preceding 5 years. 8/12 patients had bone densitometry assessed (the younger patients being excluded). 2/10 patients had mental health problems. Care was provided by a total of 4 consultants (three cared for one patient each).
Discussion
Patient preference plays a key part in the location of care for some patients with CAH, and not all want to travel to specialist clinics. Biochemical assessment and radiological assessment was acceptable but not complete in some cases. A single consultant overseeing all cases and a checklist may help address gaps. Patients with CAH in DGHs need access to newer therapies via education for caregivers and research opportunities.

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EP113

JOINT2509

Essential hypertension or primary hyperaldosteronism? Detecting the undetectable

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Introduction
Arterial hypertension is a common pathology affecting a significant proportion of the population. It can be classified into different forms, including essential hypertension and secondary hypertension essential hypertension accounts for around 90-95% of cases, and is often multifactorial in origin Obesity is a major risk factor, with obese women 3 times more likely to suffer from hypertension. Conversely, endocrine-induced hypertension is rarer. In this observation, we report a case of endocrine hypertension, under-diagnosed due to the presence of multiple cardiovascular risk factors and a borderline age.
Observation
This is a 49-year-old obese patient, with BMI of 39, treated for dyslipidemia, with 11 years history of hypertension discovered at the age of 38, revealed by grade 3 hypertension, initially followed by a cardiologist who put her on dual therapy without any secretory test. The patient was referred to us as part of goitre exploration, and secondary hypertension was suspected in view of the age of onset before 40, with uncontrolled hypertension on tritherapy. Examination revealed a BP of 170/69, grade 2 obesity with no signs of hypercorticism. The workup revealed hypokalemia at 3.5 cardiac and renal Doppler were normal a secretory work-up was requested after correction of the hypokalemia and adaptation of the treatment to avoid any risk of drug interactions. The aldosterone renin ratio was positive at 231, indicating primary hyperaldosteronism. Abdominopelvic CT revealed a 15 mm left adrenal nodule. The patient was referred for surgery with good clinical improvement.
Discussion
Overweight and obesity, especially in women, are a clear risk factor for hypertension. Endocrine hypertension can often be confused with essential hypertension, especially in obese patients, due to a similar symptomatology. To avoid overlooking an endocrine cause, a thorough clinical and biological evaluation is essential. Consideration should be given to age of onset, resistance to treatment, presence of hypokalemia. Failure to consider endocrine causes in the context of obesity can have serious hydroelectrolytic and long-term cardiovascular consequences (cererbral stroke, infarction).
Conclusion
Diagnosis of endocrine hypertension in obese patients can be complex, given the similarity of symptoms between essential hypertension and certain endocrine pathologies. consideration of specific tests can differentiate these two entities and ensure optimal management

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EP114

JOINT1364

Non-functioning adrenal cortical adenomas: analysis of 31 cases

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Background
While the non-functioning adrenal cortical adenomas do not secrete hormones, they can cause subtle, prolonged cortisol release, potentially contributing to metabolic disturbances. This highlights the need for routine screening and ongoing surveillance to manage and identify early signs of metabolic syndrome associated with this entity.
Methods
This was a retrospective and descriptive study that included 31 patients followed for non-functioning adrenal cortical adenomas in the Endocrinology Department of Hedi Chaker University Hospital in Sfax, Tunisia.
Results
The mean age of patients was 57.9 years. A female predominance was observed 60% of cases. The average BMI was 28.35 kg/m^2, and 25% of patients were classified as overweight. Obesity was identified in 25% of cases, with 3% having morbid obesity. An android obesity pattern was observed in 74% of patients. The average systolic blood pressure was 145.6 mmHg, and 32% of patients had a diastolic blood pressure $\geq$ 85 mmHg. All patients had metabolic syndrome. The mean 11 PM cortisol level was 69 ng/ml, and no patients had pathological cortisol levels. The average post low dose dexamethasone suppression test cortisol level was 10.06 ng/ml, with no patients showing a pathological suppression test. None of the patients had elevated ACTH levels ($\geq$ 50 pg/ml). Fasting blood glucose was pathological ($\geq$ 6.1 mmol/l) in 64.5% of cases. Elevated triglyceride levels ($\geq$ 1.7 mmol/l) were found in 41.9% of patients, and total cholesterol was elevated in 48.3% of patients.
Conclusion
Patients with non-functioning adrenal cortical adenomas often present with metabolic abnormalities, highlighting the importance of thorough screening and continuous monitoring to manage associated risks effectively.

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EP115

JOINT3537

Biochemically negative retroperitoneal paraganglioma: a case report

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Introduction
Paragangliomas (PGL) are rare neuroendocrine tumors located along the sympathetic or parasympathetic ganglia (1). While these tumors are commonly associated with excessive production of catecholamines, some can be biochemically silent. Biochemically negative PGL (BNPGL) are defined by normal levels of plasma and urinary metanephrines and normetanephrines, as well as plasma methoxytyramine(2). This case report presents a 59-year-old woman who was diagnosed with a biochemically negative retroperitoneal PGL.
Case presentation
She had a 14-year history of hypertension and presented with chronic right lumbar pain evolving for the past 2 years. She had no other clinical signs. Laboratory tests revealed prediabetes with an HbA1c level of 6.3%. The patient's plasma and urinary metanephrine, normetanephrine and 3-methoxytyramin levels were within normal ranges. Imaging studies revealed a 28 mm tumor with a spontaneous density of 34 Hounsfield units (HU) on abdominal CT, which exhibited intense and heterogeneous enhancement. The tumor was located near the diaphragm's pillar and the right border of the inferior vena cava. Further evaluation with MRI showed heterogeneous tumor with hyperintense T2 signal. An octreoscan demonstrated localized hyperfixation, with no additional areas of fixation noted. The tumor was successfully removed through a laparotomy. The histopathological examination of the surgical specimen confirmed the diagnosis of a paraganglioma with a PASS score of 1.
Discussion
Biochemically silent PGL are often difficult to diagnose due to their lack of characteristic biochemical markers, which makes them challenging to distinguish from other retroperitoneal masses. These tumors are more frequently found in the head and neck region, and are often associated with mutations in the SDHx genes (3). Imaging studies play a crucial role in the diagnosis of silent PGLs. Their discovery often occurs incidentally, as in this case, when imaging is conducted for unrelated clinical concerns. The management of BNPGL typically involves surgical resection with careful preoperative management with alpha- and beta-blockers in order to mitigate the risk of perioperative complications
Conclusion
Biochemically silent PGL, although rare, should be considered in the differential diagnosis of retroperitoneal masses, especially when imaging findings are suggestive of a paraganglionic origin.
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EP116

JOINT921
Osilodrostat as a bridge to surgery in patient with ectopic cushing's syndrome
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Introduction
Ectopic Cushing's syndrome is a rare condition caused by a paraneoplastic secretion of ACTH by a tumor outside the pituitary or adrenal glands. The symptoms associated with hypercortisolism are similar to other types of Cushing's syndrome but they can be more severe and have a rapid onset. Excluding pituitary adenoma and discovering the ectopic source of ACTH is crucial in the diagnostics. The treatment of choice is a surgical removal of the ACTH-secreting tumor. The surgery and recovery could however be complicated by the overt hypercortisolism and that is why a pharmacological treatment is recommended before the surgery in severe cases. There are several steroidogenesis inhibitors available including osilodrostat which is the most novel one.
Observation
We present a case of a 45-year-old man without any significant comorbidities. He was presented to an endocrinologist by his general practitioner because of a rapidly onseting and drug-resistant arterial hypertension and hyperlipidemia along with typical traits of Cushing's syndrome (central obesity, rounded face, swelling…). His early morning cortisol was elevated and not suppressible by dexamethasone and free urine cortisol was 11 times the upper limit of normal. ACTH was extremely elevated however other pituitary hormones were normal. No adenoma was visible on the pituitary MRI nevertheless there was a solitary 22 mm nodule in the upper left pulmonary lobe on the PET/CT scan. The S3 segmentectomy was indicated and to reduce the complications and improve recovery we started the osilodrostat therapy three weeks before the surgery. After one week we increased the initial dose from 20 to 40 mg daily. On the day of surgery we managed to decrease the free urine cortisol to 2 times the upper limit of normal and significantly reduce the antihypertensive therapy. The surgery was performed without any complications and an atypical lung carcinoid was then histologically described with highly positive ACTH staining. We stopped osilodrost the day after surgery and started hydrocortisone replacement instead. ACTH, serum, salivary, and urine cortisol then gradually normalised and we were able to withdraw hydrocortisone slowly. We now only follow the patient in cooperation with the pulmonary oncologist.
Conclusion
Pharmacological treatment is primarily used in patients with Cushing's syndrome who are contraindicated for surgery. However, it can be beneficial as a bridge to surgery, aiming to reduce complications and improve recovery. The novel steroidogenesis inhibitior osilodrostat, in our case, proved itself to be very capable of doing so if properly dosed.
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EP117

JOINT2637
Unusual adrenal incidentaloma: the ganglioneuroma
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Introduction
Ganglioneuroma is a rare, benign neurogenic tumor arising from sympathetic ganglion cells. It occurs mainly in the retroperitoneal region. Adrenal localization is rare. We report a case of adrenal ganglioneuroma in a 50-year-old man. The tumour was discovered incidentally on a thoracoabdominal CT scan ordered in the context of exploration for abdominal pain. The diagnosis was confirmed by pathological examination.
Observation
53-year-old patient admitted for investigation of an adrenal mass. Clinically, no hypertension, no Menard's triad and no signs of hypercorticism, with the exception of skin lesions suggestive of a hamartoma. Morphologically, abdominal CT revealed a left retroperitoneal mass, roughly oval, well limited, with regular contours, latero aortic on the left, heterogeneously enhanced after injection of contrast medium in relation to hypodense necrotic areas, measuring 110 *76mm in transverse diameter for 107mm in height. It displaces the pancreas anteriorly, making an imprint on the kidney and displacing it posteriorly, with no sign of invasion; it also displaces the spleen laterally, making intimate contact with the splenic vein anteriorly and the renal vein inferiorly; no vascular thrombosis. A CT scan focused on the adrenal glands or MRI could not be performed due to impaired renal function. Secretory work-up: Plasma methoxylates are negative. Minute braking with cortisol after braking 10ng/ml. Kalemia is normal Tumour markers are negative, as are LDH and b 2 microglobulin. A scan-guided biopsy was indicated and histological examination came back in favor of a ganglioneuroma. A meeting will be held with the urologists to decide on appropriate management.
Discussion
Ganglioneuroma is a rare benign tumor that deserves to be recognized and evoked in the presence of an adrenal mass discovered by chance. It is diagnosed histopathologically after an invasive procedure. However, as with all non-secretory incidentalomas, surgery should always follow an endocrine and radiological work-up. The possibility of local recurrence requires regular monitoring.
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EP118

JOINT3478
Stage IV lung cancer with metastases confined to the adrenal glands: a case report
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Clinical case
A 67 years old male patient with a history of right upper lobe lung adenocarcinoma (LUAD) with pleural invasion, treated with surgery, chemo- and radiotherapy, presented a small left adrenal mass documented since the initial LUAD diagnosis. The lesion never posed any interest for three years as it never caused adrenal dysfunction, it was stable in size (14 mm) and it never proved any metabolic activity on two earlier 18F-FDG PET/CT scans. In the fourth year since the LUAD diagnosis, a routine thorax-to-pelvis PET/CT revealed a single metabolically active lesion which was the already documented adrenal mass (SUVmax: 4.19), previously deemed benign, prompting the patient's referral our clinic. No endocrinological evaluation had been performed since the diagnosis. The patient lacked clinical signs of adrenal dysfunction and had normal adrenal hormone levels. Given the left nodule's history and the patient's refusal of surgery, a short-term 'watchful waiting' approach was decided. Three months after the initial presentation, a CT scan showed significant growth of the previously known left nodule (24×21×14 mm vs 14 mm), a new left adrenal mass of 14×9×15 mm and a new right adrenal mass of 16×11×16 mm. An additional head-to-pelvis PET/CT showed intense activity confined only to the left (SUVmax: 10.31 vs 4.19, respectively SUVmax: 4.88) and right (SUVmax: 5.33) adrenals. As metastatic LUAD was suspected due to the rapid changes in an incredibly short period, the therapeutic decision was bilateral adrenalectomy. Due to the patient's reluctance to the recommended treatment, only a left adrenalectomy was performed. The histopathological and immunohistochemical analysis confirmed LUAD histogenesis, with positive expression of TTIF-1 and Napsin A. Three months post-operation, an MRI revealed an increase in the size of the right adrenal nodule (23×24 mm). As the patient refused additional surgery, stereotactic radiotherapy was performed on the remaining lesion following a radiotherapy consultation, resulting in partial adrenal insufficiency.
The adrenal glands are a common site for metastasis in patients with lung cancer. There is controversy regarding the route by which the cancerous cells of the primary disease reach the adrenal gland. Unilateral adrenal metastases are deemed rare and when they do occur, the ipsilateral adrenal is typically affected first. In this case, despite the initially stable solitary lesion limited only to the left contralateral adrenal, alongside the LUAD, we would have advocated for active surveillance since the exact nature and potential progression of the adrenal mass remains uncertain.

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EP119

JOINT2040

Bilateral carotid paraganglioma: a rare entity

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Introduction
Paraganglioma is a tumor that develops at the expense of the "carotid body", which is a chemoreceptive structure located at the posteromedial aspect of the carotid bifurcation. Bilateral character is rare. We aim to report clinical and paraclinical features and thearpeutic management of bilateral carotid paraganglioma through a case report and literature review.
Observation
A female aged 68, operated for a left breast carcinoma in 2011 followed by radio-chemotherapy, in remission since 2012, consulted for a left latero-cervical swelling evolving for 2 years without signs of compression. The physical examination showed a left subangulo-mandibular swelling of 5cm, firm, painless, mobile laterally, fixed longitudinally and having a pulsatile character on palpation. A second upper right jugulo-carotid swelling of 2cm with the same characteristics was objectified on examination. The rest of the examination was without abnormalities. The cervical ultrasound showed a left formation of tissue nature, hypoechogenic, well-limited hypervascularized on Doppler, measuring 4cm located at the level of the carotid bifurcation suggesting a paraganglioma. Cervical MRI showed a large tumor mass of the left carotid bifurcation in T1 isosignal, in heterogeneous T2 hypersignal with "Flow void" with intense and heterogeneous enhancement responsible for a widening of the carotid bifurcation. MRI showed a second lesion with the same characteristics located at the level of the right carotid bifurcation. The dosage of blood and urine metanephrines returned normal. The paraganglioma was classified stage I on the right and stage II on the left according to the Shamblin classification. The patient was proposed for external radiotherapy given the bilateral nature of the tumor.
Conclusion
Carotid paragangliomas are rare neuroendocrine tumors, most often benign and non-secreting, with a slow progression. Imaging is of considerable assistance to diagnosis. Management is multidisciplinary, only surgical treatment is curative. When it is not possible, radiotherapy to reduce tumor progression may be an alternative to treatment.

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EP120

JOINT2069

Imaging phenotype over size: two cases of cavernous hemangiomas of the adrenal glands

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Cavernous hemangiomas are rare benign vascular lesions that are difficult to diagnose preoperatively. We present two cases of cavernous hemangiomas of the adrenal glands and provide radiographic clues that can hint at the correct diagnosis. The first case is an 80-year-old woman presenting with an enlarging hemorrhagic left adrenal mass measuring 72×63×66 mm. Computed tomography (CT) imaging showed that the mass exhibited marginal and nodular enhancement in the venous post-contrast phase, with no evidence of infiltration into surrounding structures. The hormonal workup was consistent with a non-functioning tumor. The mass was first identified 3 years prior and was described as heterogeneous and of unknown etiology, measuring 27×23 mm. The patient was presented at an adrenal multidisciplinary team meeting and because adrenal cortical carcinoma (ACC) could not be ruled out, the patient underwent a laparoscopic adrenalectomy. Pathohistological findings were consistent with a hemorrhagic cavernous hemangioma of the left adrenal gland. The second case is a 71-year-old woman presenting with an incidentaloma of the right adrenal gland measuring 12 mm with radiological characteristics suspicious of a pheochromocytoma (highly vascular tumor with non-contrast CT HU >20). The patient did not have clinical symptoms suggestive of pheochromocytoma, thus the diagnosis of silent pheochromocytoma was considered. The patient underwent a laparoscopic adrenalectomy with pathohistological findings consistent with a hemorrhagic cavernous hemangioma of the right adrenal gland. Adrenal cavernous hemangiomas are rare benign vascular tumors, and to the best of our knowledge, only 90 cases have been described. Due to the increase in abdominal imaging, the incidence of adrenal incidentalomas is on the rise, and cavernous hemangioms should be considered in the differential diagnosis of lipid-poor lesions. These cases highlight several points. Firstly, they demonstrate the importance of imaging phenotype. The CT reports of both cases described the lesions as heterogenous with high HU. This should raise the concern for potentially malignant lesions, metastatic lesions, or pheochromocytomas. Thus, surgical resection or close follow-up imaging should be considered despite tumor size and hormonal activity. Although these lesions are benign, the natural history is unknown because most cases have been operated. Even with close follow-up imaging, it is often difficult to rule out more sinister lesions. Thus, patients should be presented in multidisciplinary teams with a preference for surgical resection despite negative hormonal workup and size.

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EP121

JOINT3724

A rare case of silent metastatic pheochromocytoma with a breast metastasis

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Background
Pheochromocytomas are rare neuroendocrine tumors arising from chromaffin cells of adrenal medulla. Their clinical presentation is heterogeneous with various symptoms and signs related to catecholamine excess. Rarely, pheochromocytomas are biochemically and clinically silent. According to WHO 2022 all pheochromocytomas can potentially metastasize in non-chromaffin tissues. Common sites of metastasis are lymph nodes, bones, lungs and liver. Herein, we present a rare case of silent metastatic pheochromocytoma with metastasis to lungs and breast.

Case
A 46-year-old female was diagnosed with a 5 cm left adrenal incidentaloma, four years ago. Its imaging phenotype was indeterminate and endocrine work up revealed no hormone hypersecretion. The patient underwent left adrenalectomy, and the pathology examination indicated a 7 cm pheochromocytoma with intermediate risk stratification Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP score 4) and Pheochromocytoma of the Adrenal gland Scaled Score (PASS score 9). Postoperative reevaluation with I131-MIBG and 18F-FDG-PET/CT imaging were negative and the catecholamines levels were within normal levels. During the following years the patient remained asymptomatic and she underwent yearly testing with plasma or urine metanephrines/normetanephrines which remained negative. Four years post-surgery, a "suspicious" right breast lesion appeared on a screening mammogram, and the patient underwent surgical removal of the tumor. Pathology was positive for chromaffin tissue. At the same time, biochemical examination showed increased plasma 3-methoxytyramine levels (33.3 ng/l, normal range < 17), whereas the patient remained asymptomatic. 68Ga-Dotatoc and 18F-FDG-PET/CT imaging detected lung metastases, and a tyrosine kinase inhibitor (sunitinib) was initiated for further treatment. However, two months later, disease progression was noticed, and chemotherapy was recommended.
Conclusions
To our knowledge, there are only two reports in bibliography about pheochromocytomas with metastasis to the breast. In our case, the patient was asymptomatic and plasma metanephrines and normetanephrines levels were constantly normal. However, an increase of dopamine metabolite, 3-methoxytyramine, was observed at the time of metastasis. Dopamine has low affinity for a and β adrenergic receptors and this can explain why patients with dopamine-secreting pheochromocytomas are often asymptomatic.

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EP122

JOINT2147
"Adrenal incidentaloma complicated by adrenal crisis in a critically ill patient "- a case report
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Introduction
The main goals of evaluating an incidentally detected adrenal mass, termed adrenal incidentaloma (AI), are to characterize the lesion as benign or malignant based on imaging characteristics, and to determine its functionality based on hormone secretion. Non-contrast computed tomography(NCCT) scan is the intial investigation of choice. Washout percentages following intravenous contrast administration are useful in certain cases. A comprehensive endocrine assessment is crucial to rule out hormone secretion abnormalities (e.g. Pheochromocytoma, Cushing syndrome, Primary Hyperaldosteronism). Tumours smaller than 4 cm and with non-contrast attenuation values under 10 HU often do not require long-term follow-up. Management is tailored to clinical presentation and associated comorbidities.
Case Details
A 59-year-old male known case of uncontrolled type 2 diabetes and hypertension presented to the emergency department with a diabetic foot ulcer over right great toe, diffuse abdominal pain, and vomiting. After initial stabilization with iv fluids, empirical antibiotics and insulin for glycemic control, he was planned for surgical debridement. CECT Abdomen revealed cholelithiasis and a right adrenal adenoma. Further, during the hospital stay, the patient's condition deteriorated with sudden shortness of breath, drowsiness, and desaturation, necessitating intubation.

Table 1.

Hba1C	12.1
CBC	Hb-9,tc-24000, platelet-1.6 lakh
Na+	120mEq/L
K+	5.6mEq/l
Cortisol (AM)	1.04 ug/dl
ACTH	208 pg/ml
ECG	Sinus tachycardia
ECHO	Normal LV Function
Trop I	High
24 Hour urinary metanephrines	Normal
USG w/a-	Cholelithiasis
Urine C/s	Candida Albicans
Wound Pus c/s	Acinetobacter Baumanni
CECT Abdomen	Right Adrenal Adenoma (34 mm x 20 mm), baseline HU - 30
CT Adrenal Protocol	Adrenal Nodule (30x 20 mm), homogenous fluid with attenuation value of 14 HU, possibility of resolving adrenal hemorrhage
CT Pulmonary Angiogram	Normal
Renal Function Test / LFT	Normal

Suspecting pulmonary embolism, thromboprophylaxis with IV heparin was initiated, though a CT pulmonary angiogram ruled out embolism. Post-intubation, the patient developed hypotension for which he was placed on inotropes but still maintained low blood pressure. Keeping in mind the clinical profile, an adrenal CT protocol was performed, and it revealed adrenal hemorrhage. Hormonal evaluation confirmed an adrenal crisis. Steroid replacement therapy was started. His condition gradually improved and underwent successful toe amputation.
Conclusion
Although adrenal incidentalomas rarely present as adrenal crisis, critically ill patients—particularly those with infection, sepsis, or septic shock—may develop this life-threatening condition. Prompt clinical recognition and targeted hormonal evaluation are essential for the early diagnosis and treatment of adrenal crisis, which can be a potentially lethal but treatable complication in ICU settings.

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EP123

JOINT3756
A study on incidence and related characteristics of PPGLs in a well-defined population
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Phaeochromocytoma/paragangliomas (PPGLs) are relatively rare tumours and the health burden of such tumours is not very well known.
Aim
This population-based study aims to characterise all the phaeochromocytomas, paragangliomas and adrenal medullary hyperplasia diagnosed between 2010 and 2023 in Malta; looking into presentation, hormonal analysis, imaging characteristics and histology findings.
Results
29 patients were identified (22 phaeochromocytoma and 7 paragangliomas). 16 patients (55%) were males and age ranged from 21-81 years (median (IQR) 53.5 years (40-59.8)). The standardised incidence rate (SIR) was 0.35/100,000/year. The SIR for phaeochromocytoma was 0.27/100,000/year and that for paraganglioma was 0.09/100,000/year. Longest radiological tumour size ranged from 20-127mm (median (IQR) 51mm (33.5-65)). Median pre-contrast CT density was 34 Hounsfield units (IQR: 29.5-34.5). All patients except 2 underwent surgical resection of the tumours. The latter 2 patients presented late with metastasis and died soon after diagnosis. Genetic testing was done in the majority of patients and VHL, NF1 and SDHB mutations identified. 6 patients (20%) were found to have a malignant PPGL on follow up.
Conclusion
This study gives a detailed understanding of the epidemiology of PPGL in a very well-defined population. The significant rate of malignant disease emphasizes the need for long-term follow-up.

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EP124

JOINT1652
Addison's disease initially interpreted as sarcoidosis
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Background
Primary adrenal insufficiency (AI) is a rare and potentially life-threatening condition. The diagnosis can often be delayed for months. We describe a young man with a delayed diagnosis whose condition was initially suspected to be sarcoidosis. So far only four cases of elevated ACE levels as a primary finding in AI have been reported.
Case Report
A 23-year-old man was hospitalized urgently with severe salmonella enteritis in autumn 2022, presenting with total colitis, high fever, bloody stools, abdominal tenderness, and severe hyponatremia (124 mmol/l, normal range 137-145). He

was discharged in much better condition and returned to full-time work. Two months after discharge, he experienced fatigue. There were no more loose stools, and he was afebrile, but became weaker and weaker with periods of dizziness, acid reflux, epigastric pain, nausea, and some vomiting. He had a CT of the abdomen/pelvis and an abdominal ultrasound, both with normal findings. Gastroscopy revealed esophagitis grade A, and duodenal biopsies were negative for coeliac disease. After 10 months of declining general health and a weight loss of 30 kg, he was admitted to the Diagnostic Unit at our hospital due to concerns about malignant liver disease indicated by abnormal liver and bile values, ASAT 56 (15-45) and ALP 151 U/l (35-105). Blood pressure was 113/67 mmHg, pulse rate 115, sodium 135 mmol/l and potassium 4.6 mmol/l (normal range 3.6-5). The first notable finding was a hilar lymph node observed on a thoracal CT scan and an elevated ACE level of 111 U/l (18-65), which raised suspicion of sarcoidosis, and referral for bronchoscopy. The patient had no dyspnea or cough. Ferritin was elevated at 601 mg/l (30-400). Expanded blood tests confirmed primary AI with low cortisol levels at 15 nmol/l (133-537) and high ACTH levels at 362 pmol/l (1.5-14). Additional symptoms such as salt cravings, increased skin pigmentation, and muscle pain appeared. Treatment with mineralocorticoids and glucocorticoids was initiated. He improved quickly and gained 19 kg in less than four months. The bronchoscopy was cancelled, and after 3 months, the lymph node had diminished, and the ACE, liver and ferritin levels had normalized.
Conclusions
This is the fifth published case with debut of AI with high ACE without having sarcoidosis. The patient avoided an unnecessary pulmonary biopsy. Low cortisol levels in untreated AI can lead to increased inflammatory markers as ACE and ferritin.

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EP125

JOINT2674

Is adrenalectomy still required as a treatment in cushing disease?

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Introduction
Cushing disease is a very challenging endocrine disorder treated ideally by transsphenoidal surgery, with variable aggressiveness and resistance to medical treatment.
Case Report
A 44-year-old woman known with Cushing disease diagnosed 8 years ago with macroadenoma partially resected (2018) by transsphenoidal surgery (Ki67 10%), with significant tumor remnant, followed by stereotaxic radiotherapy -25Gy/5 sessions (2018). Due to bitemporal hemianopsia, a second surgery was unsuccessfully attempted (2019). In March 2020, the tumor relapse required Pasireotide 1.8 mg/day and cabergoline 1.5 mg/week increased at 8 mg/week with no biochemical or morphological response. In 2021 a partial left adrenalectomy was done. The patient presents typical symptoms of complicated Cushing's disease, including a generally altered state, a moon-shaped face, erythema and chin hirsutism. She has purple striae on the abdomen, skin and vascular fragility in the lower limbs, with multiple bruises and muscular weakness which made her unable to walk by herself. She has secondary hypertension, diabetes, secondary osteoporosis, hypercholesterolemia, gonadotropin deficiency, growth hormone deficiency, hypothyroidism under substitution therapy with Levothyroxinum. Due to local and systemic progression of the disease, she started Temozolomide with in 2022 with no results. Since 2022 she was enrolled on Relacorilant in GRACE clinical trial (CORT125134-455) with clinical response, until June 2024. Afterwards she was treated with Metyrapone 750 mg/day, followed by Ketoconazole 800mg/day without significant improvement. Last imaging showed bilateral macronodular adrenal hyperplasia. As a last therapy, right adrenalectomy was performed, considering the increased hormonal activity (ACTH 540.9 pg/mL, cortisol 48.67 µg/mL). Four days after surgery cortisol decreased to 36.5 mg/dl, and 2 weeks after the surgery, at 15.84 µg/mL. At the time of submission she is recovering from adrenal surgery.
Conclusion
This case highlights the multifactorial treatment of Cushing's disease and emphasizes the aggressiveness that this pathology can have, even after all available lines of treatment were used. Nevertheless, after the adrenalectomy, there was a noticeable improvement in biological markers. The surgery continues to represent a vital stage in the treatment journey.

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EP126

JOINT2254

Prevalence and evolution of diabetes in cushing's syndrome: a 31-year retrospective study

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Introduction
Cushing's syndrome (CS) is known to induce hyperglycemia, but the long-term prevalence and evolution of diabetes in CS remain poorly understood. This study aims to evaluate the prevalence and evolution of diabetes in CS patients over a 31-year period.
Methods
A retrospective analysis was conducted on 22 patients diagnosed with CS at the Endocrinology Department of Charles Nicolle Hospital. Data collected included demographics, clinical features, cortisol levels, and diabetes status at diagnosis, treatment initiation, and follow-up.
Results
The majority of patients (68%) presented with diabetes at the time of diagnosis, with 32% showing prediabetes. Following successful treatment and remission of hypercortisolism, 70% showed significant improvement in fasting blood glucose and HbA1c levels. Notably, there was a correlation between baseline cortisol levels and glycemic control, with higher cortisol levels associated with poorer control.
Discussion
These findings underscore the significant impact of hypercortisolism on glycemic control. The improvement in glucose metabolism after cortisol suppression further highlights the importance of managing Cushing's syndrome effectively to mitigate diabetes-related complications.
Conclusion
Cushing's syndrome has a substantial impact on the development and progression of diabetes. Remission of hypercortisolism leads to significant improvements in glycemic control, emphasizing the need for early diagnosis and targeted treatment to reduce diabetes burden in these patients.

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EP127

JOINT2276

Impact of cushing's syndrome treatment on glycemic control and diabetic complications

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Introduction
Cushing's syndrome (CS) is associated with a high risk of developing diabetes and related complications. This study assesses the impact of CS treatment on glycemic control and the development of diabetic complications.
Methods
A cohort of 22 CS patients was followed from diagnosis through treatment. Glycemic control (fasting blood glucose, HbA1c) was measured before and after treatment, and diabetic complications (retinopathy, neuropathy, nephropathy) were assessed.
Results
Post-treatment, significant improvements in fasting blood glucose (mean decrease of 23%) and HbA1c (mean decrease of 0.9%) were observed. Diabetic complications were present in 36% of patients at diagnosis but reduced to 15% post-treatment. These improvements were associated with a significant reduction in cortisol levels.
Discussion
The findings suggest that successful treatment of CS not only improves glycemic control but also reduces the risk of developing diabetic complications. The relationship between cortisol levels and glycemic control underscores the role of cortisol in the pathogenesis of diabetes in CS patients.

Conclusion
Treatment of Cushing's syndrome significantly improves both glycemic control and diabetic complications. Early and effective management of cortisol excess is essential to prevent or mitigate these complications.

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EP128

JOINT2300

Factors influencing persistence of diabetes after cushing's syndrome remission

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Introduction
While remission of Cushing's syndrome (CS) generally leads to improved glycemic control, some patients continue to experience persistent diabetes. Identifying factors influencing this persistence is crucial for optimizing long-term metabolic management.
Methods
A cohort of **22 patients**in remission from CS was assessed for glycemic outcomes. Patients were classified into two groups based on the persistence of diabetes post-remission. Several factors were analyzed, including **age, BMI, disease duration, baseline cortisol levels, and pre-remission insulin dependence**. Glycemic parameters were compared before and after remission.
Results
Among the 22 patients, 10 (45.5%) had persistent diabetes post-remission. There were no significant differences in **age (persistent vs. non-persistent: 48.2 $\pm$ 10.4 vs. 45.7 $\pm$ 9.1 years, $P = 0.42$), BMI (29.6 $\pm$ 4.8 vs. 28.9 $\pm$ 4.2 kg/m^2, $P = 0.58$), or disease duration (5.7 $\pm$ 2.1 vs. 5.2 $\pm$ 1.9 years, $P = 0.61$).**However, baseline cortisol levels were significantly higher in patients with persistent diabetes (**522.3 $\pm$ 87.6 vs. 398.4 $\pm$ 74.1 nmol/l, $P = 0.02$**). Additionally, **pre-remission insulin therapy was more frequent in patients with persistent diabetes (70% vs. 30%, $P = 0.04$)**, suggesting a possible association with beta-cell dysfunction.
Discussion
The absence of correlation with traditional metabolic risk factors (age, BMI, disease duration) suggests that **hyperglycemia persistence post-CS remission is mainly driven by the severity of hypercortisolism at diagnosis and its impact on pancreatic function**. The significant association with higher baseline cortisol levels highlights the role of prolonged glucocorticoid exposure in **beta-cell dysfunction and insulin resistance**, potentially leading to irreversible metabolic changes. Patients requiring insulin before remission appear to be at higher risk, supporting the hypothesis of **pre-existing pancreatic damage exacerbated by chronic cortisol excess**. Further studies are needed to explore long-term glucose metabolism recovery and predictive markers for diabetes resolution.
Conclusion
Although remission of CS improves glucose metabolism, **persistent diabetes is associated with higher baseline cortisol levels and pre-remission insulin dependence, suggesting a potential irreversible impact on beta-cell function**. Long-term follow-up and early metabolic interventions may help improve outcomes in these patients.

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EP129

JOINT2321

Diabetes in cushing's syndrome: secondary or type 2 diabetes

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Introduction
Differentiating between secondary diabetes caused by Cushing's syndrome (CS) and preexisting type 2 diabetes (T2D) remains a clinical challenge. While cortisol excess is known to induce hyperglycemia, it is unclear whether diabetes in CS patients resolves entirely after remission or if some patients continue to exhibit features of T2D. This study investigates the nature of diabetes in patients following CS treatment.
Methods
A cohort of **22 patients diagnosed with CS**was followed after treatment to assess glycemic outcomes. Patients were classified based on their **diabetes status at baseline (diabetic vs. non-diabetic)**, and post-treatment evaluations included **fasting blood glucose (FBG), glycated hemoglobin (HbA1c), homeostatic model assessment of insulin resistance (HOMA-IR), and beta-cell function (HOMA-B)**. Statistical analyses were performed to compare pre- and post-treatment glycemic parameters.
Results
Following remission, the majority of patients experienced **significant improvements in glycemic control**, with a **23% reduction in fasting blood glucose ($P = 0.001$) and a 0.9% decrease in HbA1c ($P = 0.008$)**. Among the **10 patients diagnosed with diabetes before CS treatment**, six (60%) achieved normoglycemia post-remission, while four (40%) remained diabetic despite cortisol suppression. Patients with **persistent diabetes**exhibited metabolic features consistent with **type 2 diabetes**, including **higher baseline insulin resistance (HOMA-IR: 3.7 $\pm$ 0.8 vs. 2.1 $\pm$ 0.6, $P = 0.01$)**and **lower beta-cell function (HOMA-B: 52.4 $\pm$ 12.7 vs. 78.9 $\pm$ 15.3, $P = 0.03$)**compared to those who achieved normoglycemia. Furthermore, this group had significantly **higher baseline BMI (31.2 $\pm$ 3.8 vs. 27.6 $\pm$ 2.9 kg/m^2, $P = 0.02$)**and a greater prevalence of metabolic syndrome components. Interestingly, a subset of patients without prior diabetes ($n = 12$) developed **impaired glucose metabolism post-remission**.
Discussion
These findings highlight the **heterogeneous nature of diabetes in CS patients**. While hyperglycemia in some individuals appears to be directly driven by cortisol excess and resolves post-treatment, others exhibit metabolic profiles characteristic of **underlying type 2 diabetes**. Persistent diabetes in CS patients may be attributed to **preexisting insulin resistance, obesity, or irreversible pancreatic beta-cell dysfunction**, rather than secondary diabetes alone.
Conclusion
Although most patients experience an improvement in glycemic control following **Cushing's syndrome remission**, a subset remains diabetic, exhibiting features suggestive of **type 2 diabetes rather than pure secondary diabetes**. These results emphasize the need for **long-term metabolic monitoring**in CS patients, particularly those with risk factors for insulin resistance. Further studies are required to determine whether targeted interventions, such as weight management and insulin-sensitizing therapies, could improve long-term glycemic outcomes.

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EP130

JOINT3643

Rare association of primary hyperaldosteronism and cushing's syndrome: clinical, hormonal, and imaging insights from a case series

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Introduction
Hypertension is a major health condition, primarily classified as essential. However, secondary causes, particularly endocrine etiologies, should be considered in specific clinical contexts, such as resistant hypertension. Endocrine etiologies include hyperaldosteronism, Cushing syndrome, and pheochromocytoma among other causes. The association between primary hyperaldosteronism and Cushing's syndrome, though uncommon, represents a documented clinical entity. This case series aims to elucidate the clinical presentations, hormonal profiles, and imaging findings of patients diagnosed with this uncommon association.
Methods
We conducted a retrospective study about patients diagnosed with endocrine hypertension due to association of Cushing syndrome and primary hyperaldosteronism. Clinical data, laboratory findings and imaging results were analyzed.
Results
We present four cases of patients (three men and one woman) referred to our department for the evaluation of secondary hypertension. The average age of the patients was 47 years (28-68). In 75% of cases, hypertension was classified as grade 3, and all patients exhibited hypokalemia, with potassium levels as low as 2 mmol/l (2-3.4). Plasma metanephrine testing returned negative results in all cases. Hormonal assessments indicated primary hyperaldosteronism, with a mean aldosterone level of 644 pg/mL(502 - 1354) and a mean aldosterone-to-renin ratio of 300 (116 - 433). The diagnosis of Cushing's syndrome was confirmed in all patients through a low-dose dexamethasone suppression test, yielding a mean cortisol level of 25 µg/dL. Notably, Cushing's syndrome was found to be ACTH-dependent in two patients, with a ACTH level of 26 pg/mL and 23. Adrenal imaging revealed bilateral adrenal hyperplasia in one patient (ACTH independent), adrenal vein catheterization demonstrated lateralized secretion to the right adrenal gland. The Other patients presented with adrenal nodules; one patient had bilateral nodules. The mean size of these nodules was 17 mm.

Conclusion
The coexistence of Cushing's syndrome and primary hyperaldosteronism is rare. Both conditions are characterized by distinct pathophysiological mechanisms leading to increased blood pressure and electrolyte imbalances. Their simultaneous occurrence poses unique diagnostic and therapeutic challenges, underscoring the importance of a comprehensive evaluation when endocrine etiologies are suspected.

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EP131

JOINT3785

Overcoming the challenge: weaning corticosteroids in glucocorticoid-induced adrenal insufficiency

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High dose prednisolone is commonly used for many inflammatory conditions. A 70-year old woman was referred to the endocrine clinic with a history of long term steroid exposure for eosinophilic granulomatosis with polyangitis (EGPA) which she continued for over ten years. She subsequently commenced biologic treatment for eosinophilia but continued on steroid treatment. She was switched to thrice daily hydrocortisone and the minimum dose she could tolerate was 5 mg on waking, 5 mg at midday and 2.5 mg in the afternoon. She remained on this dose for several years. In May 2024 she was referred to our centre to switch to once daily, low dose prednisolone. Prior to switching her 8am cortisol and ACTH values were undetectable. Following the switch to once daily prednisolone, day curves were arranged to optimize her dose. Prednisolone 3mg/day produced an 8hour level of 30 μg/l (normal values 15 to 25 μg/l). We advised her to reduce to 2mg prednisolone once a day. The patient was keen to try and reduce her steroids, therefore she commenced a weaning protocol to 1mg daily and a prednisolone level on 1mg demonstrated this was a suppressive dose for this patient. A short synacthen test (SST) on 1 mg of prednisolone per day demonstrated showed the following results T = 0min cortisol < 28nmol/l ACTH < 5ng/l T = 30min cortisol 45nmol/l T = 60min cortisol 59nmol/l In order to go below 1mg of prednisolone she switched to an equivalent dose of hydrocortisone 7.5mg once a day which has a shorter half-life. A hydrocortisone day curve confirmed that she was a slow metabolizer of hydrocortisone SST was repeated in on 5mg; T = 0min cortisol 111nmol/l, ACTH 45.6ng/l T = 30min cortisol 120nmol/l T = 60 min cortisol 125nmol/l She continues to wean from 5mg day to 2.5mg according to the protocol below and we aim to wean her off steroids completely. Individualised care for patients on long term steroids wishing to wean is paramount to success. Supporting patients to wean off steroids negates risks such as osteoporosis and diabetes caused by long term steroid use. These results suggest that conventional hydrocortisone replacement in doses as low as 7.5mg/5mg/2.5mg can cause persistent HPA axis suppression. There is a need for prospective studies to evaluate weaning protocols.

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EP132

JOINT161

Asymptomatic giant cystic pheochromocytoma, a misleading entity: a case report

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Introduction
Pheochromocytoma is a rare neuroendocrine tumor. It was a tumor arising from adrenomedullary chromaffin cells that commonly produce one or more catecholamines. They produce and secrete catecholamine. Cystic pheochromocytoma is a rare entity and mostly asymptomatic. Considering the rarity and difficulty to differentiate from simple cysts in the absence of classic clinical symptoms, we present a huge cystic pheochromocytoma.
Case Report
This is a 63-year-old patient with no previous history of the disease, who presented with a cystic phoechromocytoma revealed by low back pain, which prompted an abdominal CT scan showing a 15 cm cystic left surrenal mass, confirmed biologically by a methoxylated derivative assay that was 7 times normal. The patient did not present with Menard's triad or hypertension. She underwent laparoscopic unilateral adrenalectomy after medical preparation. The evolution was marked by the negativation of the biological work-up post-operatively and the anatomopathological examination confirmed the diagnosis.
Discussion
Cystic pheochromocytoma is a rare entity and it may be due to intralesional hemorrhage, necrosis and liquefaction. Patients with cystic pheochromocytomas are usually asymptomatic. Hormonal analysis is generally negative. the main clinical signs are represented by the non-specific triad of low back pain, digestive problems and lumbar mass. These cystic forms of pheochromocytoma pose a real problem of differential diagnosis. The differential diagnosis is made with haemorrhagic lesions, cystic lymphangiomas, adenomas, metastases, vascular tumours of the adrenal gland, hydatid cysts and other cystic masses in the vicinity. The radiological study of the adrenal gland is based on CT. The typical radiological characteristics of pheochromocytoma are a round or oval mass, well-circumscribed, homogeneous or heterogeneous measuring > 4 cm, increased attenuation on unimproved enhancement, significant vascularization of the mass. However, the CT characteristics of cystic pheochromocytomas would be a relatively thick wall, the presence or absence of septa in the mass and persistent enhancement of the wall after the administration of contrast media. On the other hand,123I-MIBG scintigraphy has a higher diagnostic specificity. 18F-FDG positron emission tomography/CT can also allow the successful visualization of pheochromocytomas. Preoperative management is essential to prevent hemodynamic instability during the intraoperative or postoperative period. The treatment of cystic pheochromocy tomas is based on surgery.
Conclusion
Measurement of methoxylated derivatives in the urine should therefore be systematically requested in the presence of any adrenal mass.
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EP133

JOINT1600

Clinical audit of outpatient short synacthen test utilisation and outcomes in a tertiary care cohort

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Background
The short Synacthen test (SST), also known as the ACTH (cosyntropin) stimulation test, is widely used to assess adrenal function. Its utilization and performance, however, is not universally standardized. The Department of Endocrinology at Singapore General Hospital has a dedicated outpatient SST service for evaluation and follow-up of patients with suspected or confirmed adrenal insufficiency.
Objective
This study aims to evaluate the utilization patterns and outcomes of SSTs performed at an endocrine unit in a tertiary hospital.
Methods
A retrospective audit of SST data is conducted for patients tested between 8 August 2024 and 7 January 2025. The choice of low-dose 1 mg SST (LD-SST) or standard-dose 250 mg SST (SD-SST) is based on the ordering endocrinologist's clinical discretion. In general, LD-SST is typically preferred for patients with suspected central adrenal insufficiency, while SD-SST is performed for all other indications. A peak stimulated cortisol of $\geq$ 500 nmol/l is considered as an adequate adrenal response.
Results
One hundred and seventy-eight SSTs were performed during the study period. All tests were completed successfully. The majority (n = 120, 67%) were LD-SSTs, and the remaining (n = 58, 33%) being SD-SSTs. Adequate adrenal responses were observed in 56% (n = 67) of LD-SSTs and 64% (n = 37) of SD-SSTs. All except 2 patients listed for LD- SST had known or suspected hypothalamic/pituitary diseases (n = 118, 98%), including pituitary macroadenoma (n = 65), pituitary microadenoma (n = 20), suprasellar meningioma (n = 4), Rathke cleft cyst (n = 4), empty sella syndrome (n = 3), clival chordoma (n = 2), lymphocytic hypophysitis (n = 1), prior cranial irradiation (n = 7), biochemical abnormalities resembling central hypothyroidism (n = 10) and central AVP deficiency (n = 1). The most common indication for standard-dose SST was for the diagnosis or follow-up of adrenal insufficiency in patients receiving exogenous glucocorticoids (n = 32, 55%). The remaining patients had clinical presentations suggestive of adrenal insufficiency (n = 18), hypothalamic/pituitary diseases (n = 4), suspected congenital adrenal hyperplasia (n = 3) and possible autoimmune polyglandular syndrome (n = 1). There were no immediate complications or adverse events following all SSTs.

Conclusion
SST is a useful and relatively easy-to-perform dynamic endocrine test in the evaluation of adrenal function. Most cases were evaluated in the context of possible central adrenal insufficiency due to hypothalamic/pituitary pathology. The high demand for outpatient SST highlights its importance in clinical practice.

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EP134

JOINT345

Primary hyperaldosteronism: diagnostic approach (endocrine-radiological)

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Introduction
Primary hyperaldosteronism (PAH) causes secondary arterial hypertension. It requires high clinical suspicion and a hormonal study to confirm hypersecretion. To start an adequate treatment after confirming the diagnosis, it is necessary to demonstrate whether the hormonal hypersecretion is unilateral (surgical treatment) or bilateral (pharmacological treatment).
Objectives
In our Hospital we have endocrinology, interventional radiology and surgery specialized in adrenal pathology to evaluate complex hyperaldosteronism cases and agree on the best diagnostic-therapeutic approach. We collect our experience in adrenal venous catheterization, the gold standard for the study of PAH.
Material and Methods
Retrospective observational study carried out at the Málaga Regional University Hospital on outpatients who underwent adrenal vein catheterization over a period of 8 years (2016-2024). We collected clinical variables, laboratory tests, imaging tests and treatment.
Results
Nine subjects were included, 66.6% women, mean age 53 (35-67) years. Most of them had hypertension, hypokalemia or incidentaloma. All of them had elevated aldosterone/renin ratio. In 5 patients the confirmatory test was captopril test and in 2 patients a saline overload test was performed (as a first test or second test in case of inconclusive captopril test) and in 3 cases no confirmatory test was performed. All of them had S/C adrenal Tc: left nodule (66.6%), right nodule (22.2%) and bilateral nodule (11.1%). To clarify the case, MRI was performed in 4 patients (2 adenomas, 1 non-adenoma criteria and another without nodules) and scintigraphy in 8 cases, most without uptake and 1 discordant (in the 3 confirmed PAHs the gamma coincided with CT in 1 case). Adrenal venous catheterization confirmed lateralization in 3 patients (2 left and 1 right) coinciding with CT findings, 1 without lateralization and 5 inconclusive/valid due to not having correctly catheterized the right adrenal vein or due to taking spironolactone. Surgical treatment (unilateral adrenalectomy) was performed in 2 of the 3 cases confirmed with catheterization. In the third PAH confirmed by catheterization, surgery was not performed due to splenorenal shunt seen on CT. 6 patients receive medical treatment with good control of BP levels.
Conclusions
Catheterization is a fundamental technique for the study and treatment of PAH. It helps with hormonal studies and imaging tests, allowing for greater precision, performing adrenalectomy in cases with clear hyperaldosteronism secondary to unilateral secretion. We need a multidisciplinary team with endocrinologists, surgeons and interventional radiology with experience in performing it.

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EP135

JOINT906

Implications of new diagnosis of adrenal insufficiency on class 1 commercial pilot licence

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Case History
We present a case of a 46-year-old female, who has past medical history of Graves disease, treated with radioiodine in 2020 and rendered hypothyroid, on a stable dose of levothyroxine 100 mg daily. She works as a commercial airline pilot holding Class 1 licence. Four years later, she presented with lethargy, dizziness and reduced exercise tolerance. Mentstrual periods were regular. She had postural hypotension and investigations revealed low 9 am cortisol of 67 nmol/l, elevated ACTH of 124 ng/l (normal <50), Renin level of 88 mU/l (normal 5.4-30) and positive adrenal antibodies. Synacthen test confirmed adrenal insufficiency. Remaining of pituitary profile was normal. She was diagnosed with primary adrenal insufficiency (Addisons disease) and her symptoms resolved after initiation of hydrocortisone and fludrocortisone. She is aware of sick day rules and has been issued an emergency steroid pack. She is deemed unfit to fly by the Civil Aviation Authority (CAA) and is currently awaiting an appointment with Occupational health and the Aviation Medical Examiner to discuss next steps.
Discussion
Both the UK Civil Aviation Authority and the European Aviation Safety Agency regard commercial pilots with Addisons disease by default as unfit to fly. A licence may be issued, valid only in multipilot operations, and provided pilots carry with them the necessary cortisone replacement and are trained to use it. The Federal Aviation Administration does not set out any specific rules and decides on a case-by-case scenario. It is also worth noting the challenges pilots with Addisons face. They need to carry their emergency hydrocortisone injection kit and an adequate supply of their medications during their working days, in case of flight delays or cancellations. Furthermore, they may need additional doses of hydrocortisone replacement when travelling across time zones. Finally, pilots will have less access to urgent medical treatment should they develop an adrenal crisis, and their co-workers will need appropriate education. For all those reasons, a careful occupational health assessment needs to be undertaken. This case highlights the impact a diagnosis of adrenal insufficiency can have on various aspects of a person's life. Its professional implications are often less well recognised and addressed, especially when compared to other endocrinology disorders such as diabetes.

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EP136

JOINT1089

Adrenal tumor in a child with salt-wasting 21-hydroxylase deficiency congenital adrenal hyperplasia

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Background
Congenital adrenal hyperplasia (CAH) has been associated with adrenal tumors (ATs). International guidelines recommend against routine adrenal imaging in adult with CAH.
Objective
To report a case of 6.4-year-old boy with salt-wasting 21-hydroxylase deficiency congenital adrenal hyperplasia (CAH 21OHD SW) complicated with adrenal tumor.
Methods
Case study.
Result
A 6.4-year-old boy of non-consanguineous Chinese parents with CAH 21OHD SW went to our clinic for a regular endocrinological follow-up. 17OHP was 125ng/ml in newborn screening. At the age of 4 weeks, he was diagnosed with CAH 21OHD SW confirmed by genetic analysis and treated with oral hydrocortisone and fludrocortisone. His CAH was being adequately managed with normal linear growth and skeletal maturation with properly adherent to therapy. The adrenal ultrasound did not show abnormalities 5.5 months ago. On physical examination, height 116cm, weight 20kg, BP 90/60mmHg. Slightly increased skin pigmentation was noted, normal male prepubertal external genitalia was observed. Laboratory tests showed FSH 0.7 IU/l, LH 0.12 IU/l, E2 <10 pg/ml, T <0.13 ng/ml, P 0.5 ng/ml. Serum 17OHP 11.54 ng/ml, A4$<$ 1.05nmol/l, Renin 8AM (supine) 12.4 UIu/mL. Normal serum AFP, ferritin and 24h urine VMA were normal with slightly elevated NSE 22.06 ng/ml. Ultrasound showed a right adrenal soft-tissue mass measuring 4.3×3.2cm. CT scan demonstrated a right adrenal soft-tissue mass measuring 3.9×3.1cm. The mass was between the right adrenal gland and the anterior part of the upper pole of the right kidney, with a clear boundary, small punctate calcification. A few patchy enhancement shadows supplied by a small branch of the abdominal aorta in the enhanced scan. The upper edge of the mass is not clearly demarcated from the lower edge of the lateral limb of the right adrenal gland. Though the mass was non-functional according to the laboratory, we decided manage the patient surgically due to the mass rapidly growth. During the open surgical approach, it was found that the right AT was hard and elastic with a clear boundary measuring 5*5*3cm. A pathology report indicated ganglioneuroma. He was followed up in our clinic at regular intervals, and was last seen about 2 years postoperatively without clinical evidence of recurrence.
Conclusion
This paper firstly reports a 6.4-year-old boy with CAH 21OHD complicated with adrenal ganglioneuroma. This benign tumor rarely occurring in CAH patients. It is recommended that imaging monitoring of ATs be an important issue of CAH management.

Key words
Congenital adrenal hyperplasia, Adrenal tumor, Monitoring.
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EP137

JOINT3574

Outcomes of bilateral adrenalectomy in patients with severe and persistent cushing's disease: a case series

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Introduction
Cushing's disease, characterized by hypercortisolism due to ACTH-secreting pituitary adenoma, requires accurate diagnosis and effective management to optimize patients' outcomes. Transsphenoidal surgery is the first-line treatment, but persistent or recurrent disease may need alternative therapies. Bilateral adrenalectomy is effective in controlling hypercortisolism. However, it carries the risk of corticotrophin tumor progression or Nelson's syndrome, necessitating long-term monitoring.
Case Presentations
We present three cases of Cushing's disease in male patients who underwent bilateral adrenalectomy after unsuccessful transsphenoidal surgeries with persistent hypercortisolism and severe comorbidities. **Case 1:**A 51-year-old male was diagnosed with Cushing's disease at the age of 44, initially presenting with hypogonadotropic hypogonadism attributed to a 7 mm pituitary microadenoma. Bilateral adrenalectomy was performed because of the disabling impact of the disease with severe hypertension, stroke, coronary artery disease, proximal muscle weakness, and worsening of preexisting diabetes. Postoperatively, the patient's comorbidities improved, ACTH levels remained elevated at 1544 pg/mL under 30 mg/day of hydrocortisone and MRI showed 3 mm microadenoma. **Case 2: The diagnosis in a** 37-year-old male was revealed by bilateral aseptic osteonecrosis of the femoral heads. The patient underwent two transsphenoidal surgeries for two different pituitary adenomas, but remission was not achieved. Persistent hypercortisolism led to disabling complications, including osteoporosis and a suspicious left adrenal mass. Afet bilateral adrenalectomy, ACTH levels were markedly elevated at 1692 pg/mL under 20 mg/day of hydrocortisone. MRI at 5 years, revealed a 3 mm pituitary microadenoma. **Case 3:**A 37-year-old male was diagnosed at the age of 20 by a 7 mm right-sided ACTH-secreting pituitary microadenoma. Over the years, the patient developed prediabetes, osteoporosis, and grade 2 hypertension. Despite undergoing two pituitary surgeries, Cushing's disease persisted. Postoperative pituitary imaging was normal, but adrenal imaging revealed four bilateral adrenal nodules ranging from 8 to 25 mm. Due to the disabling nature of the disease and the presence of adrenal nodules, bilateral adrenalectomy was performed. Postoperatively, ACTH levels were elevated at 405 pg/mL under 30 mg/day of hydrocortisone, but follow-up pituitary MRI showed no abnormalities.
Conclusion
Bilateral adrenalectomy is an effective treatment for refractory Cushing's disease, particularly in cases where transsphenoidal surgery fails to achieve remission. However, elevated ACTH levels and the potential for corticotrophin tumor progression underscore the importance of long-term monitoring with serial pituitary imaging and biochemical assessments. Early detection of tumor progression allows for timely intervention with surgery, radiotherapy, or medical therapy, optimizing patient outcomes.

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EP138

JOINT2057

Adrenal schwannoma: a case report

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Introduction
Schwannomas are tumors of the Schwann sheath of peripheral or cranial nerves. Visceral schwannomas are rare, accounting for 1 to 10 percent of all primary retroperitoneal tumors, and only a few cases of adrenal schwannomas have been reported.
Case report
A 23-year-old female patient consulted for abdominal pain, progressing in a context of weight loss of 12 kg over two months. Abdominopelvic CT scan suggested a right suprarenal retroperitoneal mass, seemingly originating from the adrenal gland, measuring 48×61 mm. It was well-defined, with a spontaneous density of 55 HU, heterogeneous, and contained calcifications. Biological tests ruled out pheochromocytoma, Conn's adenoma, and cortisol-producing adenoma. A right adrenalectomy was performed without complications, revealing a benign schwannoma (spindle cell proliferation, PS100 expression).
Discussion/Conclusion
Schwannomas are often asymptomatic and incidentally discovered during imaging for an unrelated condition, as observed in our case. Radiological diagnosis is challenging. However, imaging typically shows a solid tumor with calcifications, a cystic component, and a well-defined capsule, allowing localization and assessment of its retroperitoneal positioning. Definitive diagnosis is confirmed by histological analysis of the surgical specimen (presence of Schwann cells, positivity for S-100).

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EP139

JOINT2451

Silent pheochromocytoma: an insidious surgical finding

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Introduction
Silent pheochromocytomas constitute a rare and heterogeneous clinical entity. These tumors are characterized by the absence of signs and symptoms of catecholamine excess and normal plasma and/or urinary metanephrines. We present three cases of silent pheochromocytomas.
Case 1
A 45-year-old female was referred for evaluation of a right adrenal incidentaloma detected on abdominal ultrasound. Subsequent imaging revealed a heterogeneous 2.9 cm mass with increased density (40 HU) on CT, and a slight loss of signal intensity in out-of-phase MRI images. Clinical and laboratory evaluations were normal; the patient was normotensive, and testing for cortisol, aldosterone, and urinary metanephrines was negative. The patient underwent uneventful laparoscopic adrenalectomy without preoperative α-adrenergic receptor blockade. Histology confirmed a pheochromocytoma with a potential biologically aggressive behavior (PASS = 4).
Case 2
A 68-year-old male with hypertension and diabetes was diagnosed during COVID-19 workup with a large right adrenal incidentaloma and a lesion with irregular borders in the left kidney. On CT, the adrenal mass measured 3.6 cm, had a high density (~30 HU), and showed no signal loss in out-of-phase MRI images. The 4.9 cm kidney lesion appeared heterogeneous. Clinical examination was unremarkable, while hormonal testing excluded hypersecretion of cortisol, aldosterone, or catecholamines. A PET-CT scan confirmed both lesions' hypermetabolic nature. After multidisciplinary team discussion, the patient underwent resection of the kidney mass, followed by right adrenalectomy. No prior α-blockade was prescribed. Hemodynamic instability occurred during adrenalectomy. Histology revealed a clear-cell renal carcinoma and a pheochromocytoma with aggressive biological behavior (PASS = 9).
Case 3
A 64-year-old female with hypertension, prediabetes, and a history of surgical excision of a parathyroid adenoma was diagnosed with a 3 cm left adrenal incidentaloma upon work-up of an incident urinary track infection. Imaging suggested a non-benign lesion (high attenuation values and heterogeneity). Clinical examination was unremarkable except for paroxysmal hypertension over the previous four months. Hormonal evaluation (1 mg dexamethasone suppression test, plasma renin activity, serum aldosterone, and urinary metanephrines) was negative. ^{123}I-MIBG scintigraphy was suggestive of pheochromocytoma, and the patient was scheduled for left adrenalectomy with preoperative α-adrenergic receptor blockade. Histology confirmed the diagnosis of pheochromocytoma.
Conclusion
Despite negative biochemical testing, silent pheochromocytomas may retain some functionality. A personalized approach in terms of preoperative α-adrenergic blockade is warranted.

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EP140

JOINT2466

Ganglioneuroma in a patient with primary adrenal insufficiency: a case report

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Background
Adrenal ganglioneuroma is a rare, benign tumor originating from neural crest cells. It is usually asymptomatic and incidentally detected during imaging studies. The coexistence of adrenal ganglioneuroma with primary adrenal insufficiency (PAI) is exceptionally rare, with only one prior case reported in the literature. This case emphasizes the diagnostic challenges and management strategies in patients presenting with concurrent endocrine disorders.
Case Presentation
A 17-year-old male with a history of PAI and Hashimoto's thyroiditis was referred to our Department during the transition from pediatric to adult endocrine care. At age 14, he presented with fatigue, malaise, nausea, and skin hyperpigmentation, leading to a diagnosis of PAI after confirmatory testing. Autoimmune adrenalitis was presumed based on the positive personal/family history of autoimmunity and he received hydrocortisone and levothyroxine replacement, without adrenal imaging. At the time of referral, the patient had normal physical, sexual (Tanner V) and cognitive development. However, also clinical signs of corticosteroid overreplacement, such as overweight (BMI = 31.7 kg/m^2) and wide, purple abdominal striae were present, along with symptoms of postural hypotension and salt craving. Consequently, hydrocortisone dose was decreased, and fludrocortisone was initiated. Basal hormonal workup was consistent with PAI (low morning cortisol, elevated plasma ACTH and renin). Elevated 17-hydroxyprogesterone (17-OHPRG, 8.49 ng/ml) and negative 21-hydroxylase antibodies testing, prompted further investigation. Adrenal CT scan revealed atrophic adrenal glands, and a 5.5 cm heterogeneous lesion proximal to the left adrenal gland with high attenuation (HU > 10). In MRI, the mass appeared slightly hypointense in T1 and hyperintense in T2-weighted images. Normal very long-chain fatty acid (VLCFA) levels excluded X-linked adrenoleukodystrophy. During ACTH stimulation testing, suboptimal cortisol response (8.41 mg/dl) and increased peak 17-OHPRG (11.2 ng/ml) levels were suggestive of congenital adrenal hyperplasia (CAH). However, family screening was negative and genetic screening is pending. The patient underwent laparoscopic left adrenalectomy. Histopathological and immunohistochemical analysis confirmed adrenal ganglioneuroma.
Conclusions
This case underscores the need for a multidisciplinary approach to adrenal masses in patients with autoimmune endocrinopathies. The coexistence of ganglioneuroma and PAI, although rare, necessitates histological confirmation for accurate diagnosis and individualized management, ultimately improving patient outcomes.

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EP141

JOINT3527

Acromegaly and high-grade heart blocks: a rare situation

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Introduction
Acromegaly is a rare hormonal disorder due to hypersecretion of growth hormone (GH) by a benign pituitary tumor. Cardiac damage is a constant feature of this rare disease and is the leading cause of death in acromegaly. The specific cardiac involvement of acromegaly is characterized by myocardial hypertrophy associated with diastolic dysfunction. A significant increase of Intraventricular conduction defects and arrhythmias has been described in acromegaly. However, high-grade atrioventricular blocks are less common.
Case Report
75 years old acromegalic male with a history of hypertension and dyslipidemia, ongoing obstructive sleep apnea and exertional chest tightness. He was admitted to the Otorhinolaryngology department to undergo tracheotomy for an upper airway obstruction. The pre-anesthesia evaluation found a Mobitz II Atrioventricular block. In view of the impact of the obstructive syndrome, a tracheotomy was performed, but a shift to severe bradycardia then a transient ventricular pause occurred. Cardiac auscultation revealed normal S1 and S2 without additional heart sounds. Electrocardiogram at admission showed a bradycardia at 47 bpm related to a 2/1 Mobitz II Atrioventricular block, a right bundle branch block with QRS duration at 138ms, a left anterior fascicular bloc and an isolated premature ventricular beat. Electrophysiological study revealed prolonged HV interval indicating the need for pacemaker implantation. The patient has been implanted with a dual-chamber pacemaker then discharged from hospital.
Discussion and Conclusion
Cardiac arrhythmias and sudden cardiac death are major contributors to increased mortality in acromegaly. Elevated beat-to-beat QT variability and late potentials correlate with ventricular tachyarrhythmias. Intraventricular conduction defects and arrhythmias are common, and while high-grade atrioventricular blocks are less frequent, prevalence varies (7–40%) due to study size, control group differences, monitoring techniques, and significant arrhythmia definitions. There is evidence of the impact of treatment of acromegaly on cardiac conduction tissue. Treatment with somatostatin analogs can reduce clinically significant arrhythmias in some cases by reducing heart rate, PVBs, and QT interval. Regarded for a long time as the primary contributors to mortality in individuals with acromegaly, recent evidence suggests that acromegalic patients experiencing cardiovascular complications now exhibit a mortality rate comparable to the general population. Interstitial fibrosis and cardiac hypertrophy associated with acromegaly could promote arrhythmias and conduction abnormalities of which high-grade heart block is an exceptional manifestation. Treatments of acromegaly reduce the incidence of cardiovascular complications and have a positive impact on rhythm disturbances.
Keywords
Acromegaly, Cardiomyopathy, Arhythmia, High-grade atrioventricular blocks, Somatostatin

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EP142

JOINT3322

Not your average cushing syndrome - a case with a series of unusual complications

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Cushing syndrome is characterized by specific clinical features and several complications, including diabetes mellitus, hypertension, infections, electrolyte imbalances and pro coagulant status. In these patients, cardiovascular risk and mortality rates remain high (~10%) despite surgical cure, mainly because of the associated complications. We report the case of a 53-year-old male, who was simultaneously diagnosed with type 2 diabetes mellitus and arterial hypertension two years ago. He was referred to our Clinic from the Oro-Maxillo-Facial Surgery department, where he was admitted for multiple dental abscesses. There, hypokalemia (2.3mmol/l) was detected, as well as maximum systolic blood pressure of 180mmHg despite treatment with 3 antihypertensive medications. Biologically, we note an HbA1c level of 8.1%, despite treatment with two oral antidiabetic medications and adherence to dietary recommendations. Endocrinological assessment identified classical features of Cushing syndrome (full moon facies, buffalo hump, proximal myopathy and truncal obesity). Hormonal evaluation confirmed ACTH independent Cushing syndrome (ACTH 9pg/mL, AM cortisol 25.1mg/dL, PM cortisol 24.8mg/dL, no inhibition after 1 and 8mg dexamethasone tests); and secondary hypogonadism and hypothyroidism. The abdominal CT scan identified a 4cm right adrenal adenoma, and the patient was scheduled for surgery one month later. During this time he developed jaundice and hepatic cytolysis (maximum liver enzyme levels – 386U/l, normal hepatic profile at diagnosis), for which toxic, infectious and immunological causes were excluded. During the same time frame, the patient developed plurimicrobial, bacterial cellulitis in both arms (Escherichia coli, Staphylococcus aureus), for which hospitalization and IV antibiotics were necessary, with favorable evolution. Following surgery, treatment with Prednisone was initiated, in gradually decreasing doses until ACTH stimulation test confirmed proper hypothalamic-pituitary-adrenal axis function, so treatment was stopped. Additionally, liver function tests normalized postoperatively, suggesting that liver injury was most likely caused by Cushing-related metabolic dysfunction; systolic blood pressure dropped to around 120-130mmHg, despite a reduction in treatment; and HbA1c levels dropped from 8.1% to 4.7%, so antidiabetic medications were stopped. In conclusion, Cushing syndrome can cause a series of complications which can delay surgical treatment. Our patient developed a series of unusual complications, including plurimicrobial bacterial cellulitis in both arms and metabolic-associated hepatic injury, with normalization of liver function tests after surgery. In conclusion, swift surgical intervention, close monitoring and a highly skilled interdisciplinary team is necessary for managing these patients and the various complications that can arise secondary to Cushing syndrome.

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EP143

JOINT2265

Glycemic control and cortisol levels in patients with cushing's syndrome

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Introduction
Cortisol excess in Cushing's syndrome (CS) is a well-established cause of insulin resistance and impaired glycemic control. This study investigates the correlation between cortisol levels and glycemic control in CS patients.
Methods
We included 22 patients diagnosed with CS, assessing their baseline cortisol levels, ACTH levels, fasting blood glucose, and HbA1c at diagnosis and after treatment.

Treatment aimed at normalizing cortisol levels was initiated, and glycemic control was reassessed post-treatment.
Results
A strong positive correlation was found between baseline cortisol and fasting blood glucose ($r=0.68$, $P<0.01$), as well as HbA1c ($r=0.72$, $P<0.01$). After treatment, patients who achieved cortisol suppression showed significant improvements in both fasting blood glucose (mean decrease of 23%) and HbA1c (mean decrease of 0.9%).
Discussion
This study confirms that cortisol excess significantly impairs glycemic control in CS patients. The correlation between cortisol levels and both fasting blood glucose and HbA1c suggests that controlling cortisol levels is a key strategy for managing diabetes in this population.
Conclusion
The findings highlight the importance of cortisol suppression in improving glycemic control in CS patients. Monitoring cortisol levels may provide valuable insights into the management of diabetes in this context.

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EP144

JOINT1513

Adrenal ganglioneuroma: a rare mass and diagnostic challenge

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Introduction
Adrenal ganglioneuroma (AG) is a rare tumor comprising less than 5% of all adrenal masses. Its morphological and radiological characteristics are nonspecific, which can complicate the diagnostic process. We report the case of an AG in a 16-year-old girl.
Case Report
A patient with no medical history was referred for evaluation of an adrenal mass. She reported paroxysmal lumbar pain over the past 4 years. Clinical examination was unremarkable, laboratory tests were notable only for iron deficiency anemia. Computed tomography revealed a right adrenal mass extending across the midline, measuring 83×39×64mm, with a density of 29HU and negative absolute and relative washout. Hormonal exploration indicated that the mass was non-functioning. Magnetic resonance imaging demonstrated close conncections with the inferior vena cava, the portal trunk, the aorta, and the liver. FDG-PET scan showed a mildly hypermetabolic adrenal mass with no other pathological uptake. The pathological study concluded an AG. The patient underwent surgical resection of the mass with a straightforward postoperative course.
Discussion and conclusion
Ganglioneuroma is a benign neuroblastic tumor, with adrenal localization accounting for approximately 21% of cases. The radiological characteristics are nonspecific and can be confused with adrenal cortical carcinoma and pheochromocytoma, thus contraindicating biopsy in this context. It is often sporadic, although associations with ROHHAD syndrome, MEN2A, and Turner syndrome have been reported. Management is based on surgical resection; AG is characterized by close vascular conncetions, which complicates its surgical approach. The prognosis after surgery is favorable, and no adjuvant treatment is required.

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EP145

JOINT742

Familial form of adrenoleukodystrophy with late diagnosis of chronic adrenal insufficiency (clinical case)

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Introduction
Adrenoleukodystrophy (ADL) is a rare genetic disease characterized by abnormal metabolism of very long-chain fatty acids due to mutations in the ABCD1 gene, which leads to their accumulation in the central and peripheral nervous system, adrenal cortex and gonads. The disease has a variable clinical spectrum and prognosis.
Results
Patient U., 41 y.o., with complaints of severe general weakness, dizziness, decreased blood pressure, dyspepsia, had chronic adrenal insufficiency for the first time. ADL was established at the age of 6 (family history: my brother has ADL with severe myeloneuropathy, my cousin has cerebral ADL). Since the age of 15, he had not received special treatment, he was constantly worried about weakness, and he added salt to his food. The deterioration of the condition, provoked by errors in the diet, was accompanied by vomiting, hypotension, and progressive weakness. Seeking medical help led to the diagnosis of pancreatitis and relief from infusion therapy during the day. The condition worsened after a day - BMI - 16 kg/ m^2, skin with slight hyperpigmentation, muscles are hypotrophic, blood pressure 80-50 mm Hg. Facial hair is sparse. Laboratory data: hyponatremia (125.68 mmol/l), hyperkalemia (6.71 mmol/l), daily cortisol profile (after administration of glucocorticoids for emergency indications) 185 - 107,8 - 64,1 nmol/l (79-536 nmol/l), ACTH from 01/15/2025: at 8.00 - 1312 pg/ml (7.2 - 63.3 pg/ml), testosterone -2.4 nmol/l (8.64 – 29 nmol/l) with an increase in LH and FSH levels. The diagnosis: primary adrenal insufficiency, hopogonadism on the background of adrenoleukodystrophy with minimal manifestations of myodoneuropathy. Parenteral glucocorticoid therapy was initiated from 300 mg/day with infusion therapy with dose reduction and transfer to oral (hydrocortisone 20 mg /day in the morning, fludrocortisone 0.1 mg in the afternoon). The patient's condition improved, weakness was relieved, blood pressure was 110/70 mmHg, hyperpigmentation decreased, and electrolyte levels returned to normal.
Conclusion
In addition to neurological symptoms, ADL is accompanied by the development of adrenal insufficiency and hypogonadism, which can develop at any age.

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EP146

JOINT1581

A challenging diagnosis in a patient with primary adrenal insufficiency

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X-linked adrenoleukodystrophy (X-ALD) is a rare, genetically determined metabolic disease with strong clinical heterogeneity. It affects approximately 1/20,000 Caucasian men. Adrenomyeloneuropathy (AMN) is a variant type of X-ALD that usually occurs in adult males and primarily affects the spinal cord, often presenting as progressive spastic paralysis. We present the case of a 43-year-old man, with no family history, diagnosed in adolescence with primary adrenal insufficiency and treated with Prednisone for a relatively short duration of time (six years). Years later, he was presented to the emergency room with nausea and intractable vomiting. Upon examination, his blood pressure was 90/54 mmHg, heart rate 100 beats/min, weight 40 kg, height 165 cm. He had dry mucous membranes and hyperpigmented skin. The neurological examination was unremarkable. Cardiopulmonary examination showed no abnormalities; the abdomen was without alterations; the meningeal tests were negative. Further testing revealed hyponatremia 130 mM/l (135-145), hyperkalemia 5.6 mM/l (3.6-5.5), while routine blood tests for liver function, kidney function, lipids, blood glucose, CRP, urine, and stool routine tests demonstrated no significant abnormalities. Normal thyroid function, baseline cortisol 12 µg/dl (5-25), baseline adrenocorticotropin >2.000 pg/ml (7.2–63.4), renin >630 µUI/ml (2.8-39.9), total testosterone was 2.6 nM/l (4.16-35.36), luteinizing hormone 24.9 UI/l (2.6-6.8), follicle-stimulating hormone 9.79 UI/l (1.5-19.4). After the diagnosis of primary adrenal insufficiency, he started treatment with corticosteroids and mineralocorticoids. Three months later, he presented with rapid, severe neurological deterioration, including apathy, dysarthria, spastic paraplegia, extensive muscle atrophy, urinary, and fecal incontinence. A brain MRI scan revealed active demyelination, high bilateral symmetrical signal intensity of the white matter in T2 and Flair within the corpus callosum, corticospinal tracts at the level of the brainstem, and middle cerebellar peduncles. Spectrographic recordings showed neuronal destruction. No cervical medullary atrophy on MRI imaging of the cervical cord. Additional laboratory findings: Hepatitis B, syphilis, Borelli, and HIV tests were all negative. The determination of very long-chain fatty acids showed a high level in serum. Molecular analysis of the ABCD1 gene reported hemizygous missense pathogenic mutation c.1252C>T, p.(Arg418Trp). After the diagnosis of AMN, he continued with supplementation for his adrenal insufficiency, developed sepsis two months later due to a urinary infection, and died due to complications. This case underscores the importance of considering AMN in patients with primary adrenal insufficiency, particularly when there is neurological decline. Early identification in such cases could facilitate timely interventions that may prevent or delay disease progression.

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EP147

JOINT2589

Case of spontaneous adrenal tumour infarction resembling pheochromocytoma

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Case report

We present a case report supplemented with imaging, laboratory, and histopathological diagnostic documentation, and a review of the literature. A 50-year-old man was admitted to the Department of Endocrinology with a suspected pheochromocytoma.

History

The patient had a previously diagnosed left adrenal tumor, 4 cm in diameter, described on high-density CT. Prior to admission, he had been in the Department of Surgery for abdominal pain suggestive of renal colic accompanied by symptoms of a hypertensive crisis. An abdominal CT scan was performed, which showed a left adrenal lesion with dimensions of 5×4.5×6 cm and a density of 50 H.U. There was no evidence of hyperintense blood signal. In laboratory tests, myocardial necrosis markers and inflammatory parameters were elevated. Blood pressure was found to be elevated, ranging from 200/150 to 150/180 mmHg. Hypotensive medication was administered, and improvement was achieved after 8 days. Due to the suspicion of pheochromocytoma, a 24-hour urine collection for methoxycatecholamines was performed, which showed significantly elevated levels. Based on the ESE/ENSAT 2023 algorithm, the Multidisciplinary Team qualified the patient for excision due to a lesion diameter > 4 cm and high density on CT. Subsequently, repeat diagnostic tests were performed, and methoxycatecholamine levels in both blood and the 24-hour urine collection were within normal limits. In order to prepare the patient for surgery, treatment was modified to include an alpha-blocker. Laparoscopic resection of the periadrenal lesion was performed. Histopathological examination revealed a 3.5 cm tumor – 99% of the tumor was necrotic - surrounded by a fibrous capsule, and a fragment of normal adrenal gland with cells of the three-layered cortex was also visible.

Conclusion

The patient most likely experienced infarction or bleeding into the adrenal tumor, with abdominal pain interpreted as a symptom of renal colic. Symptoms such as hypertension, elevated myocardial necrosis markers, and increased inflammatory parameters may indicate ongoing necrosis. Literature and cases of tumor necrosis were also reviewed. There are cases of tumors such as fibroadenoma of the breast, myoma of the uterus, Warthin's tumor of the salivary gland, and even lymphoma that undergo "self-destruction" via a necrosis mechanism.

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EP148

JOINT3960

Prepubertal gynecomastia in a boy with classic 21-hydroxylase deficiency

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We report a case of a 4-year-old patient with salt wasting congenital adrenal hyperplasia who developed prepubertal gynecomastia as a symptom of insufficient substitutive therapy. The patient was treated since the 6th day of life with hydrocortisone (HC) and fludrocortisone (FC). At the age of 4years the dose of HC was 10mg/square m. Laboratory tests confirmed elevated levels of adrenocorticotropic hormone (ACTH), androstenedione and 17-hydroxyprogesterone (17-OHP), and 24-hours urine collection also revealed not enough suppression of androgens and 17-OHP metabolites. Following an increase in hydrocortisone dosage, the gynecomastia completely regressed during 3 months. In the described case, TART and other estrogen-secreting tumors were considered in the differential diagnosis, but the complete resolution of gynecomastia after increasing the dose of hydrocortisone indicates that the cause was insufficient replacement. Gynecomastia as a dominant symptom of insufficient replacement therapy in congenital adrenal hyperplasia in a boy is rarely described, and premature pubarche is much more frequently observed. A probable explanation may be the increased aromatization of adrenal androgens to estrogens in prepubertal patients.

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EP149

JOINT2552

Adrenal imaging pitfalls: a case of a giant renal liposarcoma mimicking an adrenal tumor

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Introduction

Liposarcomas are rare malignant tumors arising from adipose tissue, with the kidney being an exceptional site of origin. Due to their large size and mass effect, renal liposarcomas can mimic adrenal tumors, leading to diagnostic confusion, especially when the adrenal gland is not clearly visualized. This case highlights the challenges of adrenal imaging and the importance of histopathological confirmation in ambiguous cases.

Observation

A 64-year-old male, with no prior medical history, was referred for the evaluation of a 17 cm adrenal mass, incidentally discovered on an abdominal CT scan performed due to unexplained weight loss (17% in one month) and pelvic pain. MRI revealed a large, solid-cystic right renal mass (18.6 × 14.8 cm in axial diameter, 21.5 cm in height), with heterogeneous peripheral enhancement, multiple cystic areas, and intermediate T2 signal intensity. The mass displaced the right kidney downward, while the right adrenal gland was not visualized, raising strong suspicion of an adrenal origin. There was no vascular invasion, but the mass displaced the inferior vena cava and right renal vein. A mild right pleural effusion was also noted. Upon referral to endocrinology, the patient exhibited no signs of hypercortisolism or hypercatabolism. He had abdominal asymmetry, normal skin examination, and erectile dysfunction without gynecomastia or loss of libido. Biochemical exams showed normal plasma metanephrines, and a 1 mg dexamethasone suppression test ruled out hypercortisolism. Based on imaging and clinical findings, an adrenocortical carcinoma was strongly suspected, leading to surgical resection. However, histopathology unexpectedly revealed a high-grade dedifferentiated renal liposarcoma (FNCLCC grade 3), measuring 22 cm, with perirenal fat invasion but no vascular emboli, perineural invasion, or involvement of the renal hilum, ureter, or right adrenal gland.

Discussion and Conclusion

This case highlights the diagnostic challenges of large renal tumors and the potential pitfalls of adrenal imaging. Despite radiological findings highly suggestive of an adrenal malignancy, the true origin of the mass was renal, demonstrating how large renal tumors can compress or displace the adrenal gland, creating a misleading appearance. The absence of hormonal abnormalities, the lack of vascular invasion, and the atypical imaging characteristics should raise suspicion of non-adrenal neoplasms in similar cases. This case reinforces the importance of a multidisciplinary approach, careful interpretation of imaging findings, and the necessity of histopathological confirmation to avoid misdiagnosis.

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EP150

JOINT1244

Primary adrenal insufficiency due to recurrent episodes of unilateral adrenal infarction

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Introduction

Adrenal infarction is a rare cause of primary adrenal insufficiency that usually occurs in hypercoagulable states, resulting in life-threatening conditions. Most cases of adrenal infarction involve bilateral lesions complicated with adrenal insufficiency or a unilateral lesion without adrenal insufficiency. Cases of unilateral adrenal infarction resulting in adrenal insufficiency have been rarely reported. Herein, we present a case of recurrent episodes of unilateral adrenal infarction leading to adrenal insufficiency.

Case description

A 72-year-old woman with a history of myelodysplastic syndrome and cerebral infarction presented with sudden-onset left lumbago. The patient had taken lenalidomide for 13 months and cilostazol for thrombocytosis and prevention of cerebral infarction. Abdominal enhanced CT revealed a left swollen adrenal gland with a low-enhanced area and MRI showed a restricted diffusion of the ischemic adrenal gland, confirming the diagnosis as left adrenal infarction. The cosyntropin test revealed a peak cortisol level of 16.9 μg/dL, indicating normal adrenal function. Despite the cessation of lenalidomide, the 2nd episode of adrenal infarction developed on the right adrenal gland 3 months after the 1st episode of adrenal infarction. Plasma levels of adrenocorticotropic hormone, cortisol, and peak cortisol response to 250 μg of cosyntropin were 1996 pg/mL, 27.8 μg/dL, and 14.8 μg/dL, respectively, indicating primary adrenal insufficiency and the patient started to take 15 mg of hydrocortisone.

Conclusion

We present a case of recurrent unilateral adrenal infarction causing bilateral adrenal infarction and adrenal insufficiency. Unilateral adrenal insufficiency is rare but can

cause adrenal insufficiency when it repeatedly develops on the bilateral adrenal glands.

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EP151

JOINT2193

Addison's disease initially interpreted as sarcoidosis

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Background
Primary adrenal insufficiency (AI) is a rare and potentially life-threatening condition. The diagnosis can often be delayed for months. We describe a young man with a delayed diagnosis whose condition was initially suspected to be sarcoidosis. So far only four cases of elevated ACE levels as a primary finding in AI have been reported.
Case Report
A 23-year-old man was hospitalized urgently with severe salmonella enteritis in autumn 2022, presenting with total colitis, high fever, bloody stools, abdominal tenderness, and severe hyponatremia (124 mmol/l, normal range 137-145). He was discharged in much better condition and returned to full-time work. Two months after discharge, he experienced fatigue. There were no more loose stools, and he was afebrile, but became weaker and weaker with periods of dizziness, acid reflux, epigastric pain, nausea, and some vomiting. He had a CT of the abdomen/pelvis and an abdominal ultrasound, both with normal findings. Gastroscopy revealed esophagitis grade A, and duodenal biopsies were negative for coeliac disease. After 10 months of declining general health and a weight loss of 30 kg, he was admitted to the Diagnostic Unit at our hospital due to concerns about malignant liver disease indicated by abnormal liver and bile values, ASAT 56 (15-45) and ALP 151 U/l (35-105). Blood pressure was 113/67 mmHg, pulse rate 115, sodium 135 mmol/l and potassium 4.6 mmol/l (normal range 3.6-5). The first notable finding was a hilar lymph node observed on a thoracal CT scan and an elevated ACE level of 111 U/l (18-65), which raised suspicion of sarcoidosis, and referral for bronchoscopy. The patient had no dyspnea or cough. Ferritin was elevated at 601 mg/l (30-400). Expanded blood tests confirmed primary AI with low cortisol levels at 15 nmol/l (133-537) and high ACTH levels at 362 pmol/l (1.5-14). Additional symptoms such as salt cravings, increased skin pigmentation, and muscle pain appeared. Treatment with mineralocorticoids and glucocorticoids was initiated. He improved quickly and gained 19 kg in less than four months. The bronchoscopy was cancelled, and after 3 months, the lymph node had diminished, and the ACE, liver and ferritin levels had normalized.
Conclusions
This is the fifth published case with debut of AI with high ACE without having sarcoidosis. The patient avoided an unnecessary pulmonary biopsy. Low cortisol levels in untreated AI can lead to increased inflammatory markers as ACE and ferritin.

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EP152

JOINT2435

Elevated serum dehydroepiandrosterone sulfate in a young male without visible adrenal tumor

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Introduction
Dehydroepiandrosterone sulfate (DHEAS) levels typically increase during adrenarche, decreasing over time. Elevated DHEAS is also found in congenital adrenal hyperplasia and adrenal tumors.
Clinical Case
A 23-year-old male presented with a two-year history of left-sided painful gynecomastia. He denied any complaints of nipple discharge, decreased libido, abdominal pain, or fatigue. Over the previous 6 months, he had gained 7kg, attributing this to a resistance training regimen. He had no chronic medication and denied any previous/current anabolic steroids consumption, reporting only the use of over-the-counter creatine and Whey-protein supplements (since he started his gym routine). Pubertal development was normal. His medical history included childhood testicular trauma without lasting effects. He expressed no desire for children in the near future. Clinical examination revealed mild left retroareolar gynecomastia, normal blood pressure, and no cushingoid features. No abnormalities were found on testicular examination. Blood test revealed a normal gonadotrophic axis, with no thyroid disfunction and normal prolactine, 17-hydroxyprogesterone, and hCG serum levels, as well as normal renal and hepatic function. Two separate blood samples revealed elevated serum estradiol (first sample: 1.9 times the upper limit (TUL); second sample: 1.3 TUL) and DHEAS (first sample: 1.3 TUL; second sample: 1.6 TUL). Breast ultrasound confirmed gynecomastia without additional abnormalities. Adrenal CT did not reveal masses but suggested possible bilateral hyperplasia. A dexamethasone suppression test with 0.5mg every 6 hours for 48 hours effectively normalized DHEAS levels, with a 51% reduction from baseline.
Discussion
This is a challenging case concerning the patient's management and follow-up: is this elevated DHEAS a normal variant? Could it indicate a genetic defect in steroid sulfate transporter proteins, and if so, is it clinically relevant to perform a genetic test as it may impact his descendants? What approach should be taken for monitoring this patient, whether clinical, biochemical, or both?

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EP153

JOINT1011

When hormonal and oncologic pathologies collide: navigating management complexities of primary hyperaldosteronism with an incidental finding of renal cell carcinoma

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Introduction
Primary hyperaldosteronism (PHA), or Conn's syndrome, is a common yet underdiagnosed cause of hypertension, characterized by excessive aldosterone secretion. It is classically associated with hypertension and hypokalemia. PHA can result from unilateral or bilateral adrenal hyperplasia or aldosterone-producing adenomas. This case highlights the diagnostic and therapeutic challenges of PHA complicated by incidental renal cell carcinoma (RCC). The urgency of managing a potentially malignant renal mass may conflict with the need for precise localization of aldosterone hypersecretion through adrenal vein sampling (AVS).
Case Report
A patient with persistently low potassium levels was referred for endocrine evaluation due to uncontrolled hypertension despite being on three antihypertensive agents. Initial investigations revealed a significantly elevated aldosterone-to-renin ratio (ARR), strongly suggestive of primary hyperaldosteronism. Given the high pre-test probability, further confirmatory testing was deemed unnecessary. A CT scan of the adrenal glands identified an 11 mm left adrenal nodule, consistent with an adrenal adenoma, but also incidentally revealed a suspicious left renal mass, concerning renal cell carcinoma (RCC). This finding prompted an urgent referral to the Urology team, and the patient was subsequently reviewed by a specialized Renal Cancer Unit for multidisciplinary discussion. From an endocrine perspective, adrenal vein sampling (AVS) was recommended to confirm the source of aldosterone hypersecretion. However, this required a 6-week washout period from Spironolactone, which posed a significant delay. Given the urgency of addressing the renal mass, the Urology team advised proceeding with kidney surgery without delay for endocrine concerns. The complexities in management arise from the need to balance timely intervention for the renal mass with the diagnostic precision required for PHA. The adrenal gland will be preserved during kidney surgery to allow for future AVS if needed. Post-surgery, the patient will continue medical management of PHA, with the possibility of targeted treatments such as aldosterone synthase inhibitors in the future.
Conclusion
This case highlights the challenges of managing concurrent primary hyperaldosteronism and renal malignancy, particularly when diagnostic and treatment timelines conflict. Multidisciplinary collaboration between Endocrinology, Urology, and Oncology teams is essential to optimize outcomes.
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EP154

JOINT1854

Bilateral gynecomastia revealing adrenocorticaloma

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Adrenal cortical carcinoma is a rare malignant tumor of the adrenal cortex and represents 0.5-2% cases per million per year with peaks of occurrence in the first decade between 40 and 50 years of age. The main circumstances of discovery are hormonal hypersecretion in 40%-70% of cases and tumor syndrome in 40%-60% of cases. Hyperestrogenism is revealed in men by gynecomastia or a drop in libido with testicular involution. We report the case of a 57-year-old patient, with no particular history, admitted for treatment of a left adrenocortical tumor discovered by bilateral gynecomastia evolving for 6 months. The clinical examination reveals a patient in altered general condition (weight loss, profound asthenia, anorexia), bilateral gynecomastia present for 6 months, decreased libido and abdominal pain. There are no signs of hyperadrenocorticism or palpable abdominal mass. The hormonal assessment shows an increase in the precursors of adrenal androgens 17OHP, D4androstendione, SDHEA. Major hyperestrogenism is found and there is no biological hypercortisolism. Thoraco-abdomino-pelvic CT scan revealed a large left adrenal tumor mass with a malignant appearance suggestive of corticoadrenaloma with hepatic metastases invading the left renal vein and the infrahepatic IVC. A biopsy of the adrenal mass performed externally came back in favor of a left adrenocorticaloma with positive immunohistochemistry, synaptophysin and Melan A. The evolution in the hospital environment was noted by a hypercalcemia probably paraneoplastic, the initiation of bisphosphonates was deferred given the altered general condition of the patient who died following a state of hemorrhagic shock. Feminizing adrenocortical tumors or estrogen-secreting adrenal tumors are extremely rare. They are mainly observed in men and children in whom the main symptoms are breast enlargement. Their diagnosis is mainly based on the assessment of estrogens. A mixed secretion attested by the elevation of adrenal precursors and a large tumor argue in favor of malignancy. Treatment should be based on surgery associated with op'DDD or aromatase inhibitors with or without standard or targeted chemotherapy. The prognosis depends on the stage of the tumor at the time of diagnosis and the course of the disease, but in general the final prognosis is extremely poor, especially in adults in whom benign tumors are exceptional.

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EP155

JOINT3522

Plasma steroid profiling in early diagnosis of adrenocortical carcinoma

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Introduction
Early and accurate diagnosis of adrenocortical carcinoma (ACC) is essential for improving prognosis. Recent studies highlight the potential of plasma steroid profiling in diagnosing malignancy in adrenocortical tumors.
Objective
This study aimed to evaluate the diagnostic value of 11-deoxycortisol in identifying ACC.
Materials and Methods
Two patients with suspected ACC and one patient with suspected recurrent disease underwent clinical, biochemical and imaging evaluation in our tertiary care center. Serum steroids, including 11-deoxycortisol, were quantified using liquid chromatography-tandem mass spectrometry (LC-MS/MS).
Results
Two patients with large incidental adrenal masses showed significantly elevated levels of 11-deoxycortisol (1167 ng/dL and 1242.3 ng/dL, respectively, compared to the upper reference limit of 33 ng/dl). These levels correlated with tumor size. Both patients **presented with hyperandrogenism and cortisol secretion.** In the first case, 11-deoxycortisol level normalized following complete tumor resection, but in the second case the level remained elevated as the tumor was not amenable to radical resection. The third patient showed elevated 11-deoxycortisol level during follow-up (689 ng/dL), **allowing early detection of recurrence of a** clinically silent **tumor. Histopathological examination confirmed the presence of ACC in all cases.**
Conclusion
Our findings suggest that 11-deoxycortisol may serve as a valuable biomarker for the early diagnosis of ACC and for monitoring *potential* recurrence after surgery, **thereby improving patient outcomes.**

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EP156

JOINT1377

Non-neoplastic hypercortisolism state and adrenal incidentaloma: a clinical challenge?

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Introduction
The diagnosis of Cushing's syndrome (CS) can be challenging for endocrinologists due to its multifaceted presentation. Accurate differentiation between non-neoplastic hypercortisolism (NNH) states, formerly known as Pseudo-Cushing's syndrome (PCS), and true CS is crucial, as their treatment approaches and outcomes vary significantly.
Case Report
A 37-year-old female patient with a medical history of hypertension, Iron-deficiency anemia, and depression. Family history revealed a background of familial hypertension. The patient was admitted for the exploration of a 14mm hypodense left adrenal mass, with radiological features suggestive of adenoma. Clinical examination revealed grade II obesity (body mass index 38 kg/m^2) with an android phenotype, along with a moon face, supraclavicular and dorsocervical fat pads, and a buffalo hump. However, no other overt clinical features of Cushing syndrome were noted such as facial plethora, purple striae marks, or proximal myopathy. Blood pressure was well-controlled with calcium channel blockers. The patient had undergone investigations for secondary hypertension, excluding renal parenchymal disease, renal artery stenosis, coarctation of the aorta, obstructive sleep apnea, thyroid dysfunction and hyperparathyroidism. Laboratory studies were conducted to assess for adrenal hyperfunction. The aldosterone-to-renin ratio (ARR) and catecholamine excess were negative. However, midnight cortisol and urinary-free cortisol tests were elevated. An oral overnight 1mg dexamethasone suppression test (DST) was performed, which revealed appropriate suppression of serum cortisol to 10ng/ml, thus excluding the diagnosis of endogenous hypercortisolism.
Conclusion
Non-neoplastic hypercortisolism (NNH) states refers to various conditions responsible for mild-to-moderate hypercortisolism, resulting from overactivation of the hypothalamic-pituitary-adrenal axis. The main conditions implicated in NNH comprise: neuropsychiatric disorder, alcohol abuse, insulin-resistant obesity, polycystic ovary syndrome, and end-stage kidney disease. We concluded that the cortisol abnormalities in our patient were due to NNH state, caused by obesity and depression. The concomitant presence of a non-functioning adrenal adenoma further complicated the diagnosis in this case.

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EP157

JOINT1092

An incidental adrenal mass misleading to surgical intervention: a case of misleading imaging findings

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A 15-year-old female with a history of splenectomy following a road traffic accident complicated by intestinal obstruction and laparotomy at age of 8, was referred in 2024 for evaluation of left adrenal incidentaloma. The lesion has been discovered in abdominal CT scan performed to investigate recurrent urinary tract infection (UTIs). Up on her review in our clinic, she had no hypertension, hypokalemia and symptoms suggestive of pheochromocytoma or Cushing's syndrome. Her menarche started at age of 13 and has reported regular menstrual cycles with no hirsutism or acne. There was no personal or family history of endocrinopathies, HTN, or stroke in young. On physical examinations she was well-developed with no Cushingoid features or hyperandrogenism. Biochemical tests were normal including a cortisol suppression of 1.0 mg/dl with 1 mg dexamethasone suppression test and plasma metanephrine. Adrenal CT scan demonstrated a suspicious characteristic of a large (4.8 x 4.5 cm) well-defined left suprarenal homogenous lesion of (49 HU precontrast, 101 HU venous phase and 70 HU delayed) with absolute washout of 59.6% and indeterminate relative washout of 30.7%. For that, androgen levels were requested and came normal and has been referred to urology team for surgical intervention. The patient underwent laparoscopic adrenalectomy, which was converted to open surgery due to extensive adhesions from the previous abdominal surgery. Intra-operatively, the left adrenal gland appeared normal and a left peri-adrenal area mass was noted and excised. The histopathological examination of the excised tissue revealed unremarkable splenic tissue, with no evidence of malignancy.

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EP158

JOINT1628

Adreanal hystopatology in primary aldosteronism: single centre expiriance

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Introduction
Primary aldosteronism (PA) is the most frequent secondary hypertension, reaching about 5% of all hypertensive population. It is believed that two thirds of PA cases are caused by bilateral idiopathic hyperplasia (BIH) of adrenal cortex. Subjects with PA due to aldosterone-producing adenoma (APA) are diagnosed easier among hypertensive, mostly due to clinical picture of hypokalaemia.
The aim of this study was to analyse the type of histopathologic features in patients with primary aldosteronism treated in our Centre for Endocrine Surgery and compare to the finding in adrenal tumour operated due to hypercorticism.
Material and methods
Our study included 40 patients with primary aldosteronism (PA group) and one control group, of 20 patients with hypercorticism due to adrenocortical tumour, 10 with Cushing' syndrome (CS) and 10 with subclinical CS (SCS).
Results
There was no significant difference between groups related to the age ($P = 0.147$), nor sex distribution, although a higher number of women in all groups was recorded ($P = 0.099$). Systolic and diastolic blood pressures were significantly higher in PA group ($P = 0.005$ and $P = 0.002$ respectivaly), with the lowest levels in NFA+HT group. The significanteley higher mean arterial pressure (MAP) was also found in PA group ($P = 0.001$). The largest tumour size was measured in CS+SCS group, then in PA group ($P < 0.001$). All patients with PA had low serum potassium level. On light microscopy, aldosterone-producing adrenal cortical adenomas appear partially or completely encapsulated, with a compressed fibrous rim or fibrous "pseudocapsule" at the expansile borders of the tumor. The morphology of individual cells may be quite heterogeneous, with varying proportions of 4 different types of cells: clear cells resembling zona fasciculata cells, cells resembling ZG cells, compact cells indistinguishable from those of the zona reticularis, and a group of cells designatedas "hybrid" cells with cytologic features of both zona fasciculata and ZG cells.
Conclusion
We founded that the hybrid celles indipendetly or with ligt cells like zona fscicullata has been predominated in 60% cases with PA, most frequently then in the group SCS+CS.

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EP159

JOINT670

A rare case of vanishing bilateral adrenal masses

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Introduction
With advancements in imaging technology and its widespread use, adrenal incidentalomas have become a frequent finding. Most cases involve non-functional, irreversible adrenal enlargements. However, reports of reversible adrenal enlargements remain limited.
Case Report
We explored a 68-year-old man, with metabolic hyperferritinemia without HFE mutation and partial splenectomy, for bilateral adrenal masses suspect of malignancy. In July 2024, he had a fever and lost weight (4kgs). All infectious causes were excluded (PCR triplex (including SARS-CoV-2), tuberculosis, B/C hepatitis, HIV, tropical diseases) and an empiric antibiotic treatment was suspended after 7 days due to no improvement. After a two months fever, the PET scan (08/2024) showed one 35 mm intensely hypermetabolic left adrenal mass, 2 intensely hypermetabolic right adrenal masses (13 mm on the medial arm, 11 mm in the body) and three intensely hypermetabolic latero-aortic adenopathies. The abdominal scanner (10/2024) detailed basal density, absolute and relative wash out: left adrenal: 30 HU/36%/25%, 1st right adrenal lesion: 19 HU/82%/ 66% and 2nd lower right adrenal lesion: 25 HU/ 55%/41%. The hormonal work-up showed: normal basal ACTH (25.4 pg/ml) and cortisol values (303.9 nmol/l), an optimal response after Synacthene testing (peak at 502.3 nmol/l), correct cortisol after 1mg DST (<27.6 nmol/l), normal midnight serum cortisol (114.7 nmol/l), and free urinary cortisol/24h (28.7 mg/24h), normal serum and urinary metanephrines and normetanephrines, normal Chromogranin A, normal testosterone but a low DHEA-S [0.8 umol/l – (6.2-7.7 umol/l)] and normal 17-OH-progesterone. A surgical excision of the left adrenal mass was preferred to an adrenal biopsy or lymph node biopsy. However, the pre-surgical PET scan (11/2024) showed almost complete regression of the adrenal masses, with only a persistent diffuse and moderately hypermetabolic thickening of the left adrenal, a non-fixing right adrenal and almost complete regression of the latero-aortic adenopathies. The surgery was canceled. We retained an etiological doubt. Adrenal hemorrhage was unsuspected with first images, but an MRI performed in 11/2024 showed a few hypovascular left adrenal nodules, compatible with adrenal hematomas. SARS-CoV-2 infection may cause bilateral adrenal masses compatible with the onset of the febrile episode. Adrenal lymphomas are associated with splenomegaly (impossible to evaluate in our patient), adrenal failure and abnormal hemogram (absent) and no spontaneous regression. An adrenal biopsy will be performed if the suspicion remains high during the follow-up.

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EP160

JOINT688

A case of sheehan syndrome presenting with acute coronary syndrome: a case report

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Sheehan's syndrome is a form of post-partum complication where pituitary gland necrosis occurs as a result of sudden large volume blood loss during or after delivery. In this case report, index patient presented with chest pain, easy fatigability and dyspnea. The patient was managed as a case of acute coronary syndrome with positive troponin I. On the 3rd day of hospitalization, no clinical improvement noted warranting further work up and deeper review of history and physical examination. Suspicions for the involvement of pituitary gland was include when upon review of history, the patient presented with complains of amenorrhea, agalactorrhea, sparse thin hair and persistent hypotension. Serum cortisol, low thyroid hormones, hypoglycemia and pituitary magnetic resonance imaging were obtained supporting the diagnosis of Sheehan's syndrome with acute coronary syndrome.

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EP161

JOINT3437

Cushing's disease in a patient presenting for oculomotor palsy-a diagnostic and management conundrum

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Background
Oculomotor palsy is an infrequent presentation in Pitnet patients, due to pituitary apoplexy or tumour compression, with other causes being exceedingly rare. We present a case of Cushing's disease (CD) which associated a vascular cause of oculomotor palsy.
Aim
To describe the diagnosis and management challenges due to concomitant pituitary and parasellar disease.
Case presentation
A 66-year-old woman presented to the ER in Dec 2024 for recent onset unilateral right eye blindness and ophthalmoplegia. A CT scan demonstrated bilateral cavernous sinus masses with intense contrast uptake and she was referred to our endocrine department, following neurosurgical consultation. On examination there was complete right sided ophtalmoplegia and blindness, and pre-existing right hemiplegia from an ischemic stroke (2012). The history was not suggestive of pituitary apoplexy. No obvious signs of endocrine disease were noted. Prolactinemia was minimally elevated (25.3 ng/ml) and there was no pituitary insufficiency. Baseline cortisolemia was 809,65 nmol/l and ACTH=48.81 pg/ml. 11PM cortisol was high and unsuppressed by 1mg overnight dexamethasone (744 nmol/l) and LDDST (670,3 nmol/l), suggesting an invasive corticotropinoma. Contrast-enhanced

head MRI demonstrated bilateral cystic parasellar masses highly suggestive of intracavernous carotid aneurysms. The pituitary appeared compressed between the cavernous sinuses and presented a T1-hypointense micronodule. Pituitary MDT recommended cerebral angiography with the aim of flow-diverter treatment of aneurysms (pending). We initiated ketoconazole treatment, well-tolerated at 400 mg/day.
Conclusion
The differential diagnosis of compressive parasellar masses includes other lesions besides PitNet. Our patient presented bilateral intracavernous carotid aneurysms and CD, mimicking an invasive corticotropinoma. Aneurysm treatment is prioritary. When pituitary surgery is not feasible, as in this case, medical treatment is necessary for hypercortisolism. Pituitary surgery and radiotherapy remain therapeutic options following carotid aneurysm endovascular repair.

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EP162

JOINT831

Ectopic secretion of ACTH: diagnosis and management a case report

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Introduction
Cushing's syndrome (CS) is the set of symptoms associated with hypercorticism, the ectopic origin of ACTH, is more expressive and can be caused by a variety of tumours. We report this case in order to highlight this special features.
Case report
33 year old female with frank clinical and biological AXTH dependent cushing's syndrome, with normal pituitary MRI and adrenal CT scan. An octreoscan was performed, showing a thyroid and lymphonodal lesions suggesting ectopic secretion of ACTH. We proposed symptomatic treatment with ketoconazole followed by appropriate surgical management, with a good improvement after surgery.
Discussion
Ectopic ACTH secretion is a rare cause of hypercorticism, and octreoscann is a major diagnostic tool. Surgery combined with symptomatic treatment represents the essence of treatment.
Conclusion
ACTH-dependent cushing's syndrome with ectopic secretion remains a very rare entity that can be difficult to diagnose and manage.

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EP163

JOINT53

Late diagnosis of classic simple virilizing congenital adrenal hyperplasia in a young female

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Introduction
The approach to amenorrhoea, hirsutism and virilisation in a young female is an important though uncommonly encountered scenario in general Endocrinology. We present a case of a 28-year-old patient who presented with secondary amenorrhoea, hirsutism and virilisation, and was subsequently diagnosed with congenital adrenal hyperplasia (CAH), likely secondary to 21-hydroxylase deficiency (classic simple virilising type).
Case Presentation and Management
Our patient is a 28-year-old Chinese lady referred to Endocrinology for secondary amenorrhoea. She had a history of epileptic seizures secondary to a right frontal cavernoma on long term carbamazepine. Other significant history included ambiguous genitalia in infancy requiring corrective surgery at 18 months, and hirsutism with excessive body hair growth starting in adolescence. She was also on long term hydrocortisone 10 mg nightly since childhood for hypocortisolism diagnosed during a hospital admission for fever and diarrhoea. There was no history of a salt wasting crisis in infancy or childhood. On examination, she exhibited significant hirsutism (Ferriman-Gallwey score 9), as well as signs of virilisation including voice deepening, temporal balding, acne on her face and chest, and increased muscle mass. Examination of her external genitalia revealed a normal labia majora and minora and genital orifices. There was some evidence of clitoromegaly, although this was confounded by post-surgical changes and scarring. There were no abdominal masses nor undescended gonads in the inguinal region. Investigations showed a high testosterone level within the male range with a markedly raised 17-hydroxyprogesterone level, confirming the diagnosis of CAH. Morning cortisol levels were low with elevated ACTH levels and lack of cosyntropin response, consistent with primary hypocortisolism. Aldosterone levels were adequate. Trans-abdominal pelvic ultrasound showed a normal sized uterus and ovaries. The patient was diagnosed with CAH likely secondary to 21-hydroxylase deficiency (classic simple virilising type). Our patient was started on oral dexamethasone at night, which was subsequently changed to oral prednisolone twice a day, resulting in significant improvement in hirsutism and acne, as well as return of menses. Special attention was given to her concurrent carbamazepine administration which would increase clearance of the administered glucocorticoids.
Discussion and Conclusion
The presentation of secondary amenorrhoea with virilisation in a young female is uncommon, with CAH being one of the possible causes. We will discuss the management of CAH (particularly with regard to steroid choice) and how it can be individualised to incorporate patient's preferences, desired goals for fertility and comorbidities.

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EP164

JOINT243

Pheochromocytoma: case report

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Pheochromocytomas are rare tumors located in the adrenal medulla, that derives from the chromaffin cells and produce catecholamines. It has an annual incidence of approximately 0.8 per 100,000 person-years. Sustained or paroxysmal hypertension (HT) is the most frequent sign of pheochromocytoma. Classically, pheochromocytoma manifests as spells with the following 4 characteristics: headaches, palpitations, diaphoresis and severe hypertension. Here we describe the case with classical presentations of pheochromocytoma.
Case presentation
A 41-year-old female, without known co-morbidities, presented with episodes of high blood pressure (BP) of 220/110mmHg, headache, palpitation, tremor and sweating during last 20 days. On physical examination, she had pale skin and no other change. Electrocardiogram showed sinus tachycardia, 140bpm, incomplete RBBB, (-T1) V1-V6. The troponin I level was 5.78pg/mL (N 0-20). Echocardiography was not significantly abnormal. Laboratory studies revealed an elevated urinary metanephrines secretion of 493 mg/24h (normal value under 312 mg/24h) and also an elevated urinary normetanephrine of 515 mg/24h (normal value under 445 mg/24h). An abdominal computed tomography (CT) scan was performed, and a 6 cm large tumor in the left adrenal gland was found in. There were no other significant changes. A diagnosis of pheochromocytoma was made. Treatment with alpha- and beta-adrenergic blockers were initiated to adequately normalize BP prior to surgery. After 10 days, the patient successfully underwent laparoscopic left adrenalectomy. Histopathological evaluations confirmed the diagnosis of pheochromocytoma. After surgery, the patient's medications were discontinued and BP and blood sugar were in a normal range. The patient was advised to do genetic testing and to return regularly for outpatient visits.
Conclusion
Pheochromocytoma responsible for less than 1% of patients presenting with hypertension. Although a rare condition, pheochromocytoma can be life-threatening, due to hypovolemia, catecholamine cardiomyopathy or respiratory disorder and should be considered as a differential diagnosis, especially in young patients presenting with unexplained hypertension, chest pain and cardiac dysfunction.

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EP165

JOINT2967

COVID-19 and Addison's disease

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COVID-19 virus has been found to attack the endocrine system. In particular, it has been shown to affect the thyroid gland. Cortisol secretion has also been shown to be affected by the SARS-CoV-2 virus. The aim was to describe the case of a patient who developed adrenal crisis due to an acute infection by the SARS-CoV-2 virus. A female patient aged 51 had hypotension and hypoglycemia for a period of about 6 months. She had also noticed hyperpigmentation of her skin and her oral mucosa. She developed an acute infection with fever and cough and was found to be positive for the COVID-19 virus. As the infection developed, she had nausea, hypotension, hypoglycemia and finally shock. Hydrocortisone was administered and the patient improved instantly. Adrenal insufficiency was diagnosed. An interferon-gamma release assay - Quantiferon - performed was negative ruling out tuberculosis. Anti-adrenal antibodies were positive. The patient was given hydrocortisone orally 30 mg daily in divided doses for the treatment of adrenal insufficiency. In conclusion, the case of a patient is described who had adrenal insufficiency of an autoimmune etiology and was diagnosed after acute infection from the SARS-CoV-2 virus which induced circulatory shock and an adrenal crisis. Hydrocortisone administration was followed by instant recovery and the patient was diagnosed with adrenal insufficiency and was treated accordingly.

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EP166

JOINT3905

Revealing adrenal tumors as a primary cause of secondary high blood pressure

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Introduction
Adrenal masses include a range of pathologies, with benign forms being more common than malignant ones. These masses are sometimes discovered in patients with paroxysmal or resistant arterial hypertension and may represent a potentially treatable cause, accounting for 5 to 10% of secondary elevated blood pressure cases.
Objective
This study aims to highlight the clinical, biological, and morphological characteristics of adrenal tumors diagnosed in patients with elevated blood pressure.
Patients and Methods
Retrospective, descriptive, and analytical study including 46 patients hospitalized for the management of adrenal masses in the Department of Endocrinology, Diabetology, Metabolic Diseases, and Nutrition at CHU Ibn Rochd in Casablanca, over a 5-year period (2019-2024). Statistical analysis was performed using Excel.
Results
The study involved 46 patients with a sex ratio of 0.77. The average age was 45 years. The average duration of high blood pressure was 7 years, with 34% of patients on triple therapy, 36% on dual therapy, and 30% on monotherapy. Blood pressure was only controlled in 21% of cases. Tumors identified included pheochromocytomas in 30% of cases, adrenal adenomas in 22%, and other types of tumors in 48%. Computed tomography (CT) was performed in 32 patients, and MRI in 14, revealing adrenal tumors with an average size of 41 mm. Surgical management was carried out in 40 patients, with tumor resection, and adrenalectomy was performed in 6 patients. The outcome showed remission in 71% of patients, the other 29% having desecalated from triple therapy to bi-tharpy in 18% and monotherapy in 11% of cases.
Conclusion
Adrenal masses are a diverse group, often underdiagnosed, yet they play a significant role in the potential remission of elevated blood pressure

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EP167

JOINT1909

Partial 21-hydroxylase deficiency in a 7-year-old: a rare cause of precocious puberty

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Background
A 7-year-old girl was referred for advanced growth (+2 SD), obesity (+3 SD), hirsutism (Ferriman-Gallwey score: 10), and precocious puberty.
Case Presentation
Initial investigations ruled out Cushing syndrome with a normal dexamethasone suppression test. Hormonal evaluation revealed an intermediate 17-hydroxyprogesterone (17-OHP) level (8 ng/mL), and the Synacthen stimulation test confirmed partial 21-hydroxylase deficiency with a rise in 17-OHP to 15 ng/mL. Hyperandrogenism was confirmed with elevated delta-4 androstenedione and testosterone levels. Adrenal insufficiency was excluded.
Management and Outcome
Hydrocortisone therapy (10 mg/m^2/day) was initiated, leading to rapid improvement in hyperandrogenism and stabilization of growth velocity.
Conclusion
This case highlights the importance of considering partial 21-hydroxylase deficiency in children presenting with hyperandrogenism and precocious puberty. Early diagnosis and glucocorticoid therapy ensure favorable outcomes and prevent complications.

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EP168

JOINT2033

Vagal paraganglioma: a diagnostic surprise

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Introduction
The vagal paraganglioma (VP) arises from paraganglionic tissue located along the vagus nerve. This neoplasm represents less than 5% of all head and neck paragangliomas. Advances in imaging have aided the diagnosis and assessment of this disease.
Aim
To study clinical presentation, radiological features and therapeutic management of vagal paraganglioma through a case report and review of literature.
Observation
A 66-year-old patient with a history of total thyroidectomy followed by iratherapy for papillary thyroid carcinoma consulted for a 2cm high laterocervical swelling in the left IIA sector, mobile and firm. The rest of the ENT examination was without abnormalities. The cervical ultrasound suggested a lymph node recurrence of her thyroid carcinoma. The cervical CT scan showed a left subangulo-mandibular formation, oval, opposite the carotid glomus, heterogeneous, richly vascularized with an intense and heterogeneous PDC suggesting adenomegaly of suspicious appearance, given the clinical context. The patient underwent a cervicotomy. Intraoperatively, the mass was richly vascularized, adherent to the vagus nerve and located at the level of the left carotid bifurcation. A complete excision of the mass was performed with simple postoperative course. The final anatomopathological examination of the surgical specimen concluded that it was a vagal paraganglioma. No recurrence or metastasis was noted after a 2-year follow-up.
Conclusion
Vagal paraganglioma, although rare, should be part of the differential when faced with a hypervascular cervical mass to avoid intraoperative surprises.

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EP169

JOINT398

Hypertension secondary to primary hyperaldosteronism

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A 69-year-old male was referred to the Endocrinology clinic for evaluation of adrenal-origin hypertension. Despite being on optimized doses of four antihypertensive drugs, including two diuretics (amlodipine 10 mg, losartan 100 mg, chlorthalidone 50 mg, hydralazine 100 mg, and spironolactone 300 mg), his blood pressure remained poorly controlled. His history revealed resistant hypertension since age 32, raising suspicion of a secondary cause. In 2021,

clinical and cardiological evaluations were undertaken ahead of surgery for a left-sided cervical tumor, initially suspected to be a schwannoma with pheochromocytoma. During surgery, the tumor was identified as a benign fusocellular neoplasm affecting the vagus nerve. Despite this, his hypertension and hypokalemia persisted, prompting further investigation. Initial laboratory tests revealed elevated serum aldosterone levels (39.8 ng/dL), suppressed plasma renin activity (0.1 ng/mL/h), and recurring hypokalemia (ranging between 2.9–3.6 mEq/l). Two assessments of urinary metanephrines showed normal levels, renal function was preserved, and sleep apnea was excluded as a contributing factor. An MRI identified bilateral adrenal nodules, raising the suspicion of an endocrine etiology for his refractory hypertension. By 2023, his persistent hypertension and refractory hypokalemia prompted repeated evaluations, confirming elevated aldosterone levels, suppressed renin, and a high aldosterone-to-renin ratio. Imaging showed stable bilateral adrenal nodules, with the most notable being a 2.2 × 1.8 cm lesion in the left adrenal gland's posterior limb. Adrenal vein sampling revealed markedly increased aldosterone secretion from the left adrenal gland, confirming unilateral primary hyperaldosteronism. In April 2024, the patient underwent successful left adrenalectomy. Histological analysis confirmed a benign corticomedullary adenoma. Postoperatively, blood pressure monitoring in May 2024 demonstrated normalized systolic and diastolic readings throughout the day. Spironolactone was discontinued, and the patient maintained control with atenolol, losartan, and a reduced dose of amlodipine (5 mg). Three months later, all biochemical markers, including creatinine, aldosterone, potassium, and renin levels, were within normal limits. This case underscores the critical need to investigate secondary causes of hypertension, especially in patients with resistant or early-onset disease. Early diagnosis and appropriate treatment of primary hyperaldosteronism not only optimize blood pressure control but also correct electrolyte imbalances and significantly reduce long-term cardiovascular risks. A multidisciplinary approach remains essential for achieving the best outcomes.

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EP170

JOINT3962

A lesson for life!

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Introduction

The discovery of a suspicious pulmonary nodule with adrenal metastasis is a frequent occurrence in the context of a work-up for pulmonary neoplasia. Pathological evidence is usually provided by biopsy of the primary mass. Biopsy of the secondary lesion, particularly the adrenal lesion, is also a second alternative in the event of failure or inaccessibility of the primary lung tumour. We report the case of a patient whose biopsy of the adrenal mass revealed a pheochromocytoma without any complications.

Observation

The patient was 63 years old and smoked 20 packs a year. He complained of a cough that had been treated as acute bronchitis. Physical examination was unremarkable. There was no biological inflammatory syndrome. A chest X-ray was performed when the clinical symptoms persisted. It revealed a pulmonary nodule projecting from the right pulmonary hemichamber. A chest CT scan was performed to better characterise the nodule. We found a lobulated pulmonary nodule with a 12*6mm long axis. The patient also presented with a left adrenal lesion of 10 mm whose enhancement kinetics were consistent with malignancy and in particular a secondary lesion. A pet-scan showed fixation of the 2 lesions with an SUV of 3 and 2.6 respectively. A CT-guided biopsy of the pulmonary nodule concluded that there was chronic and acute pulmonary inflammation. The decision taken at the multidisciplinary consultation meeting was to biopsy the adrenal mass. Metanephrine assay was not requested. The biopsy was performed without incident. Pathological examination revealed a pheochromocytoma. The patient underwent wedge surgery for his pulmonary nodule and left adrenalectomy.

Conclusion

The originality of our case lies in the fact that this patient, who was not hypertensive, underwent a biopsy of an adrenal mass to obtain anatomopathological proof of his bronchopulmonary cancer, which was carried out without incident. Pathology revealed a pheochromocytoma for which the biopsy should have been contra-indicated. It was a non-secreting pheochromocytoma. The lesson to be learnt is that adrenal nodules, regardless of their size or the context of suspected pulmonary neoplasia, even in the absence of known hypertension, should not be manipulated before assessing metanephrine levels.

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EP171

JOINT1440

Diagnosis and management of recurrent ipsilateral pheochromocytoma due to medium sized adrenal tumor with renal vascular invasion

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Introduction

Pheochromocytoma, a relatively rare (<0.05%), catecholamine-secreting tumor, is almost always lethal unless recognized and appropriately treated. Clinical and biochemical manifestations are mainly caused by excess circulating catecholamines and hypertension. Sustained or paroxysmal hypertension associated with headaches, sweating, or palpitations, occurs in 95% of patients, but at least 5% are normotensive. All patients with manifestations should be investigated for pheochromocytoma. Plasma free metanephrines and fractionated urinary metanephrines are the most sensitive (≅100%) chemical tests for diagnosing sporadic and familial pheochromocytomas. For suspected metastatic disease use of 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/CT scanning is recommended. 2 Surgical resection is successful in 90% of cases. Pheochromocytomas <5 cm in diameter can be removed laparoscopically; larger tumors should be removed by open surgery. Drug treatment prior to and during surgery is mandatory.

Care Report

54 y/o male patient was hospitalized in our clinic due to hypertensive crises. Upon investigation recurrent pheochromocytoma was suspected and was recommended to repeat laboratory tests, including urinary and plasma metanephrines and normetanephrines, which revealed significantly elevated values and patient was advised to perform 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/CT. Further MRI imaging revealed nonhomogenous, hypovascular adrenal tumor of about 5-6 cm with suspected left renal artery and vein invasion. Imaging tests demonstrated recurrent disease. Patient was referred to a high volume adrenal surgeon. Laparoscopic adrenalectomy and ipsilateral nephrectomy was performed in short time with patient's perioperative management by a multidisciplinary team approach. During a follow up visit 1 week after surgery patient doesn't complain of increased blood pressure or palpitations, has no need of antihypertensive medications. Patient is advised to perform genetic testing to exclude familial pheochromocytoma. Follow up laboratory tests of metanephrines and normetanephrines are planned 4 weeks after surgery.

Conclusion

Pheochromocytomas are rare, mostly benign catecholamine-producing tumors of chromaffin cells of the adrenal medulla or of a paraganglion. If remaining unrecognized or untreated, they can be a life-threatening condition. Therefore, the most important message of this case report is to stress the importance of patient education about the diagnosis and follow up visits with the specialist. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K, Young WF Jr; Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline

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Bone and Mineral Metabolism

EP172

JOINT689

Phosphate as the earliest marker of metabolic bone disease of prematurity

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Objectives

Metabolic bone disease of prematurity (MBDP) is characterized by skeletal undermineralization. The risk of MBPD increases significantly in infants born before completing 28 weeks of gestation or those with extremely low birth weight (ELBW; <1,000 g). The most common biochemical changes in MBDP include hypophosphatemia and hyperphosphatasemia. Serum phosphate levels tend to decrease earlier than the elevation of serum alkaline phosphatase (ALP). In this study, we aimed to investigate the optimal screening time and cutoff values of phosphate for MBDP screening.

Methods

We conducted a retrospective study of medical records from premature infants hospitalized in the neonatal intensive care unit (NICU) at Korea University Ansan Hospital between 2020 and 2023. Infants with gestational age <32 weeks or birth

weight <1,500 g were included. Those who died or had incomplete data were excluded. MBDP was defined as a serum ALP level >900 U/l and serum phosphate below 5.5 mg/dl within the first 3–5 weeks of life. We evaluated serum calcium, phosphate, and ALP that measured every week, along with wrist radiographs at 6 weeks of age.
Results
A total of 95 infants were included in this study. Of these, 23 (24.2%) met the MBDP criteria. The prevalence rate of MBDP was 57.7% (15/26) in ELBW infants. The MBDP group had a significantly lower mean gestational age [26.8±2.2 weeks vs. 29.7±2.2 weeks, $P<0.001$] and lower mean birth weight [885.5±269.2 g vs. 1296.6±314.9 g, $P<0.001$]. The duration of TPN, establish of full feeds, caffeine use, and steroid use were longer in MBDP group: 30 (21-48) vs. 15.5 (10-23.5) days, 34 (21-51) vs. 15.5 (11-26) days, 74.0±26.9 vs. 40.0±27.2 days, and 10 (0-13) vs. 0 (0-0) days, respectively ($P<0.001$). Infants with MBDP had significantly higher serum ALP levels at 2 weeks [741.09±48.18 U/l vs. 516.26±27.23 U/l, $P<0.001$], and lower serum phosphate levels at 1 week [3.38±0.30 mg/dl vs. 4.07±0.17 mg/dl, $P<0.001$]. The optimal phosphate cutoff at 1 week was 3.85 mg/dl, with 70% sensitivity and 53% specificity. Wrist X-rays at 6 weeks revealed signs of rickets in 16 (69.6%) infants with MBDP, compared to 13 (18.1%) infants without MBDP ($P<0.001$).
Conclusion
Decreased serum phosphate levels in the first week of life were associated with an increased risk of developing MBDP. Since phosphate levels decline earlier than ALP levels rise, meticulous monitoring of infants with low phosphate levels in the first week of life is necessary for early detection and intervention.

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EP173

JOINT87

Double trouble: when combination therapy does more harm than good

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Introduction
Osteoporosis management is often tailored to the specific risk of the patient. Treatment classes include anti-resorptive medications versus anabolic agents. Theoretically, synergistic activity would provide greater efficacy than monotherapy, yet this has not been studied in detail.
Objectives
The purpose of this study is to assess the effectiveness of combination therapy with both bisphosphonates and teriparatide compared to sole therapy with bisphosphonates in relation to pathological fractures and bone mineral density.
Methods
A retrospective study was performed with TriNetX Global Collaborative Network, accessing de-identified data from 143 healthcare organizations. Cohorts A was defined based on the diagnosis of osteoporosis and receiving treatment with both a bisphosphonate and teriparatide ($n = 16,308$), and cohort B was defined based on the presence of osteoporosis and receiving treatment with a bisphosphonate alone ($n=548,405$). All genders were analyzed, and no age-limit was included. An observation period was defined as 1 day after the index event, ending 5 years after. Cohorts were balanced with propensity score matching, with $n = 16,754$ per cohort. Cohorts were balanced for age at index, race, tobacco use, systemic corticosteroid therapy, body mass index, alcohol abuse, calcium and vitamin D supplementation, diagnosis of vitamin D deficiency, family history of osteoporosis, prior history of fractures, and baseline Z-score of the lumbar spine and hip. Key outcomes assessed included pathologic fractures at the hip, vertebrae and unspecified sites, and bone mineral density (Z-score) at both the hip and lumbar spine.
Results
The average age at index was 69.3 +/- 11.3 years, with 73.3% white and 85% female. Data demonstrated there was a greater risk for pathologic fracture (site unspecified) with combination therapy over monotherapy (Relative Risk 3.734, 95% CI: 2.821-4.944, $P< 0.0001$), as well as for collapsed vertebra (Relative Risk 1.816, 95% CI: 1.507-2.187, $P< 0.0001$). There was no significant difference in risk of pathologic fracture between the two cohorts (Relative Risk 1.285, 95% CI: 0.693-2.378, $P = 0.4255$), nor of the Z-score of the hip ($P = 0.8839$) and lumbar spine ($P=0.3612$).
Conclusion
This study demonstrates bisphosphonate monotherapy outperformed combination therapy (bisphosphonate and teriparatide) in reducing fracture risk, with no difference in bone mineral density enhancement. These findings suggest an antagonistic relationship (rather synergistic) in the presence of two differing therapeutic classes (anti-resorptive and anabolic). Further studies are needed to concur such findings.

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EP174

JOINT3974

Compromised muscle strength in patients with hypophosphatasia

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Introduction
Hypophosphatasia (HPP) is a rare metabolic bone disorder characterized by low levels of tissue-nonspecific alkaline phosphatase (TNSALP) due to mutations in the ALPL gene. Deficiency of this alkaline phosphatase (ALP) isoform has been associated mainly with bone and dental disorders. However, although muscle alterations are frequent, muscle functionality is a scarcely evaluated aspect in patients with PPH. The aim of this study was to demonstrate the functional and structural impairment of bone and skeletal muscle in HPP.
Materials and Methods
Observational study of adult subjects with a genetic diagnosis of HPP and healthy controls, matched for sex, age and body mass index (BMI). The following clinical variables were collected: muscle strength measured with Jamar dynamometer; quadriceps rectus femoris muscle mass (Y-axis, X-axis, area and circumference) measured with ultrasound (Sonosite S-Nerve®); fat-free mass (FFM) and bone mineral density (BMD) in total hip, femoral neck (FN) and lumbar spine determined by dual-energy X-ray absorptiometry. Statistical analysis was performed with IBM SPSS v.26.
Results
Thirty-four PPH cases (48 years±18; 55% women), matched for age, sex and BMI with a control group, were analyzed. Median and interquartile range (IQR) of bone (BMD), muscle (dynamometry, Y-axis, X-axis, area and circumference), adiposity and biochemical (ALP) parameters were determined in both groups. Age-adjusted dynamometry values were significantly lower in the HPP group (28.6Kg vs 34.3; $P = 0.039$). Similarly, significant differences were observed in BMD of FN (0.8g/cm2 vs 0.9; $P = 0.034$) with the HPP group presenting lower values. No significant differences were observed in muscle mass. Analyzing muscle strength values in relation to ALP quartiles, a positive correlation was observed between both variables, highlighting significant differences between the first and fourth quartiles ($P = 0.003$). Multiple linear regression results showed an independent association between ALP levels and muscle strength (B=0.103 (95%CI 0.032-0.175), $P = 0.005$).
Conclusions
Impaired muscle strength was observed independently of muscle mass in patients with HPP, especially in those with more decreased ALP levels, suggesting that ALP level seems to be an important determinant of muscle strength. This could be related to bone status, particularly at the femoral level.

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EP175

JOINT3088

Adolescent body mass index and osteoporosis risk: a nationwide study of one million israeli adolescents

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Background
There is limited data regarding adolescent weight among healthy individuals and its trajectory through early adulthood with respect to bone health. We assessed the association between adolescent body mass index (BMI) and osteoporosis risk while accounting for BMI change during early adulthood.
Methods
A retrospective cohort study including Israeli-born adolescents (468,907 women; 614,584 men) aged 16-19 years, who were evaluated for military service from 1967-2019 and followed for osteoporosis outcome until 2022 using the Maccabi Healthcare osteoporosis registry. Weight and height were measured to calculate BMI at adolescence and additional sociodemographic and medical data were collected. Cox proportional hazard models were applied. Adult BMI measurement was available for 74% of the study population and was used to assess the effect of adolescence-to-adulthood weight trajectory on incident osteoporosis. Health status at baseline and incident cancer and diabetes throughout adulthood were strictly controlled.
Results
21,497 (4.58%) women and 6,929 (1.13%) men were enrolled in the osteoporosis registry during a cumulative follow-up of 19,400,208 person-years. There was a gradual decrease in crude incidence rate (event/10^5 person-years) from 330.2 among extreme underweight ($<$3rd percentile) toward 78.9 in the obese group ($\geq$95th perc.). Corresponding adjusted HRs for osteoporosis ranged from from 1.89 (1.74-2.04) to 0.83 (0.77-0.88) in women and 1.79 (95%CI 1.62-1.99) to 1.05 (0.94-1.16) in men (with normal BMI as the reference group). There were no differences in incident risk for those with mild vs. severe adolescent obesity. The highest risk was recorded for those who sustained underweight from adolescence to adulthood. Weight gain from underweight at adolescence was associated with a lower risk for osteoporosis. These findings persisted when analysis was restricted for individuals with unimpaired health.
Conclusion
BMI category at a young age and its trajectory to adulthood have a significant effect on the risk for osteoporosis in adult life.

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EP176

JOINT1407

Mineral-bone disorder in chronic kidney diseases as early atherosclerosis indicators

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Introduction
The complex pathophysiology of mineral-bone disorders in chronic kidney disease (CKD) starts very early, when calcium and phosphorus are deposited in the walls of blood vessels and heart valves instead of bones, increasing the cardiovascular (CV) risk in these patients. An additional aggravating circumstance is the onset of secondary hyperparathyroidism, which, in addition to increasing CV risk, also contributes to increasing the risk of bone fractures. In this vicious circle, one of the biggest treatment challenges is how to regulate serum calcium levels, bearing in mind that calcium substitution with necessary vitamin D leads to an increase in the product of serum calcium and phosphate (CaxP), which contributes to the development of vascular calcifications and CV risk.
Objective
To determine the serum calcium values in patients with CKD in relation to the disease stage and to examine the relation with other parameters of mineral-bone disorder and the carotid intima media thickness (IMT) as well, as indicators of the early process of atherosclerosis.
Methods
This study was conducted as a cross-sectional study. It included 88 patients with all stages of CKD. The patients were classified into stages according to the estimated glomerular filtration rate (eGFR) according to MDRD (Modification of Diet in Renal Disease Formula). The carotid IMT was measured in accordance with the recommendations of the Mannheim Consensus.
Results
Of tested individuals 56% were women, average age of 63. The mean value of calcium was 2.35 ± 0.21 mmol/l and stayed within the reference values in all stages of CKD, while the mean value of IMT was 1.10 ± 0.20 mm with pathological values already identified from stage 2 of CKD. The CaxP values were positively correlated with serum creatinine ($r=0.65$, $P<0.001$). The pathological values of parathyroid hormone (PTH) were registered from stage 3 of CHD and were positively correlated with CaxP ($r=0.46$, $P<0.001$). The patients with PTH $>$600 ng/l had significantly higher values of serum calcium and phosphate, CaxP and IMT. The IMT was positively correlated with CaxP ($r=0.25$, $P<0.5$), PTH ($r=0.24$, $P<0.5$) and creatinine ($r=0.28$, $P<0.01$).
Conclusion
Advanced CKD is accompanied by an increase in calcium and phosphate products with the onset of the atherosclerosis, which is why careful monitoring of the mineral status of these patients is of significance for their outcome. A difficulty in correcting the mineral status would be a reason to consider a bone biopsy and adjustment of the treatment approach.

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EP177

JOINT3951

Bridging osteoporosis and glucose metabolism: the insulin sensitivity benefits of denosumab

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Introduction
Denosumab is a monoclonal antibody used in osteoporosis treatment because of its role in reduction of bone turnover through the inhibition of the RANKL/RANK pathway. While this pathway is primarily found in bone tissue, it is also expressed in the liver. Recent research suggests that inhibition of this pathway with denosumab therapy may lead to enhanced insulin sensitivity. However, data is still limited on this topic.
Methods
This retrospective study included patients with severe osteoporosis treated with denosumab in a tertiary center. Data at most recent follow-up were compared with data before denosumab treatment initiation, via paired-samples t-tests. Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR).
Results
A total of 59 patients were included, with a mean age of 73.5 ± 10.5 years; 89.9% (n =53) were female. Mean denosumab treatment duration was 37.9 ± 16.9 months. Before denosumab treatment, 18.6% (n =11) of patients had type 2 diabetes (T2D), 61% (n =36) were prediabetic and 20.4% (n =12) had no glucose metabolism abnormalities. Out of the patients with T2D, all but one had good glycemic control before initiating denosumab therapy: 10 patients had HbA1c levels $<$7.5%, and 1 patient had a HbA1c level of 8.8%. At most recent follow-up, both mean fasting insulinemia (13.8 ± 1.8mg/dL vs 9.1 ± 0.9mg/dL, $P=0.016$) and mean HOMA-IR (4.01 ± 1.5 vs 2.38 ± 0.9, P = 0.019) significantly decreased compared to pre-denosumab treatment levels. However, this was not accompanied by a significant decrease in mean fasting plasma glucose levels (111.7 ± 28mg/dL vs 100.5 ± 25mg/dL, P = 0.35) nor in mean HbA1c levels (6.1 ± 0.8% vs 5.9 ± 0.6%, P = 0.064).
Discussion and conclusions
Denosumab was associated with significant reductions in insulin resistance in this population of patients with severe osteoporosis. These results are particularly relevant considering insulin resistance is a known risk factor for osteoporotic

fractures. However, it is still unclear whether this reduction in insulin resistance can lead to actual improvement of clinical outcomes in T2D and prediabetes. The fact that most patients included in this study either did not have diabetes or had good glycemic control pre-denosumab may have contributed to the lack of significant decrease in HbA1c and fasting plasma glucose levels. Further studies including a larger sample of patients with T2D may help show whether the effects of denosumab on insulin resistance could improve glycemic control.

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EP178

JOINT2310

Diagnostic accuracy of choline pet in primary hyperparathyroidism with negative localization studies: a preliminary analysis

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Introduction
In patients with primary hyperparathyroidism (PHPT), preoperative localization of hyperfunctioning parathyroid glands is essential for proper surgical planning, particularly for minimally invasive procedures. The most used localization techniques include ultrasound, thyroid scintigraphy, and four-dimensional computed tomography (4D-CT). When these conventional imaging modalities yield inconclusive or negative results, choline positron emission tomography (PET) has emerged as a promising alternative for gland localization.
Objective
To describe the baseline characteristics of patients who required choline PET as a localization study for PHPT.
Materials and Methods
This is a preliminary descriptive study including 16 patients diagnosed with PHPT between January 1 and December 31, 2023. The primary aim of this phase was to analyze the baseline characteristics of these patients, with a second phase planned to evaluate the correlation between PET findings and surgical outcomes. Demographic data, biochemical parameters, and imaging results were assessed.
Results
A total of 16 patients were included, of whom 75% were women, with a mean age of 59 $\pm$ 14 years. The mean baseline biochemical values were parathyroid hormone (PTH) 119 $\pm$ 45 pg/mL (reference range: 15–65 pg/mL), total serum calcium 10.6 $\pm$ 0.6 mg/dL, and vitamin D 34 $\pm$ 16 ng/mL. Regarding imaging studies, thyroid ultrasound identified a suspicious lesion in 25% of cases, scintigraphy in 20%, and 4D-CT in 28%. In 50% of cases, all conventional imaging techniques were negative, and no complete agreement among the three modalities was observed. Choline PET detected a suggestive lesion in 87.5% of cases. Localization findings on PET were concordant with scintigraphy in 19%, with ultrasound in 19%, and with 4D-CT in 19% of cases.
Conclusions
Choline PET appears to be a promising imaging modality for the localization of hyperfunctioning parathyroid glands in patients with PHPT, particularly when conventional imaging techniques yield negative or inconclusive results. This preliminary study provides a foundation for future research aimed at evaluating the correlation between PET findings and surgical outcomes.

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EP179

JOINT566

Juvenile primary hyperparathyroidism revealed by genu valgum

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Introduction
Primary hyperparathyroidism is a rare condition in young individuals, primarily characterized by renal manifestations such as nephrolithiasis or nephrocalcinosis. Bone involvement, although less frequent, may present as limb deformities, often misdiagnosed as other bone lesions, thereby delaying diagnosis and appropriate management.
Case Report
An 18-year-old male with no significant medical history was hospitalized for primary hyperparathyroidism with severe hypercalcemia (3.28 mmol/l) and markedly elevated PTH levels (1500 ng/mL). His medical history revealed progressive asymmetry of the lower limbs, culminating in genu valgum and gait disturbances, which led to an orthopedic consultation. Initial MRI findings suggested an aneurysmal bone cyst of the left femur, prompting surgical indication. However, a second orthopedic opinion noted diffuse bone demineralization on standard radiographs, leading to a phosphocalcic workup. The diagnosis of primary hyperparathyroidism was confirmed by biochemical tests. Cervical ultrasound revealed a left parathyroid adenoma (24 $\times$ 16 mm), further corroborated by parathyroid scintigraphy showing hyperfunction in the same region. No renal involvement was identified. A multiple endocrine neoplasia (MEN) panel was negative, ruling out a syndromic origin. The patient underwent surgery, with favorable clinical and biochemical outcomes.
Discussion and Conclusion
This case highlights an atypical form of juvenile primary hyperparathyroidism dominated by bone manifestations, such as brown tumors, misdiagnosed as benign lesions like aneurysmal bone cysts, leading to a genu valgum deformity. Although less common than renal manifestations, bone involvement should prompt a phosphocalcic workup, especially in the presence of diffuse bone demineralization, before considering precipitous surgical management.

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EP180

JOINT94

Boxed in: should the black box warning for osteosarcoma be retired for good?

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Introduction
Two anabolic agents, namely teriparatide (parathyroid hormone analogue) and abaloparatide (parathyroid hormone-related peptide analogue), are approved by the Food and Drug Administration for osteoporosis. *in vitro* studies however, noted a heightened risk for osteosarcoma among rodents, for which a black box warning was given, as well as a limit of exposure; only recently has the two-year limit for Teriparatide been removed, however, an 18-month limit persists with abaloparatide. It should be noted, however, that the dosages used *in vitro* were supraphysiologic compared to those used in humans. Current recommendations are to only continue teriparatide beyond two years after shared decision making.
Objectives
Teriparatide has been on the market since 2002, and abaloparatide since 2017; as a result, the purpose of this retrospective cohort study is to evaluate the risk for osteosarcoma in patients with osteoporosis who are treated with an anabolic agent (teriparatide or abaloparatide). This study will address the validity of the black box warning of osteosarcoma in anabolic agents.
Methods
Anonymized data was collated through TriNetX Collaborative Network, encompassing 143 healthcare organizations globally. Cohorts were defined based on osteoporosis and the presence of an anabolic agent (teriparatide or abaloparatide) (n = 47, 489) and those with osteoporosis without an anabolic agent (n = 2, 686, 945). Cohorts were balanced with propensity scoring, delivering a balance of n = 46, 909. There was no age limit (upper or lower) for study inclusion, and all genders were included. The primary outcome of interest was the relative risk for the development of osteosarcoma (malignant neoplasm of bone). Timeframe was set as from at least one day following drug exposure to the present. Cohorts were matched for age at index and current age, gender, race, history of malignancy, and Paget's disease of bone.
Results
After matching, the mean age at index was 68.3 +/- 11.6 years, with 84.5% of the cohort being female, and 70.4% white. When assessing the risk for osteosarcoma, there was no significant difference between the group treated with anabolic agents and those without (Relative Risk 0.714, 95% CI: 0.476-1.072, P = 0.1024).
Conclusion
The results from this study suggest there is no heightened risk for osteosarcoma with anabolic agents teriparatide or abaloparatide. Perhaps the black box warning is unnecessary and should be dropped upon further advisory committees.

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EP181

JOINT2181

Risk factors for osteoporosis in children with hyperthyroidism under iodine-deficient conditions in the Republic of Uzbekistan

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Relevance
Childhood is critical for skeletal development, with peak bone mass accrual during this period. By puberty's end, bone mass reaches 86–100% of adult levels. Thyrotoxicosis disrupts bone remodeling, causing osteoporosis, osteosclerosis, and a 10% loss per cycle, with BMD declining by up to 28%. Identifying predictors of bone metabolism impairment is essential for early diagnosis, prevention, and treatment.
Materials and Methods
This study included 97 healthy children and 146 with hyperthyroidism. Thyroid hormones, autoantibodies, osteocalcin, parathyroid hormone (PTH), vitamin D, calcium, phosphorus, and alkaline phosphatase were quantified using the Cobas e 411 Hitachi immunochemical analyzer (Hoffmann-La Roche, Switzerland). BMD was assessed via dual-energy X-ray absorptiometry (DXA) using the Stratos densitometer (Diagnostic Medical Systems, France).
Results
ROC analysis demonstrated that osteocalcin (AUC = 0.72; 95% CI: 0.52–0.91; P= 0.05), anti-TSH receptor antibodies (AUC = 0.71; 95% CI: 0.51–0.91; P = 0.05), anti-TPO antibodies (AUC = 0.70; 95% CI: 0.51–0.90; P = 0.05), b-CrossLaps (AUC = 0.70; 95% CI: 0.50–0.90; P = 0.05), and vitamin D (AUC = 0.63; 95% CI: 0.53–0.74; P = 0.01) were significant predictors of total-body BMD reduction in pediatric hyperthyroidism. Conversely, thyroid hormone levels, PTH, calcium, and alkaline phosphatase had an AUC of 0.5, aligning with the null hypothesis. Further stratification of vitamin D and osteocalcin levels in relation to BMD reductions at different DXA sites identified osteocalcin >100 ng/mL (AUC = 0.65; 95% CI: 0.55–0.74; P = 0.05) and vitamin D <20 ng/mL (AUC = 0.70; 95% CI: 0.59–0.80; P = 0.05) as reliable markers. These were "good" predictors for total-body and femoral BMD loss and "satisfactory" for lumbar spine BMD. The strongest predictor of vitamin D deficiency-related outcomes in pediatric hyperthyroidism was anti-TSH receptor antibodies (AUC=0.84; 95% CI: 0.68–0.99; P< 0.001).
Conclusions
ROC analysis in pediatric hyperthyroidism highlights the role of autoimmune activity and vitamin D deficiency in bone metabolism dysregulation. Autoimmune mechanisms may accelerate bone demineralization, underscoring the need for targeted diagnostic and therapeutic strategies.

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EP182

JOINT2588

Autosomal dominant hypocalcemia type 1 (ADH1): management during pregnancy

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Autosomal dominant hypocalcemia type 1 (ADH1) is a genetic disorder caused by a heterozygous activating mutation in the calcium-sensing receptor (*CASR*) gene. This mutation decreases the receptor's sensitivity to low serum calcium, leading to hypocalcemia and low or inappropriately normal levels of parathyroid hormone (PTH). There are only a few reported cases of pregnancies in individuals with ADH1 likely due to the complex physiological changes that occur during pregnancy. These include placental production of PTH-related protein (PTH-rp), expansion of plasma volume, increased fetal calcium demands, and renal hyperfiltration. These factors can disrupt calcium homeostasis, potentially exacerbating maternal hypocalcemia and increasing the risk of fetal hyperparathyroidism as a result of chronic intrauterine hypocalcemia. In women with ADH1, an additional mechanism of non-PTH-mediated hypercalciuria is present, which can worsen renal dysfunction during pregnancy. Furthermore, there is a risk that the fetus may inherit the condition, further complicating the management of these pregnancies. We present the case of a 39-year-old woman who has been under follow-up at our clinic, since being diagnosed with ADH1 at age 30 due to asymptomatic hypocalcemia. Her initial biochemical profile revealed corrected serum calcium (cCa) of 7.64 mg/dL, PTH 17 ng/l and 24-hour urinary calcium excretion of 138 mg/24h. At her most recent pre-pregnancy follow-up, her cCa level was 8 mg/dL. At 15 weeks of pregnancy, her cCa level was of 7.76 mg/dL, while on a regimen of 250 mg of elemental calcium and no calcitriol. Her treatment was progressively increased, and by week 27, with calcium supplementation of 1000 mg/day and calcitriol at 1.25 mg/day, her cCa had risen to 8.6 mg/dL, PTH was 5.1 ng/l and 24-hour urinary calcium was 250 mg/24h. Therapy was maintained, and at 36 weeks, her cCa reached 9.6 mg/dL, PTH was <4 pg/mL, and 24-hour urinary calcium had increased to 572 mg/24h. A cesarean section was performed at 38 weeks. Five days after birth, the neonate exhibited normal calcium levels of 10.1 mg/dL. One month postpartum, during lactation and with unchanged therapy, her cCa level was 8.7 mg/dL. This case highlights the importance of continuous monitoring of calcium levels in individuals with ADH1 to prevent both maternal and fetal complications. Although the literature report urinary complications such as pre-eclampsia and eclampsia, no such events occurred in this patient. Ongoing surveillance of calcium levels in both the mother and the infant remains critical during lactation.

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EP183

JOINT2230

Do patients with ehlers–danlos syndrome and a history of fractures have lower bone mineral density?

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Background
Joint hypermobility and instability are among the main risk factors for fractures in patients with Ehlers–Danlos syndrome (EDS). Such fractures, which may affect bone biomechanics, may be due to low bone mineral density (BMD). The purpose of this study was to assess bone density in patients with a hypermobile and classical subtype of EDS and a history of fractures.
Material and methods
The study involved a prospective assessment of 30 female patients, with either hypermobile or classical EDS. The patients were divided into two groups. Group 1 comprised patients with no history of fractures (n =13), and group 2 comprised patients with a history of fractures (n =17). All patients were evaluated in terms of their lumbar spine and femoral neck BMD (g/cm2) and parameters of calcium and phosphate metabolism.
Results
The evaluated groups showed no differences in terms of such parameters as neck left femur BMD (0.947±0.135 vs. 0.931±0.113, P = 0.934), total left femur BMD (0.975±0.115 vs. 0.932±0.141, P = 0.408), L1 BMD (1.242±0.252 vs. 1.113±0.147, P = 0.113), L2 BMD (1.296±0.198 vs. 1.202±0.195, P = 0.157), L3 BMD (1.359±0.205 vs. 1.264±0.188, P = 0.123), L4 BMD (1.280±0.200 vs. 1.244±0.194, P = 0.483), or L1–L4 BMD (0.129±0.206 vs. 1.212±0.171, P = 0.263). There was no significant correlation between a history of fractures and femoral neck BMD (Spearman's R -0.016, P = 0.935), total (Spearman's R -0.159, P = 0.4), or L1–L4 (Spearman's R -2.09, P = 0.266).
Conclusions
A history of fractures in patients with classical or hypermobile EDS is not associated with significantly lower BMD in such locations as neck and total left femur or L1–L4.

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EP184

JOINT3310

Duchenne muscular dystrophy and risk of fracture

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A high risk of fractures was reported in a patient with duchenne muscular dystrophy (DMD) which could be due to inmobilization, the pathophysiology of the disease, treatment with glucorticoids (GCs) and increased BMI. Knowledge of the risk factors for the disease contributes to creating preventive strategies that reduce co-morbidities and improve the quality of life in these patients.
Objetive
To assess the incidence of first fractures and factors contributing to risk of first fracture in children with DMD
Methods
A retrospective analysis of a cohort of patients with Duchenne Muscular was carried out A total of 27 children under 18 years of age with clinical and molecular diagnosis of DMD were enrolled. The study was approved by the ethics committee and all procedures were performed following the Declaration of Helsinki. The study began in 2010, a total of 27 children were referred to our endocrinology service for their evaluation. Anthropometric variables were evaluated at the start of the study and during follow-up. In addition, annual spine radiographs were performed. Data on long bone (LBF) and vertebral fractures (VF) were recorded. Questionnaires about calcium intake and mobility were also administered. The variables are summarized in mean (SD), median (IQR) and percentage according to their nature.
Results
The age of DMD diagnosis was 6.52 ± 2.83y and the follow-up time was 7.77 ($\pm$ 4.57y). Age of starting GCs was 8.12 ± 2.45y and average daily was 0.6 ± 0.12 mg/k/d. 7 children with new fractures (VF or LBF) were observed during this period, median time 5.07 (RIQ 3-6.66y). Cumulative incidences was 0.26 or 26%. Children with fractures presented a delay in the age of diagnosis (8 vs 5.5 y) and increased BMI ($P = 0.01$). No differences were observed in biochemical markers, vitamin D, time and dose of corticosteroids between fractured and non-fractured.
Conclusion
We observed a high incidence of fractures in this population, which highlights the importance of a multidisciplinary approach and the creation of strategies to reduce modifiable risk factors to improve the quality of life of these children. BMI could be a risk factor to take into account when considering treatment strategies in these patients.

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EP185

JOINT968

Osteogenesis imperfecta: a novel mutation in the COL1A1 gene and 8 new patients in Greece

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Background
Osteogenesis imperfecta (OI), is a rare, generalized connective tissue disorder comprising a heterogeneous group of inherited bone dysplasias with variable phenotypic features and genetic causes. Patients present with low bone mass and bone fragility, substantial growth deficiency and, occasionally, other associated secondary features, including blue sclerae, hearing loss and dentinogenesis imperfecta. The disease is caused mainly by autosomal dominant mutations in type I collagen, or in collagen-related genes with different inheritance patterns. Although there is no clear phenotype – genotype association, the genetic classification of OI helps in detecting specific phenotypic features of the different types of the disease. In the present study, we performed the genetic analysis of 8 new patients with clinical features of osteogenesis imperfecta, in the frame of definitive diagnosis, management and family genetic counselling.
Materials and Methods
Whole exome sequencing was performed and a panel of genes associated with short stature, joint hypermobility, bone fragility or blue sclerae was analysed. The acceptable mean depth of the analysis was 60 and the gene coverage 97%. Any detected pathogenic or likely pathogenic variant was confirmed by Sanger sequencing. The detailed clinical features of the patients were recorded and further analysed based on the type of the genetic change observed.
Results
We found 7 different pathogenic genetic variants in 8 different patients, including frameshift (5/8), missense (2/8) and splicing changes (1/8) in the *COL1A1* gene and a missense mutation in the *COL1A2*. One of the observed genetic variants in exon 46 of the *COL1A1* gene has not been previously reported (p.Ala1134Leufs*39). Almost all patients (90%) had severe generalized osteoporosis, mild joint hypermobility, varying degree of multiple fractures and blue sclerae. None of the patient-carriers of frameshift mutations had experienced fractures in utero, during labour or during the newborn period. The patient-carriers of point mutations were diagnosed perinatally. No differences were found regarding the phenotypic variability between the two groups of mutations.
Conclusions
Eight new patients with phenotypic features of osteogenesis imperfecta were genetically diagnosed with pathogenic mutations in *COL1A1* and *COL1A2* genes, thus, being classified in OI type I, III and IV. Despite the small number of genetically tested patients, it is noteworthy that no phenotypic sign has been reported in utero or during the newborn period for the patients-carriers of frameshift *COL1A1* mutations.

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EP186

JOINT1792

Clinical and molecular profiles of 14 new patients with X-linked hypophosphatemia (XLH) in greece

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Background
X-linked hypophosphataemia (XLH;#307800), is a rare metabolic disorder and the most common form of hereditary hypophosphatemic rickets. Patients present with renal phosphate waste resulting in hypophosphataemia, rickets and osteomalacia due to elevated serum FGF23. The disease is caused by inactivating variants throughout the *PHEX* gene (*300550) which encodes a 749 amino acid transmembrane protein. These variants are predicted to cause loss of protein function, with the majority producing a truncated protein, while controversy exists regarding genotype-phenotype correlation. In the present study, we performed the genetic analysis of 14 new patients with clinical features of hypophosphatemic rickets, in the frame of definitive diagnosis and selection of treatment.
Materials and Methods
All 22 exons and their flunking intronic regions of the *PHEX* gene were analysed using direct sequencing. The detailed clinical features of the patients were recorded and genotype-phenotype correlations were performed.
Results
We found 10 different pathogenic genetic variants in 13 different patients, including frameshift, splicing, missense and nonsense changes in the *PHEX* gene, affecting the extracellular sequence of the protein. Two of the observed genetic variants have not been previously reported (c.2051_2061dup; c.1525A>C). One patient did not reveal any pathogenic variant either by sequencing or MLPA. All patients presented with disproportionate short stature and bowing of the legs; 4/14 osteoarthritis, 8/14 bone pain, 5/14 fractures, hypophosphatemia, and normal to high serum PTH and ALP. Patients carriers of truncated mutations experience more severe phenotypes than patients with missense mutations.
Conclusions
This is the first study describing the detailed molecular and clinical profiles of X-linked hypophosphatemic patients in Greece. Most of them have, recently, started receiving burosumab, a fully humanized monoclonal antibody that neutralizes circulating FGF23, and their response to treatment is being recorded.

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EP187

JOINT3271

Bone metabolism in refractory rickets: a comparative study of treatment-compliant, non-compliant, and healthy children

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Background
Refractory rickets, though rare, significantly contributes to bone health-related morbidity in both children and adults. Non-invasive biochemical markers can offer insights into bone remodelling, but their use in children with resistant rickets remains largely unexplored.
Objective
To assess the bone metabolism in children with refractory rickets using bone turnover markers.
Methods
In this single-center, cross-sectional study, children ($\leq$18 years) with refractory rickets were enrolled. Refractory rickets was defined as failure to achieve radiological healing after 12 weeks, despite a cumulative dose of 300,000 IU of vitamin D. Exclusions included nutritional rickets, chronic kidney disease, and use of glucocorticoids or anticonvulsants. Diagnosis was confirmed either biochemically or via clinical exome sequencing. Patients were categorized into hypophosphatemic rickets (HPR), vitamin D–dependent rickets (VDDR), and renal tubular acidosis (RTA). Rickets severity was assessed using the Rickets Severity Score (RSS). Non-compliance was defined as worsening of RSS with non-adherence to prescribed therapy for 3 months over past year. Age- and gender-matched normal controls were also included. Bone turnover markers, C-telopeptides of type I collagen (CTX, resorption) and procollagen I N-propeptide (P1NP, formation) were assessed early morning after overnight fasting.
Results
Thirty-nine children [53% female, 9.69 (4.39) years and 64% compliant] were included, with genetic confirmation in 29 (75%) cases (HPR: 62%, VDDR: 20%, RTA: 18%) along with 39 controls. Bone resorption marker CTX was 2077 pg/ml (1532–2886), and bone formation marker P1NP was 690 ng/ml (586–1080) in our patient cohort, with no significant intergroup differences [CTX: $P = 0.289$, P1NP: $P = 0.465$]. However, both markers were significantly higher in patients than controls [CTX: 1561 (1250–1860) pg/mL, $P = 0.004$; P1NP: 450 (400–484) ng/mL, $P<0.001$]. A significant positive correlation was found between serum CTX with P1NP ($r=0.405$, $P = 0.016$), and between CTX with RSS ($r=0.400$, $P= 0.026$). Notably, P1NP was significantly elevated in the compliant group as compared to the control group [753.1(293.7) versus 449.8 (57.7) ng/ml, $P<0.001$] while no significant difference was noted in CTX [1818.4 (610.2) versus 1542.8 (380.1) pg/ml, $P = 0.09$]. In contrast, both CTX and P1NP were significantly elevated in the non-compliant group compared to controls [CTX 3482.5 (1340.9) versus 1542.8 (380.1) pg/ml, $P<0.001$; P1NP 939.6 (359.3) versus 449.8 (57.7) ng/ml, $P<0.001$].
Conclusions
To conclude, children with refractory rickets exhibit higher bone turnover compared to controls. Treatment adherence disproportionately reduces bone degradation relative to bone formation. This can contribute to improved bone health on follow up.

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EP188

JOINT707

Relationship between vitamin D deficiency and low bone mineral density in children with inflammatory bowel diseases

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Objective
Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition associated with gastrointestinal and bone complications like vitamin D deficiency and osteoporosis. Inflammation during childhood and adolescence, critical periods for bone growth, can impair bone development. This study examines the prevalence of vitamin D deficiency and impaired bone health in pediatric IBD patients and evaluates the impact of vitamin D supplementation on bone metabolism.
Methods
This retrospective study included 287 pediatric patients under 19 years old who visited the pediatric gastroenterology and nutrition clinic. Among these, 230 (80.1%) were diagnosed with CD and 57 (19.9%) with UC. Data collected at diagnosis included height, weight, dual-energy X-ray absorptiometry (DEXA) results, 25-hydroxyvitamin D levels, and various biochemical markers.
Results
At diagnosis, vitamin D deficiency ($<$20 ng/mL) was observed in 87.3% of CD patients and 71.9% of UC patients ($P = 0.004$). Average 25-OH vitamin D levels were 13.76 ± 6.77 ng/mL in CD and 16.49 ± 9.96 ng/mL in UC. Lumbar z-scores were -0.74 ± 1.12 for CD and -0.25 ± 1.03 for UC ($P = 0.028$). In 249 patients receiving vitamin D supplementation, serum vitamin D levels significantly increased from a baseline of 13.83 ± 7.06 ng/mL to 27.32 ± 10.25 ng/mL at one year ($P = 0.003$). Additionally, lumbar spine z-scores improved significantly from -1.03 ± 1.05 to -0.54 ± 1.06 during the same period ($P< 0.001$).
Conclusion
Pediatric IBD patients have a high prevalence of vitamin D deficiency and reduced bone density at diagnosis. Early initiation of vitamin D supplementation significantly improves bone health, highlighting its role in managing bone complications in pediatric IBD.

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EP189

JOINT3425

Novel association between cohen syndrome and low alkaline phosphatase, a potential new subgroup of hypophosphatasia

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Introduction
Cohen Syndrome is a rare autosomal recessive disorder caused by mutations in the VPS13B gene. It is characterized by distinct facial features, mitral valve prolapses, and neurological defects, along with endocrine and musculoskeletal manifestations such as joint laxity, scoliosis, knee deformities, short stature, pubertal delay, and growth hormone deficiency. The underlying pathophysiology is thought to involve impaired protein glycosylation, particularly at the Golgi apparatus. Alkaline Phosphatase (ALP), a glycosylated enzyme involved in bone metabolism and turnover, is affected by glycosylation defects. We hypothesized that individuals with Cohen Syndrome may exhibit low ALP levels, which could potentially represent a new form of hypophosphatasia.
Aim
This study aimed to explore the relationship between Cohen Syndrome and low ALP levels, investigating whether this could signify a new subgroup of hypophosphatasia.
Method
A retrospective review was conducted on nine Cohen Syndrome cases diagnosed at our institution. ALP levels were measured for all patients, and radiologic evaluations were performed to assess skeletal abnormalities. The incidence of low ALP in this cohort was compared to the general population rate of approximately 5%.
Results
Among the nine patients with Cohen Syndrome, 44% (4/9) had low ALP levels, significantly higher than the general population rate ($P = 0.0006$). Radiologic evaluations revealed bone abnormalities in some patients, including fractures. Specifically, 22% of the individuals had fractures, and one patient with a low-trauma fracture and diffuse osteopenia on X-rays. These findings suggest a potential link between low ALP and skeletal manifestations in Cohen Syndrome, pointing to disturbances in bone metabolism that may be indicative of a new form of hypophosphatasia.
Conclusion
This study identifies a novel association between Cohen Syndrome and low alkaline phosphatase levels, suggesting the possibility of a new subgroup of hypophosphatasia. The significantly high rate of low ALP among our cohort warrants further investigation into the role of bone metabolism in Cohen Syndrome. Confirmatory tests (serum pyridoxal 5'-phosphate and urine phosphoethanolamine) for hypophosphatasia are planned, and these findings could inform future therapeutic strategies. This novel subgroup could provide valuable insights into bone health in genetic disorders, potentially guiding targeted treatments.

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EP190

JOINT2832

A rare cause of short stature: the journey to diagnosing hypophosphatemic rickets with hypercalciuria

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Background

Bone metabolic conditions causing short stature result from genetic, hormonal, or metabolic abnormalities that impair bone growth and strength. Among them, hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is an extremely rare autosomal recessive disorder caused by mutations in the SLC34A3 gene, which encodes for the proximal tubular transporter NaPi-IIc, thus leading to impaired phosphate reabsorption and subsequent hypophosphatemia, hypercalciuria and impaired bone mineralization. The diagnosis can be challenging, particularly when presenting with severe growth impairment. We report a case of HHRH initially suspected as growth hormone deficiency due to short stature and delayed bone age, ultimately leading to an unexpected diagnosis.

Case Presentation

A 10-year-old boy presented with severe short stature (-4.13 SDS), genu varum, and chronic joint pain. He was born at term with a normal birth history, breastfed for 13 months, and had normal psychomotor development. There is no family history of rickets or other metabolic bone disease. Initial evaluation revealed low IGF-1 (105 ng/mL), bone age delayed by 2 years, and an appropriate growth hormone response to arginine stimulation testing, ruling out growth hormone deficiency. Laboratory investigations showed persistent hypophosphatemia (serum phosphate 2.3 mg/dL), with normal levels of serum calcium (9.54 mg/dL) and 25-hydroxyvitamin D (34.89 ng/mL), and elevated alkaline phosphatase (543 U/l). Urinary analysis confirmed hypercalciuria (292 mg/24h) and reduced tubular phosphate reabsorption (TMP/GFR = 0.92 mmol/l). Additionally, 1,25-dihydroxyvitamin D was elevated (126 pg/mL), whereas serum PTH was reduced (8.19 pg/mL) and fibroblast growth factor 23 (FGF23) was undetectable, supporting the diagnosis of HHRH. The radiologic assessment revealed a rickets severity score of 7/10. No images of renal calcifications were found on the abdominal ultrasound.

Conclusion

The biochemical profile—persistent hypophosphatemia, suppressed PTH, hypercalciuria, elevated 1,25-dihydroxyvitamin D, and low FGF23—helped differentiate HHRH from other phosphate-wasting disorders, such as X-linked hypophosphatemia, autosomal dominant/recessive hypophosphatemic rickets, Dent disease or Fanconi syndrome. Nonetheless, genetic testing remains necessary for confirmation. Unlike other forms of hypophosphatemic rickets, phosphorus supplementation alone is the primary treatment, while active vitamin D metabolites should be avoided due to their potential to worsen hypercalciuria. Despite linear growth improvement seen with oral phosphate supplementation, isolated case reports additionally considered human recombinant growth hormone therapy with improved outcomes.

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EP191

JOINT153

Successful treatment of autosomal dominant hypophosphatemic rickets with burosumab: a case report

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Background

Autosomal dominant hypophosphatemic rickets (ADHR) is a rare genetic disorder characterised by FGF23-mediated phosphate wasting and impaired bone mineralisation. Mutation renders FGF23 resistant to degradation. Iron deficiency stimulates transcription levels of FGF23 and aggravates the disease. Conventional treatment with phosphate and active vitamin D analogues is challenging and commonly not optimal. Treatment with oral iron has no long-term results. Burosumab, a monoclonal antibody against FGF23, has shown efficacy in X-linked hypophosphatemia (XLH), but its use in ADHR remains unexplored. We present data for the first 12-month treatment with burosumab in ADHR patients.

Case Presentation

A 19-year-old female with ADHR, confirmed by FGF23 R176Q/W mutation, presented with severe symptoms, including bone pain and muscle weakness. Her weight was 40 kg, height 145 cm, sitting height 77 cm, arm span 142 cm, BMI 19.0 kg/m^2. One year prior, she had a low-energy fracture of the diaphysis right femur, which was complicated by non-union. Her bone mineral density (BMD) was low for age and sex (Z-score L1-L4 -4,4 SD, Z-score femoral neck -4,4 SD, Z-score hip -4,7 SD) and TBS was normal (1.358). Laboratory tests were as follows: 25OH vitamin D 37,7 nmol/l, P 0,39 mmol/l (0,74-1,52), corrected Ca 2,18 mmol/l (2,10-2,60), alkaline phosphatase (AP) 4,95 µkat/l (0,55-1,64), bone-specific AP (BSAP) 93,6 µg/l (4,7-27,0), iPTH 31 ng/l (16-68), TRP 80 % (>85 %), TmP/GFR 0,41 mmol/l (0,84-1,23). Treatment with calcitriol and phosphate did not resolve the symptoms. We started treatment with burosumab (40 mg every 28 days). Phosphate supplementation was discontinued seven days before initiation. Her fracture healed. Within 2 months, the patient reported significantly reduced bone and muscle pain, improved muscle strength, and regained mobility without crutches. BMD increased by 11.7% at the lumbar spine and 14.2% at the hip after 5 months, with further improvements of 46.6% and 36.2%, respectively, after 10 months. Serum phosphate levels increased but did not normalise, and AP rose to 12,96 µkat/l and BSAP to 350 µg/l in the first 3 months before starting to normalise. Transient hyperphosphatemia occurred with concurrently increased iron supplementation, necessitating dose adjustment of burosumab.

Conclusion

Burosumab is potentially an effective treatment for ADHR, demonstrating rapid symptom relief, improved BMD, and enhanced fracture healing. While burosumab was well-tolerated, careful management of concurrent iron therapy is essential to avoid hyperphosphatemia. Further studies with larger cohorts are needed.

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EP192

JOINT3336

Buschke–ollendorff syndrome in a mother-child duo: a rare cause of short stature and skeletal dysplasia

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Introduction

Buschke–Ollendorff syndrome (BOS) is a rare, autosomal dominant skeletal dysplasia caused by LEMD3 gene mutations. It is characterized by osteopoikilosis (OPK), benign sclerotic bone lesions, and connective tissue nevi. Although often asymptomatic, BOS may be mistaken for malignant or metabolic bone diseases, leading to misdiagnosis. Short stature, scoliosis, and other skeletal anomalies have been associated with BOS. We present a mother and child diagnosed with BOS after evaluation for bone pain and short stature.

Case report

A 40-year-old woman presented to the orthopedic clinic with progressive bone pain, particularly in both shoulders and arms, for one year. Radiographs revealed multiple, well-defined, symmetrical sclerotic lesions in the epiphyses and metaphyses of both shoulders. These points were located in the cancellous bone tissue and the inner bone cortex bilaterally located in the epiphyses and metaphyses. She has been consulted the radiology department and diagnosed osteopoikilosis. Due to her history of short stature (146 cm, -2.66 SD), and skeletal findings, her 7-year-old son was referred for endocrinological evaluation. The child presented with short stature and intermittent right knee pain. He was born at 37 weeks gestation, weighing 2650 g. His height was 107 cm (-3 SD), weight 19 kg (-1.67 SD), and BMI 16.6 kg/m^2 (+0.62 SD) with a target height of 167 cm (-1.37 SD). There was a proportional short stature. He was prepubertal. His father's height was within the normal range His neurodevelopment and dentition were normal. His physical examination revealed multiple connective tissue nevi on the anterior abdominal wall and left gluteal region. Radiographs of the child's right knee showed multiple sclerotic lesions resembling the "dripping wax" pattern of melorheostosis, consistent with OPK. Whole-body imaging confirmed widespread poikilotic bone lesions. Laboratory tests, including calcium, phosphorus, alkaline phosphatase, inflammatory markers, and IGF-1

and GH test, were normal. Bone age corresponded with chronological age. Genetic testing was cofirmed an LEMD3 mutation leading to a BOS diagnosis. Mother also presented with the same LEMD3 mutation.
Conclusion
BOS is a rare disorder that can present with skeletal dysplasia, short stature, and unexplained bone pain. In cases of familial OPK or unexplained short stature, genetic testing is crucial for accurate diagnosis and appropriate management. Due to the broad spectrum of clinical manifestations, establishing a strong pediatric-adult transition in care a multidisciplinary approach is vital for long-term monitoring and preventing complications associated with BOS.

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EP193

JOINT45

At the crossroads: femoral osteonecrosis in β-thalassemia major

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Introduction
β-thalassemia major is a chronic hemolytic disorder that leads to iron overload due to frequent blood transfusions. This iron accumulation can cause a range of metabolic, endocrine, and skeletal complications. One rare but severe complication of β-thalassemia major is femoral osteonecrosis, a condition characterized by the loss of blood supply to the femoral head, resulting in progressive bone death. While more common in sickle cell disease, femoral osteonecrosis is less frequently reported in thalassemia patients. Early detection and management of this condition are crucial to preventing irreversible joint deformities and improving long-term functional outcomes.
Case Presentation
A 17-year-old female patient with β-thalassemia major, diagnosed at birth, was receiving regular blood transfusions every three weeks and iron chelation therapy. She was admitted for the evaluation of primary amenorrhea. On physical examination, the patient showed severe growth retardation with a weight of 30 kg and a height of 145 cm (BMI = 14 kg/m^2). Vital signs were stable, and cardiovascular and pulmonary exams were unremarkable. Orthopedic examination showed limited hip movement with pain on mobilization. Imaging studies included a pelvic MRI confirmed bilateral femoral osteonecrosis. Additionally, a pituitary MRI demonstrated anterior pituitary atrophy, likely secondary to iron overload. Laboratory tests showed elevated ferritin levels, indicating iron overload, along with reduced FSH and estradiol levels, suggesting endocrine dysfunction.
Discussion
Femoral osteonecrosis is a rare but serious complication in β-thalassemia major patients, with potential mechanisms including chronic anemia, iron overload, and marrow hyperplasia. Iron overload can damage tissues and disrupt blood flow, particularly in bones such as the femoral head, contributing to osteonecrosis. Marrow hyperplasia in thalassemia can also compress blood vessels, further compromising blood supply. Although femoral osteonecrosis is commonly seen in sickle cell disease, its occurrence in β-thalassemia major underscores the importance of vigilant musculoskeletal monitoring in these patients. Early detection through clinical and radiological assessment is crucial, as delayed diagnosis can lead to joint deformities, chronic pain, and loss of function.
Conclusion
This case emphasizes the need for early identification and regular monitoring of skeletal complications in patients with β-thalassemia major. While femoral osteonecrosis is a rare complication, its impact on a patient's quality of life can be significant if not detected and managed promptly. Multidisciplinary care, including appropriate management of iron overload and timely orthopedic intervention, is essential to prevent long-term functional impairment. Regular musculoskeletal evaluation is recommended to ensure early detection and intervention for this potentially debilitating condition.

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EP194

JOINT1334

Treatment conundrums in newly recognized early-onset osteoporosis caused by heterozygous WNT1 mutation

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Introduction
As molecular genetic testing became more available, we are now able to better identify different molecular causes of monogenic osteoporosis. Unfortunately, their treatment remains uncertain.
Clinical case
An 18-year-old male presented in our clinic with a history of multiple fractures preceded by medium intensity traumas, occurring from age seven. Although none of them were classic fragility fractures, their frequency prompted further investigation. He had normal development and no other clinical features. Endocrine work-up was normal, except for a mild functional hyperprolactinemia. Serum osteocalcin and beta-crosslaps were within range. He had a low bone mineral density for age and sex, with Z scores of -2.5 DS (lumbar) and -2.9 DS (left femoral neck). We suspected osteogenesis imperfecta, advised genetic consult and recommended oral bisphosphonates (not administered due to poor compliance). Five years later, the patient managed to obtain a genetic test, showing a heterozygote mutation of WNT1 gene, consistent with autosomal dominant early onset osteoporosis. No new fractures occurred since last visit. Repeated osseous metabolism markers showed a slightly elevated alkaline phosphatase and normal, though in the lower range, osteocalcin and beta-crosslaps. He had a slight leukopenia and no other notably endocrine or metabolic disturbances with stationary BMD.
Discussion
Fratzl-Zelman *et al*[1] demonstrated that this mutation is associated with low bone turnover osteoporosis, rendering bisphosphonate treatment inefficient, in line with other reports[2] of bisphosphonates showing no effects in these patients. Moreover, they showed that teriparatide treatment produced little to no improvement. Other study showed a positive effect of teriparatide, although rising questions regarding increased bone marrow adiposity in these patients[3]. Romosozumab could be a potential targeted treatment.
Case resolution and conclusions
Lifestyle modification was advised and given the stable clinical and densitometric evaluation, treatment initiation was postponed. As more cases of monogenic WNT1 osteoporosis are recognized, more studies are necessary to find an appropriate treatment plan. So far, different treatment choices have conflicting outcomes.
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EP195

JOINT3413

Hypercalcemia in primary hyperparathyoidism: when should ENT be alerted?

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Introduction
Primary hyperparathyroidism is the leading cause of hypercalcemia. It can be asymptomatic and discovered incidentally, or revealed by recurrent kidney stones, bone pain, or cardiac and digestive symptoms.
Materials and Methods
This retrospective study includes 22 cases of primary hyperparathyroidism treated with parathyroidectomy between 2021 and 2023.
Results
The study involved 22 patients, predominantly women, (M/F ratio: 0.18) with a mean age of 58.72 years. All patients had hypercalcemia with elevated

parathyroid hormone (PTH) levels. The average preoperative calcium and PTH levels were 2.82 mmol/l and 389 pg/mL. Twenty-three percent of patients were asymptomatic, 45% reported bone pain, and 27% had a history of kidney stones. Other symptoms were present in 32% of patients. ENT examinationwas normal in 21 cases. One patient had a left paramedian anterior basicervical swelling, measuring 1 cm firm, mobile. Ultrasound suggested a retrothyroidal nodule, with some uncertainty regarding its origin. Scintigraphy confirmed the diagnosis in all cases. All patients underwent parathyroidectomy, with removal of the pathological parathyroid gland. Four patients also underwent a lobectomy for thyroid nodules. Histopathology revealed parathyroid adenoma in 86% and pseudo-adenomatous hyperplasia in 14% of the cases. Postoperative calcium and PTH levels decreased starting on postoperative day 2, with average values of 2.36 mmol/l and 39 pg/mL respectively.

Conclusion

Primary hyperparathyroidism remains the most common cause of hypercalcemia. The role of the ENT surgeon is crucial in the therapeutic management once the diagnosis is established. Postoperative outcomes following surgery are remarkable.

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EP196

JOINT3309

Cartilage -hair hypoplasia due to double heterozygosity for the RMRPn.97_98dup mutation and the RMRPn.25_-12dup mutation in a girl with asymmetrical short stature and brachydactyly

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Introduction

Cartilage-Hair Hypoplasia (CHH) is presenting as a group of disorders resulting from mutations in the RMRP gene, which produces a non-coding RNA to which proteins bind to form an enzyme called mitochondrial RNA processing endoribonuclease (RNaseMRP). The RNaseMRP enzyme is involved in important cellular processes (DNA replication in mitochondria/ribosome assembly/cell cycle control). Biallelic loss-of-function mutations in RMRP have been reported in individuals with CHH, which present clinically as growth failure/skeletal abnormalities (metaphyseal dysplasia/brachydactyly/delta-shaped epiphyses) and extraskeletal features (hair hypoplasia/immunodeficiencies/anemia/malignancies).

The aim is to present a girl with short stature with continuous failure to growth, thin scalp hair and concomitant pathological radiological findings.

Patients/Methods

A 13-year-old adolescent girl (height 128cm/Tanner stage III/no menarche) has been followed since the age of 23/12 years. She is the 4th child of parents with tall stature (father187cm/mother170cm/without phenotypic deformities), born by cesarean section (weight 3010gr/length 50cm). Individual's history reports a decrease in body length and growth rate since infancy, whereas family history reveals father with a single kidney/mother with cardiac arrhythmia. At the first visit short stature/lordosis of the spine/short phalanges of the fingers of upper and lower extremities/mild varus knee patterns /hyperextensibility of the joints and fine hair on the head were found. Radiologically, widening and hardening of the articular surfaces with a beak-like appearance on the medial surface were found. A comprehensive investigation was performed (nutrition/karyotype/growth hormone secretion tests/thyroid function/celiac disease/bone metabolism). Genetic analysis of the RMRP gene was performed.

Results

Laboratory investigation revealed normal findings. The short stature gradually worsened with a striking increase in the asymmetry of the upper/lower body ratio. The patient presented with multiple lateral elbow dislocations. New bone metabolism tests showed pathological findings (low procollagen I levels/ high DPD/cre levels), indicative of reduced bone formation-increased bone resorption. The combination of clinical and laboratory findings led to genetic testing for skeletal malformations and RMRP gene, which confirmed the patient's double heterozygosity of RMRPn.97_98dup mutation (pathogenic) and RMRPn.25_-12dup mutation (likely pathogenic), inherited from the father and mother, respectively. The patient is closely monitored for growth/puberty but also for early diagnosis of any concomitant events of the disease (immunodeficiencies/-malignancies/anemia).

Conclusions

This rare case is the first description of CHH in Greece. In the diagnosis of the disease, clinical and radiological suspicion is very important. RMRP gene should also be required in genetic testing since its mutations lead to early diagnosis of comorbidities that are crucial for the patients' lives.

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EP197

JOINT262

Effect of sacubitri/valsartan on bone turnover markers in patients with dilated cardiomyopathy

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Background

Heart failure (HF), particularly dilated cardiomyopathy (DCM), is frequently associated with comorbidities, including osteoporosis and increased fracture risk. This heightened risk is potentially linked to shared pathophysiological mechanisms, such as chronic inflammation and neurohormonal activation. Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), has demonstrated significant benefits in HF management. However, its impact on bone metabolism remains unclear. This study investigated the effect of sacubitril/valsartan on bone turnover markers in patients with DCM.

Methods

This prospective, observational study enrolled 60 patients diagnosed with DCM (left ventricular ejection fraction $\leq 40\%$) and New York Heart Association (NYHA) functional class II-III. Patients were divided into two groups: the sacubitril/valsartan group ($n = 30$) received standard HF therapy plus sacubitril/valsartan, while the control group ($n = 30$) received standard HF therapy alone. Serum levels of bone turnover markers, including bone-specific alkaline phosphatase (BSAP, a marker of bone formation), C-terminal telopeptide of type I collagen (CTX, a marker of bone resorption), and osteocalcin (OC, another marker of bone formation), were measured at baseline and after 6 months of treatment.

Results

At baseline, no significant differences were observed in bone turnover markers between the two groups. After 6 months, the sacubitril/valsartan group demonstrated a significant decrease in CTX levels (mean change -12.5 pg/mL, $P < 0.05$) compared to the control group (mean change $+2.1$ pg/mL, $P = 0.32$). BSAP and OC levels did not show statistically significant changes in either group. The change in CTX correlated positively with the change in N-terminal pro-B-type natriuretic peptide (NT-proBNP), a marker of cardiac stress, in the sacubitril/valsartan group ($r = 0.45$, $P < 0.05$). This suggests that the reduction in bone resorption may be related to improved cardiac function.

Conclusion

This study suggests that sacubitril/valsartan may have a beneficial effect on bone metabolism in patients with DCM by reducing bone resorption, as evidenced by a decrease in CTX levels. The correlation between changes in CTX and NT-proBNP suggests a potential link between improved cardiac function and reduced bone resorption. Further large-scale, randomized controlled trials are needed to confirm these findings and explore the underlying mechanisms. These findings highlight the potential pleiotropic effects of sacubitril/valsartan beyond its established cardiovascular benefits.

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EP198

JOINT776

Clinical, biochemical and radiological features of LRP5 gene variants in children: case series and literature review

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Introduction

Alterations in the low-density lipoprotein receptor-related protein 5 (*LRP5*) gene are associated with primary bone fragility, leading to recurrent low-energy fractures. Heterozygous carriers typically exhibit a milder phenotype, with reduced bone mass observed early in childhood. This study aims to describe the clinical features and therapeutic outcomes of a pediatric cohort with heterozygous LRP5 gene variants.

Case Series

This retrospective study includes 7 pediatric patients (5 males, 2 females) from 3 Italian Pediatric Endocrinology Centers, aged 6 to 17 years (mean age at diagnosis: 9.1 years). Their height ranged from -1.2 to +1.3 SDS, and BMI from -0.7 to 3.0 SDS. Eight distinct heterozygous LRP5 variants were identified (6 missense, 2 nonsense), with most classified as variants of uncertain significance (VUS) and 2 deemed likely pathogenic. One patient carried the c.1709G>A; p.(Arg570Gln) variant, previously reported as pathogenic in the homozygous state. Before diagnosis, patients had between 0 and 4 low-trauma fractures, with 4 out of 7 presenting multiple spontaneous vertebral fractures. Bone and joint pain were reported by 5 out of 7 patients (71%) at presentation. All but two underwent bisphosphonate therapy (one is scheduled to start), and one patient also received denosumab. During a follow-up period ranging from 9 months to 4 years, none experienced new fractures. Bone mineral density (BMD) improved in all patients, with an observed increase ranging from 3% to 103% (mean increase: 51%). Those with vertebral compression fractures showed evidence of stabilization or partial reshaping. No adverse effects related to therapy were reported in this cohort.

Discussion and Conclusion

This case series highlights the clinical variability associated with *LRP5* gene variants in pediatric patients and underscores the effectiveness of bisphosphonate therapy in improving BMD and reducing fracture risk. The identification of predominantly VUS variants provides valuable insight into the genetic landscape of LRP5-related bone disorders. Our findings contribute to the expanding knowledge of LRP5 mutations and their association with primary bone fragility in children, underscoring the critical role of molecular diagnostics. Understanding the genetic basis of the disease not only improves diagnosis but also offers deeper insights into its pathophysiology, potentially informing more targeted therapeutic approaches. While bisphosphonates remain the current standard of care, further research is needed to explore precision therapies targeting Wnt signaling and other pathways affected by LRP5 mutations. A personalized approach, tailored to the specific genetic variant and clinical presentation, may further optimize long-term bone health in affected children.

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EP199

JOINT263

Bone turnover markers and their associations with longitudinal changes in bone mineral density and trabecular bone score in children and adolescents with graves' disease

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Background

Adults with Graves' disease (GD) exhibit reduced bone mineral density (BMD) and impaired trabecular bone microarchitecture, both of which typically improve with euthyroid status. However, data on these changes in adolescents are limited, and factors influencing them remain unclear.

Objectives

To evaluate bone turnover marker (BTM) concentrations, longitudinal changes in BMD and trabecular bone score (TBS), and factors associated with these changes in adolescents with GD.

Methods

We enrolled 42 adolescents with GD who had baseline data available for lumbar spine BMD (LSBMD) and BTM concentrations measured on the same date. BTM concentrations were converted to Z-scores. On the study date, follow-up LSBMD was measured. TBS, a measure of trabecular bone microarchitecture, was analyzed using iNsight™ software version 2.2. Annual percentage changes in LSBMD (%ΔLSBMD/y) and TBS (%Δ206;TBS/y) were calculated. Time-weighted (TW) concentrations of free T3 (FT3), free T4 (FT4), and TSH were determined over the follow-up period.

Results

Participants (74% female, mean age 13.5 ± 3.1 years, 90% Tanner stage ≥2, median [Q1–Q3] disease duration 1.3 [0.3–4.2] years, 45% receiving levothyroxine following radioiodine therapy [RAIT]) had a median follow-up duration of 2.2 (1.3–2.9) years. At baseline, four (10%) participants had a height-adjusted LSBMD Z-score ≤-2, and 2 (5%) had a TBS Z-score ≤-2. Participants with RAIT had longer disease duration ($P<0.001$), higher LSBMD Z-score ($P = 0.002$), and lower total procollagen type 1 N-terminal propeptide (P1NP) Z-score ($P = 0.01$) compared to those receiving antithyroid drug (ATD) therapy. %ΔLSBMD/y correlated positively with baseline FT3 ($P = 0.011$), TW FT3 ($P<0.001$), P1NP Z-score ($P = 0.001$), and osteocalcin Z-score ($P = 0.011$), and negatively with disease duration ($P<0.001$), RAIT ($P<0.001$), baseline TSH ($P<0.001$) and TW TSH ($P = 0.037$). %ΔTBS/y correlated positively with body mass index (BMI) Z-score ($P = 0.022$). Regression analysis revealed that P1NP Z-score was positively associated with %ΔLSBMD/y adjusting for age, sex, Tanner stage, BMI Z-score, disease duration, TW FT3, and TW TSH ($P<0.001$).

Conclusions

Adolescents with GD have a high prevalence of low LSBMD. Improvement in LSBMD during treatment is positively associated with FT3 and negatively with TSH concentrations over the follow-up period, while TBS improvement is associated only with BMI. Furthermore, P1NP independently predicts LSBMD improvement, suggesting its potential as a prognostic bone biomarker.

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EP200

JOINT1857

Palopegteriparatide for the treatment of autosomal dominant hypocalcemia type 1 (ADH1)

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Introduction
Autosomal dominant hypocalcemia (ADH) type 1 is a rare form of hypoparathyroidism, caused by heterozygous, inherited or de novo, activating mutations in the CASR. The management of patients with ADH1 is challenging. They are usually treated as "common" primary hypoparathyroidism with conventional therapy or PTH analogues due to either absence of accurate diagnosis or to limited access to the proper therapy (calcilytics which function as negative allosteric modulators of the CaSR).
Case presentation
A 33-year-old man, diagnosed with ADH1 and Bartter's Syndrome (c.2486A>G in exon 7 of the *CaSR* gene) and Chronic myeloid leukemia (CML) was followed at the outpatient department. He was treated with calcium carbonate 500mg 1x2, alfacalcidol 1 mg 1×1, cholecalciferol 800UI 1×1, hydrochlorothiazide 25mg 1×1, rhPTH (Natpar) 75-100 mg 1×1 and magnesium supplements. He also received dasatinib for the CML. However, his management was not optimal. His serum corrected calcium was ranged from 6.1 to 8.9 mg/dl (normal range: 8.5 to 10.5 mg/d), serum phosphate level was ranged from 3.7 to 4.5 mg/dL (2.7-4.5), serum magnesium was ranged from 1.3-1.6 mg/dl (1.6-2.4), and he had a pronounced hypercalciuria (urine calcium: 520- 863 mg/24h). In October 2024 palopegteriparatide (Yorvipath) was initiated (18mg 1×1) and titrated. Almost three months after the initiation of the treatment (January 2025) the patient is treated with palopegteriparatide (Yorvipath) 30mg 1×1 and hydrochlorothiazide 25mg ½ x1) while he is independent form calcium supplements and alfacalcidol. His serum corrected calcium is 9.6 mg/dl, serum phosphate level is 3.3 mg/dL, serum magnesium was 2.1 mg/dl (1.6-2.4), and the 24h urine calcium is 390 mg/24h.
Conclusion
Until the launch of the calcilytics, palopegteriparatide (Yorvipath) may represent a valuable alternative for the management of ADH1.
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EP201

JOINT532
Vitamin d replenishment and its effectiveness on bone health in children receiving antiepileptic drugs: a randomized controlled trial
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Background
Antiepileptic drugs (AEDs) are well known to affect bone health adversely, most importantly due to vitamin D deficiency associated with use of AEDs. It is rational to monitor vitamin D status in such children to detect vitamin D deficiency/insufficiency and then to replenish vitamin D (cholecalciferol). Currently there is no consensus regarding the recommended dose of vitamin D supplementation in children receiving AEDs.
Objectives
Our objective was to detect vitamin D insufficiency in children on AEDs at baseline and then, to determine the effectiveness of two internationally accepted vitamin D (cholecalciferol) supplementation dosage (1200 IU daily vs. 400 IU daily) on bone health and vitamin D status in children on AEDs.
Methods
A Randomized controlled trial on subjects receiving antiepileptic drugs and attending Neurology outpatient department at SGPGIMS, Lucknow. We supplemented cholecalciferol in subjects receiving AEDs and having vitamin D insufficiency (serum 25OHD < 20 ng/ml) in two randomized oral dosage groups 1 and 2 (1200 IU daily vs. 400 IU daily, respectively) along with 500 mg of elemental calcium. Subsequently, we analyzed the changes in serum 25OHD and other bone health markers (Serum calcium, phosphorus, alkaline phosphatase, intact PTH, P1NP and beta CrossLaps) at the baseline and at 3 months between the two groups.
Results
Out of 70 participants, 60 (86%) were found to have vitamin D insufficiency (25OHD < 50 nmol/l). At 3 months follow-up, the group 1 had achieved vitamin D sufficiency status in all participants (23/23) whereas only 18/25 (70%) participants in the group 2 achieved vitamin D sufficiency status. The 25OHD level (mean ± SD, nmol/l) was significantly higher in group 1 as compared to group 2 (80.5 ± 24.2 vs. 50.1 ± 14.5; $P < 0.001$). Group 1 had significantly lower intact PTH level (mean ± SD, pmol/l) (3.4 ± 1.4 vs. 5.2 ± 1.8; $P < 0.01$), significantly lower ALP level (186 ± 68 vs. 298 ± 145; $P < 0.01$) and significantly lower beta CrossLaps level (1186 ± 208 vs. 1592 ± 428; $P < 0.001$), when compared to group 2. On paired t-test to analyze the changes (from the baseline to the 3 months follow-up), revealed that the changes towards improvement in the serum 25OHD level, ALP, intact PTH and beta CrossLaps were significantly more in group 1. The intervention was safe as none developed toxic levels of serum 25OHD (> 250 nmol/l), hypercalcemia and nephrocalcinosis.
Conclusion
A higher oral vitamin D replacement dose (1200 IU per day) is safe and achieves a better vitamin D level and vitamin D sufficiency state along with significantly improved biochemical markers of bonehealth.
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EP202

JOINT383
The achondroplasia roadmap
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Introduction
Achondroplasia is a type of skeletal dysplasia that effects the length and shape of bones, most apparent in the arms, legs and head. While it is the most common cause of short stature, only 1 in 25,000 children are born with achondroplasia, with about 250,000 people world-wide with the condition. Parents, healthcare professionals and others lack resources to support children in navigating the emotional and social challenges they face growing up.
Methodology
Leaders from 11 achondroplasia patient associations among them also parents and individuals with the condition participated in guided discussions to define the life milestones and related medical, emotional and social issues families and children often face. The co-created Achondroplasia Roadmap is an interactive, visual information tool that presents topics including genetic counseling, medical issues, navigating the social environment and promoting independence, presenting each topic at key phases of development: pre-natal, birth-2 years of age, 3-6 years, 7-12 years and 13-18 years. After 12 months, the same patient representatives were asked to report on key indicators to assess how and in what contexts the Roadmap has been utilized, along with metrics including number and type of events where it was presented, audience, and social media reach and impressions.
Results
Data will be presented on the utilization of the Achondroplasia Roadmap and feedback from the community in the first 12 months.
Conclusions
In addition to improving parents' knowledge about the condition, expectations are that the Roadmap is an important resource for facilitating conversations with healthcare professionals, teachers, peers and others, in order to increase understanding about the challenges faced by families and children with achondroplasia. *The Roadmap was developed by the International Council of Achondroplasia Patient Association Leaders, an ad hoc body representing 11 countries, with support from BioMarin*.
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EP204

JOINT3466

A rare case of genetically confirmed X-linked dominant hypophosphatemic rickets in a 7-year-old girl from Kazakhstan

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Introduction
X-linked dominant hypophosphatemic rickets (XLH) is a rare hereditary disorder characterized by chronic progressive phosphate wasting due to excessive fibroblast growth factor 23 (FGF23) activity. This condition typically manifests with delayed motor development, gait abnormalities, progressive skeletal deformities, lower limb pain, impaired growth, craniosynostosis, dental abscesses, and hypotonia. Biochemically, it presents with hypophosphatemia, elevated alkaline phosphatase (ALP), and a reduced tubular maximum phosphate reabsorption per glomerular filtration rate (TmP/GFR). Radiographic findings include widened growth plates in both upper and lower limbs, reflecting severe rickets-related skeletal abnormalities.
Case Report
We present the case of a Kazakh girl born in 2017, who was admitted to the pediatric endocrinology department with complaints of lower limb deformities, gait disturbances, and shin pain during prolonged walking. Clinical examination revealed significant growth retardation, severe varus deformity of the lower limbs, hypertelorism, and multiple dental caries. Additional phenotypic characteristics included an antimongoloid slant of the eyes, a flat nasal bridge, and a prominent forehead. Renal ultrasound detected bilateral nephromegaly, while radiographic imaging confirmed severe lower limb deformities, cortical thinning, and metaphyseal irregularities in both upper and lower limbs. The severity of rickets was assessed as 2 points out of 5 on the Radiographic Severity Score (RSS) scale. Genetic analysis through whole-genome sequencing identified a heterozygous deletion on the X chromosome (chrX:22202815-22216826) encompassing 16 exons of the *PHEX* gene (NM000444.6), confirming a pathogenic variant associated with XLH. Biochemical analysis further demonstrated disturbances in phosphorus metabolism, including elevated ALP 522.90 U/l (82.00 - 383.00), hypophosphatemia 0.85 mmol/l (0.95 - 1.85), increased urinary phosphorus excretion, and decreased TmP/GFR 0.71 mmol/l (1.15 - 2.6).
Conclusion
The patient was diagnosed with X-linked dominant hypophosphatemic rickets based on clinical, biochemical, genetic, and imaging findings. Targeted therapy with burosumab (Crivit) was initiated at a dose of 0.8 mg/kg subcutaneously every two weeks. This case highlights the importance of early genetic testing, comprehensive metabolic evaluation, and targeted treatment in improving outcomes for patients with XLH.

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EP205

JOINT2378

Tumor-induced osteomalacia: the bone metabolism version of the princess and the pea

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Tumor-induced osteomalacia (TIO) is a rare cause of bone demineralization, primarily affecting adults. It results from the hypersecretion of fibroblast growth factor 23 (FGF23) by typically benign, small, and elusive mesenchymal tumors, which can arise anywhere in the body, but are most commonly found in the lower limbs. Excess FGF23 reduces renal phosphate reabsorption in the proximal tubules, and inhibits the activation of 25-OH-vitamin D, thereby impairing intestinal phosphate absorption. Consequently, patients develop non-specific yet debilitating symptoms, including fatigue, chronic pain, muscle weakness, fragility fractures, and mobility impairment. We report the case of a 59-year-old female referred to our endocrinology department for progressive bone pain, muscle weakness, and multiple fragility fractures (ribs, femur, tibia, talus, and calcaneus). Extensive hematologic, rheumatologic and orthopedic evaluations revealed persistent hypophosphatemia. Renal phosphate wasting was confirmed by a low tubular maximum reabsorption of phosphate to the glomerular filtration rate (TmP/GFR) for her age. Elevated FGF23 levels, along with low 25-OH-vitamin D and 1,25-$(OH)_2$-vitamin D, raised suspicion of an FGF23-secreting tumor. Magnetic resonance imaging (MRI) identified a 50/24/64 mm mass in the retrocrural space, initially suggesting a paraganglioma. However, biochemical studies ruled out a secretory paraganglioma. Surgical excision confirmed a mesenchymal neoplasm, establishing the diagnosis of TIO. Postoperatively the patient experienced significant symptomatic improvement, including relief from pain and depression, along with restored mobility. Biochemical follow-up demonstrated normalization of FGF23, high 25-OH-vitamin D, 1,25-$(OH)_2$-vitamin D, normal serum phosphate, and phosphaturia. Diagnosing TIO remains challenging due to the difficulty in locating the causative tumor. However, it should be considered in patients with unexplained progressive muscle weakness, bone pain, and multiple fragility fractures. Early recognition and appropriate biochemical and imaging workups are crucial for timely diagnosis and treatment. While wide surgical resection remains the gold standard, newer approaches such as minimally invasive radiofrequency ablation, radiotherapy, or cryoablation are under investigation. This case is particularly notable due to the tumor's unusual size and retrocrural location, initially raising the suspicion of an alternative diagnosis.

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EP206

JOINT745

Premature girl with unusual skeletal dysplasia

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Background
Girl six months old was referred in Sept. 2020 to the pediatric endocrinologist, due to short stature approximately -6 SD and skeletal changes. Antenatally: growth retardation, acute section in week 29+4, SGA was noted. Birth weight was 745 gram, birth length was 33 cm. Head circumference normal. Apnea episode early. Initial feeding difficulties. Bilateral conductive hearing loss was discovered.
Material
X-ray findings: Full body X-ray showed shorter humerus, ulna and femur. Single longitudinal vertebrae with suggested fish shape. Lab. values: Jon-Calcium 1,38 mmol/l, Phosphate 2,0 mmol/l, Mg 0,97 mmol/l, TSH 11 mIE/l, T4 17 nmol/l, Alat 0,35 µkat/l, ALP 3,4 µkat/l, PTH 1,07 pmol/l- new sampling 3,3 pmol/l, 25-OH Vitamin D 101 nmol/l (new sampling 84 nmol/l).
Results
Microarray and skeletal dysplasia panel testing returned negative results, prompting whole-genome analysis. This analysis identified two pathogenic DNA variants in the *SLC10A7* gene in a compound heterozygous state: c.722-16A>G and c.773+1G>A. These variants lead to the production of a truncated and dysfunctional protein, impairing glycosylation. The parents were found to be heterozygous carriers, each for one of the variants. The findings are consistent with the condition "Short stature, amelogenesis imperfecta, and skeletal dysplasia with scoliosis" (OMIM# 618363). This rare skeletal dysplasia is caused by a congenital glycosylation defect and follows an autosomal recessive inheritance pattern. Associated features may include abnormal facial characteristics, hearing impairment, and intellectual disability. To date, this diagnosis has been reported in only a small number of patients. In January 2025 the girl is followed in the endocrine clinic, neonatal clinic including psychologist contact, the audiologist, specialist dentist, pediatric orthopedist, and nutrition team. Now at age 4 her height is 91,9 cm (-3 SD) and weight is 14 kg (-2 SD). She has an increasingly abundant vocabulary and has become more independent in her physical movement.
Conclusion
Whole genome sequencing (WGS) analysis revealed an unusual form of skeletal dysplasia caused by a congenital glycosylation defect. The condition is characterized by disproportionate short stature, defective tooth enamel formation and sometimes severe scoliosis. In cases with unclear symptoms and suspected syndrome perform WGS analysis and follow the patient over time.

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EP207

JOINT750

Isolated mild hypocalcemia as the initial manifestation of previously undiagnosed Coeliac disease

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Background
Coeliac disease (CD) is an autoimmune disorder triggered by gluten in genetically predisposed individuals causing intestinal inflammation and villous atrophy leading to malabsorption of essential nutrients. While hypocalcaemia is a known complication due to impaired absorption of calcium and vitamin D, it is rarely the presenting symptom of undiagnosed coeliac disease. This case highlights the diagnostic challenge when mild hypocalcaemia leads to the discovery of an underlying gastrointestinal disorder.
Case Presentation
A 63-year-old male presented with a history of fatigue, intermittent paraesthesia, and muscle cramps. He denied any symptoms of overt tetany. Laboratory investigations revealed low serum calcium (2.12), borderline low 25-hydroxyvitamin D level (35), normal phosphate, magnesium, and raised PTH suggesting secondary hyperparathyroidism. Renal and liver function test results were normal. A 24-hour calcium-to-creatinine ratio was less than 0.01. He was commenced on Vitamin D replacement. After being adequately replaced with Vitamin D, he however remained persistently hypocalcaemic. PTH or even partial Vitamin D resistance was initially suspected as potential causes. The patient was started on a trial of Calcium carbonate. However, the patient's symptoms persisted, prompting further investigations. The patient underwent a screening test for coeliac disease at a primary care centre, which revealed elevated Anti-transglutaminase (anti-tTG) antibody levels. Notably, the patient had no gastrointestinal symptoms, such as diarrhoea or weight loss, which are commonly associated with coeliac disease. The patient declined endoscopy and biopsy and hence could not ascertain the tissue diagnosis of coeliac disease. However, strong positive anti-tTG antibody levels and a family history of coeliac disease were sufficient to confirm the diagnosis clinically.
Management and Outcome
The patient was started on a strict gluten-free diet. Over several months, his serum calcium normalised, and his symptoms resolved. Emphasis was placed on nutritional counselling, including fortified foods and lifestyle modifications.
Conclusions
This case emphasises the importance of considering coeliac disease in patients presenting with unexplained hypocalcaemia, especially when accompanied by nonspecific symptoms such as fatigue and muscle cramps. Early recognition of coeliac disease can prevent the complications associated with nutrient malabsorption and lead to effective management. This case also underscores the need for comprehensive evaluation when mild hypocalcaemia is detected without clear dietary or metabolic causes and emphasis on further evaluation and investigation given persistent symptoms albeit in the setting of mild hypocalcemia should be made as was evident in this patient.

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EP208

JOINT2704

New clues that may connect the circulating irisin levels to glucose status and bone turnover markers in postmenopausal women (project IRI-OP-OB)

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Background
Irisin, a muscle-released hormone, interferes with the metabolism regulation, including settling the metabolic rate, and recently proved being pro-active in the mater of bone formation.
Objective
To check the circulating irisin levels in menopausal women in relationship with glucose profile assays and bone turnover markers on two different age groups.
Methods
This was a bi-centric, transversal, clinical study, in menopausal women without prior diagnosis of osteoporosis. Inclusion criteria were: confirmation of menopausal status and age over 50. Exclusion criteria were: insulin therapy, specific anti-osteoporotic medication, active cancers or functioning endocrine tumors at any gland, current exposure to glucocorticoid or GLP-1 agonists, end-stage CKD. The protocol included blood testing for irisin (ELISA, MyBioSource), bone turnover markers: osteocalcin, P1NP, beta-CrossLaps (ECLIA, Roche), fasting glucose (photometry, Abbott), insulin (CLIA, Beckman Coulter) and 2-hour assays amid oral 75 g-glucose tolerance test and A1c glycated hemoglobin (photometry, Roche).
Results
Two age groups: A (older than 50 to 60 y, $n = 18$) and B (older than 60 to 70 y, $n = 19$) were analyzed. Group A (55.61 $\pm$ 2.99 y) versus group B (66.11 $\pm$ 2.92 y) showed no significant differences with respect to irisin, osteocalcin, P1NP, beta-CrossLaps, fasting glycaemia, insulin, HbA1c. We found no correlation between irisin and bone turnover markers but a statistically significant positive correlation with 2-h glucose in each group ($r = 0.394$, $P = 0.042$ and $r = 0.462$, $P = 0.028$), and fasting insulin plus 2-h insulin for group A ($r = 0.543$, $P = 0.005$ and $r = 0.41$, $P = 0.033$). A borderline significance was established in group A with respect to irisin-HbA1c correlation ($r = 0.294$, $P = 0.08$).
Discussions and conclusions
So far, the correlation with glucose profile markers seems more important than the correlation with bone turnover markers. Circulating irisin levels are relevant for the muscle-bone-fat cross talk and they might serve as metabolic biomarkers.

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EP209

JOINT1159

Evaluation of a new IDS beta crosslaps® (CTX-I) assay for the iSYS automated analyzer

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Introduction
The bone resorption marker C-terminal telopeptide of Type I collagen (β-CTX-I), measured in plasma or serum is used to assess bone metabolism and therapeutic response in bone disorders. Studies have shown poor agreement in results between commercial assays for β-CTX-I and harmonization of assays has been proposed by the IFCC-IOF Committee for Bone Metabolism to achieve widely and interchangeably use of the assays.
Objective
To evaluate the performance of a new Beta CrossLaps® (CTX-I) (IDS-NEW) assay from Immunodiagnostic Systems (IDS) and to compare it with the existing IDS-iSYS CTX-I (CrossLaps®) assay (IDS-OLD) and the Roche Elecsys® β-CrossLaps/serum assay (ELECSYS).
Methods
Patient EDTA plasma samples were obtained. Precision of the IDS-NEW assay was assessed by measuring two patient pools (one around the geometric mean for premenopausal women and one at a higher level). Each level was run on every weekday in a period of two weeks, $n = 30$. Both the IDS-ISYS (iSYS) and IDS-i10 (i10) platforms were used. Correlation between the IDS-NEW assay, the current IDS-OLD assay and the ELECSYS assay were evaluated by measuring patient samples in parallel on the different assays.
Results
Precision of the IDS-NEW assay is shown in table 1. Parallel analysis of patient samples ($n = 68$) using the IDS-NEW assay on the iSYS and i10 system showed a high correlation ($R^2 = 0.994$, $P < 0.0001$) with a negligible bias of 0.5 ng/l ($P = 0.9177$). Method comparison between the IDS-NEW and IDS-OLD assays ($n = 93$) showed a high correlation ($R^2 = 0.983$, $P < 0.0001$) with a non-significant bias of 28 ng/l ($P = 0.1203$). However, a complex systematic bias with the IDS-NEW assay giving higher values at low concentrations and lower values at high concentrations compared to the IDS-OLD was seen. Finally, parallel analysis of patient samples ($n = 40$) on the IDS-NEW assay and the Elecsys assay showed a high correlation (0.9841, $P < 0.0001$) with a mean bias of 14 ng/l ($P = 0.2523$). A possible lower correlation between the assays was observed at concentrations below 200 ng/l. New reference intervals for children will be presented.

Table 1.

Level	CV (%)	SD
Medium (340 ng/l)	4.6	15.5
High (839 ng/l)	3.9	33.0

Conclusions
- There is a high correlation between the IDS-NEW and the ELECSYS assay.
- Steps towards harmonization of the IDS-NEW assay with the ELECSYS assay have now been taken. However, whether interchangeable use of the two assays for monitoring individual patients over time is yet to be determined

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EP210

JOINT3616

Evaluation of children with persistently low ALP levels

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Objectives
Alkaline phosphatase (ALP) consists of a group of isoenzymes found in many body tissues including the liver, bone, kidney, placenta, and intestine. ALP levels change with age and are measured at the highest level with increased growth. Elevated serum ALP levels are a marker of some pathological conditions, and the approach to increased serum ALP levels is better determined. In contrast, information about the approach to patients with low ALP levels is more limited. We aimed to evaluate the etiological distribution of patients with persistently low ALP levels and the demographic and clinical characteristics of infants and children diagnosed with hypophosphatasia (HPP).
Methods
This retrospective study included 0-18 years of children having low ALP levels between September 2019 and July 2024. Patients were divided into permanent and transient low ALP levels. Patients diagnosed with HPP were further examined.
Results
1825 patients with low ALP levels according to age and gender were identified. Of these patients, 79 patients were between 0-1 age (1 patient permanent, 78 patient transient) 1320 patients were between 1-11 ages (48 patient permanent, 1272 patients transient), 352 patients were between 11-13 ages (16 patient permanent, 336 patient transient), 74 patients were between 13-18 ages (15 patient permanent, 59 patient transient). 10 (0.54%) patients had a diagnosis of HPP. In the permanent subgroup without a diagnosis of HPP, calorie depletion (anorexia, malnutrition) was most frequent. Six of the children diagnosed with HPP were female and four were male. Two patients were investigated for short stature; one patient for hypercalcemia, hypercalciuria, epilepsy, and neuromotor developmental delay; one patient for respiratory distress and hypotonia; a patient was diagnosed while being followed up and treated with acute myeloid leukemia, one patient was diagnosed during a routine check-up, and one patient was diagnosed while his sibling was diagnosed. Seven different variants were detected in 9 families, all previously reported variants. Two of the variants were homozygous and five were heterozygous.
Conclusions
In our study involving a pediatric patient group, a wide range of disorders associated with low ALP activity were examined. In the case of persistent low ALP and additional specific symptoms, HPP should always be considered as a differential diagnosis. HPP presents differently in different age groups. While severe forms in young children are better known, unawareness or misinterpretation of symptoms in milder forms may lead to a delay in the diagnosis of milder cases in childhood or adolescence.

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EP211

JOINT2574

A rare cause of hypoparathyroidism: kenny caffey type 2 - case report

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Background
Hypoparathyroidism is a disorder in calcium homeostasis that is caused by inadequate secretion of parathyroid hormone, either due to an alteration in its synthesis, secretion or action. In children there may be different genetic etiologies. It can be classified as isolated or syndromatic hypoparathyroidism, within which we find Kenny Caffey syndrome. We describe a patient with a diagnosis of Kenny caffey type 2.
Case report
A two-month-old child was referred to the Pedro Elizalde hospital with a diagnosis of hypocalcemia secondary to hypoparathyroidism and suspicion of Degeorge syndrome. On physical examination, her phenotype was peculiar, finding elphoid fascies and hypoplasia of the facial mass, with micrognathia and microphthalmia, relative macrocephaly, large anterior fontanelle, severe short stature and a micropenis. Laboratory tests showed normocytic normochromic anemia, elevated transaminases, inhibited pH with hypocalcemia, hyperphosphatemia and increased vitamin D for the age range. His kidney function and other hormonal axes were normal. The echocardiogram showed an atrial septal defect and mild pulmonary stenosis. Whole body x-rays revealed tubular long bones and medullary space with stenosis. Fish was performed for 22q11.2 deletion and was normal. A clinical exome was performed without finding positive results, and ruling out Kenny Coffey type 1 and alterations in the CASR, PTH and GCMB. Kenny coffey type 2 is suspected, and exome expansion is requested and a variant of uncertain significance in heterozygosity was identified in the. FAM111A, c.913A>G p.(Arg305Gly). At this time, the genetic results of the parents are awaited.
Conclusions
Kenny Caffey syndrome type 2 is a heterogeneous disorder with multiple manifestations. Early diagnosis helps prevent comorbidities and provide better interdisciplinary follow-up.

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EP212

JOINT2523

The role of surgery in tertiary hyperparathyroidism with ectopic localization

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Introduction
Tertiary hyperparathyroidism (THPT) results from prolonged secondary hyperparathyroidism, often following hemodialysis, when the parathyroid glands become autonomous, leading to overproduction of PTH and persistent hypercalcemia. This condition may involve ectopic glands (thymus, mediastinum, or other locations), complicating diagnosis and treatment. Clinically, THPT manifests as severe hypercalcemia, vascular and tissue calcifications, osteopathy, and cardiovascular complications. When medical treatment (cinacalcet, vitamin D) fails, surgery becomes an essential option, particularly in cases involving ectopic glands.
Case Observation
A 20-year-old female patient with chronic kidney failure (on hemodialysis for 4 years) presented with a progressively developing swelling of the maxillary bone over the past 2 years. PTH levels were measured at 4028 pg/mL.
Renal ultrasound: Chronic nephropathy with simple renal cysts on the right kidney.
Cervical ultrasound: Two nodular formations in the mediastinal region suspected to be ectopic parathyroid nodules.
CT scan (thorax-abdomen-pelvis): Multiple axial and peripheral lytic lesions associated with signs of bone resorption, an expansive lytic lesion centered on the maxillary bone consistent with a brown tumor, fibrous dysplasia of the mandible and cranial vault, and homogeneous splenomegaly.
Discussion
Ectopic parathyroid glands, present in 14–45% of cases, pose diagnostic challenges that require precise localization using Tc99m-sestamibi scintigraphy or MRI. Surgical indications include refractory tertiary hyperparathyroidism unresponsive to medical treatment (cinacalcet, vitamin D), persistent hypercalcemia (>11 mg/dL) with complications (calcifications, osteopathy), and identified or suspected ectopic glands. Total parathyroidectomy with autotransplantation, combined with bilateral thymectomy and, if necessary, mediastinal exploration, is the optimal surgical strategy for these complex cases. This approach enables rapid reduction of PTH and calcium levels, significant clinical improvement, and prevention of long-term complications. A multidisciplinary approach involving endocrine surgeons, nephrologists, and radiologists is essential to ensure durable outcomes.
Conclusion
Surgery plays a central role in the management of tertiary hyperparathyroidism with ectopic glands. Accurate preoperative localization and appropriate postoperative management (calcium and vitamin D supplementation) are essential to minimize complications and ensure long-lasting outcomes.

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EP213

JOINT2317

Do patients with ehlers–danlos syndrome and a history of fractures have calcium and phosphate metabolism disturbances?

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Background
Patients with Ehlers–Danlos syndrome (EDS) are at an increased risk of fractures whose etiology is chiefly associated with joint hypermobility and instability. One of the possible risk factors for fractures are calcium and phosphate metabolic disorders. The purpose of this study was to investigate calcium and phosphate metabolic disorders in patients with a hypermobile or classical EDS subtype and a history of fractures.
Material and Methods
The study involved a prospective assessment of 30 female patients, with either hypermobile or classical EDS. The patients were divided into two groups based on their fracture history. Group 1 comprised patients with no history of fractures (n =13); group 2 comprised patients with a history of fractures (n =17). All patients were evaluated for parameters of calcium and phosphate metabolism.
Results
The two study groups showed no differences either in terms of such parameters as total calcium (2.41±0.09 vs. 2.39±0.08, P = 0.691 [mmol/l]), parathyroid hormone (41.68±15.63 vs. 43.73±15.19, P = 0.805 [pg/ml]), vitamin 25OH-D (28.2±10.8 vs. 32.44±20.35, P = 0.786 [ng/ml]), alkaline phosphatase (8.6±2.33 vs. 10.24±2.78, P = 0.133 [µg/l]), beta-CrossLabsCTX (0.43±0.2 vs. 0.36±0.2, P = 0.336 [ng/ml]), and osteocalcin (21.7±6.59 vs. 19.72±8.04, P= 0.341 [ng/ml]) levels, or in terms of EDS subtypes: classical (n =5 (38.5%) vs. n =6 (35.3%), P = 0.901) and hypermobile (n =8 (61.5%) vs. n =13 (76.5%), P = 0.399) EDS. Inorganic phosphorus levels were significantly lower in group 2 than in group 1 patients (3.19±0.51 vs. 3.85±0.59, P = 0.003). There was a significant negative correlation between a history of fractures and inorganic phosphorus levels (Spearman's R -0.559, P = 0.001).
Conclusions
Patients with EDS and fracture history may exhibit abnormal calcium and phosphate metabolism manifesting in the form of low phosphorus levels.

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EP214

JOINT3211

Not just another adenoma: the diagnostic challenges of atypical parathyroid lesions

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Atypical parathyroid adenomas are rare and difficult to diagnose, since their histopathological features overlap with both benign parathyroid adenomas and parathyroid carcinoma. These tumors lack definitive criteria for malignancy, but exhibit worrisome histologic findings such as: increased mitotic activity, trabecular growth patterns and fibrous bands. Clinically, these tumors cause signs and symptoms of primary hyperparathyroidism and hypercalcemia; while imaging modalities, including neck ultrasound, Sestamibi scintigraphy, can identify them. However, definitive diagnosis requires histopathological assessment. We report the case of a 74 year old male, with a history of prostate cancer, who was undergoing routine follow up imaging when a CT scan incidentally identified a lesion posterior to the left thyroid lobe; the scan also revealed multiple pelvic and spinal osteolytic bone metastases, the largest measuring 40x16 mm. Of note, the patient was completely asymptomatic. Endocrinological assessment revealed normal thyroid function, hypercalcemia(Ca=13,3 mg/dl), hyperparathyroidism(1741 pg/ml), low-normal vitamin D levels (20,59 ng/ml) and hypercalciuria (367,2 mg/24h). Neck ultrasound showed a well defined, hypoechoic, highly vascularized mass(3,22x4,9x2,86cm) posterior to the left thyroid lobe, raising suspicion of a parathyroid lesion. BMD-DXA revealed severe osteoporosis in the distal forearm(T score= 5,9) and decreased bone mineral density in the lumbar spine and femoral neck. Hypercalcemia persisted despite intravenous and oral hydration, so intravenous ibandronic acid was administered. A sestamibi thyroid and parathyroid scintigraphy confirmed a large hyperfunctioning parathyroid lesion on the left side, along with a smaller hyperfunctioning inferior right parathyroid lesion and a suspicious thyroid nodule in the lower two-thirds of the left lobe. Additionally, a bone scan identified suspicious bone lesions in the skull as well as the axial and appendicular skeleton. One month later, the patient underwent parathyroidectomy and thyroidectomy, and the histopathological report confirmed an atypical parathyroid adenoma. A bone biopsy was recommended, but has not yet been performed. This case highlights the diagnostic challenge of hypercalcemia in a patient with a history of malignancy. Although the presence of osteolytic bone lesions initially suggested metastatic prostate cancer, distinguishing between malignancy and parathyroid bone disease proved more difficult than expected. This distinction is crucial, since parathyroid bone disease may improve postoperatively, while metastatic disease would persist or progress. Close follow-up and monitoring are essential to reach a correct diagnosis and ensure patient's well-being in the postoperative period.

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EP215

JOINT2423

Bone and mineral metabolism alterations in newly diagnosed hyperthyroid patients

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Introduction
Advanced hyperthyroidism (HT) is characterized by high bone turnover, leading to osteoporosis. This disorder has rarely been reported in newly diagnosed hyperthyroid patients. This study aimed to determine the calcium-phosphate metabolism profile and bone mineral density (BMD) in patients with newly diagnosed HT.
Methods
A cross-sectional study was performed at the endocrinology department of Charles Nicolle Hospital in Tunis, Tunisia including newly diagnosed patients with HT from Juin to December 2023. We didn't include pregnant, breast-feeding or menopausal women, subjects with co-morbidities (hyper or hypoparathyroidism, inflammatory bowel disease, malabsorptive disorder, renal disease, chronic liver disease, Cushing's disease, hypogonadism) or having history of drug use (steroid, bisphosphonates, calcium or vitamin D). Biochimical markers of calcium-phosphate metabolism involving: corrected calcium, phosphate, parathyroid hormone (PTH) and 25-hydroxyvitamin D (25(OH)D) were assessed. BMD measurements were performed at the lumbar spine and the femoral neck.
Results
The study included 43 newly diagnosed hyperthyroid patients. The majority were female, comprising 31 individuals (72.1%). Mean age of participants was 39.1 ± 10.3 years. Graves' disease was the most frequent etiology (90%) followed by toxic multinodular goiter. Mean levels of free thyroxine (FT4) and thyrotropin (TSH) were respectively 3.2 ± 1.8 ng/dl [NR: 0,7–1,8 ng/dl] and 0,03 ± 0,01 mUI/l [NR: 0,4 – 4 mUI/l]. Hypercalcemia (corrected calcium >2.5 mmol/l) and hyperphosphatemia (phosphate >1.45 mmol/l) were observed in 23.3% and 18.6% of patients, respectively. The majority of patients (60%) had a PTH level below 40 pg/ml, within the lower half of the normal range [NR: 15–60 pg/ml]. Twenty-nine patients (76.4%) had vitamin D insufficiency (25(OH)D <20ng/dl). Osteoporosis (T-score ≤ -2.5) and osteopenia (T-score between -2.5 and -1.0) were found in 14.7% and 26.5% of patients, respectively. The comparison between patients with and without osteoporosis showed significantly higher FT4 levels in patients with osteoporosis (P = 0.01). Receiver operating characteristic (ROC) analysis identified a significant FT4 cut-off value for predicting osteoporosis. The ROC-determined cut-off was 4,7 ng/dl (2.6 times the upper limit of normal) with a sensitivity of 60 % and a specificity of 93 % for predicting osteoporosis. Calcium, phosphate, PTH and 25 (OH)D were similar in the two groups of patients (P>0.05).
Conclusion
Our study showed that accelerated bone turn over occurs early in HT, causing an imbalance in calcium-phosphate metabolism. Reduced BMD correlates with disease severity. Osteoporosis should be assessed when FT4 levels exceed 2.6 times the upper limit of normal in newly diagnosed HT.

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EP216

JOINT2031

Parathyroid cysts: about 10 cases

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Introduction
Parathyroid cysts are a rare clinical and histological entity; they represent 0.5% of parathyroid pathology and 1% of cervical cystic masses. They are rarely revealed by a palpable cervical swelling and are often an operative discovery. They can be non-functional or responsible for hyperparathyroidism. The aim of this work is to specify the clinical, paraclinical and therapeutic profile of these cysts
Material and methods
Our work is a retrospective study of 10 cases of parathyroid cyst discovered peroperatively collected in the ENT and CCF department.
Results
Our series has collected 10 cases of parathyroid cyst. There were 10 women, with an average age of 50 years. The reason for consultation was paramedian cervical swelling in all cases. The cervical ultrasound performed in all cases was in favor of a thyroid nodule in most cases. The biological assessment was normal. Fine needle aspiration cytology was not performed given the significant size of the swellings (> 3 cm) leading to the indication of surgery. The diagnosis was made intraoperatively. The anatomopathological examination confirmed the diagnosis of parathyroid cyst.
Conclusion
Parathyroid cyst is rarely considered in the presence of cervical swelling. They are generally discovered intraoperatively, however the diagnosis can be made by measuring parathyroid hormone in the puncture fluid. The treatment is surgical. Monitoring of calcemia postoperatively is necessary.

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EP217

JOINT1101

A complex case of developmental anomalies, endocrinopathies, and neurological symptoms: albright hereditary osteodystrophy (AHO)

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Background
Albright hereditary osteodystrophy (AHO) is a rare genetic disorder caused by mutations in the stimulatory GTP-binding protein, Gαs, in the GNAS gene. It exists both with and without multihormone resistance-termed pseudohypoparathyroidism type 1A(PHP1A) and pseudo-pseudohypoparathyroidism(pseudo-PHP). AHO is characterized by obesity, short metacarpals, subcutaneous ossifications, round facies, varying degrees of cognitive impairments, and typically short adult stature.
Case Presentation
A 13-year-old female with the following complaints: retardation of psychomotor development, short stature, disturbance of gait, and pain in the joints admitted to the endocrinological department. She is the 2nd child of the family, was born at 38 months gestational age and antenatally was found to have deformity of the skull. In the 7th month, she was diagnosed with "Congenital hypothyroidism" with hypocalcemia and was prescribed Levothyroxine, which she takes up to this day. On physical examination: Height-114cm, weight-58kg, BMI-44.6kg/m2, height SDS- - 7.05. The patient presents with developmental anomalies, including short stature and macrocephaly, with moon-shaped facies and a flat nasal bridge. The proximal segments of the upper limbs are shortened, accompanied by brachydactyly and positive metacarpal sign. The left lower extremity is shorter than the contralateral limb and there is evident hemihypertrophy and subcutaneous thickening is palpable in the area of the tarsal joint. The lower extremities are deformed, contributing to gait disturbances. The skin examination reveals numerous hyperpigmented macules distributed over the face and body, resembling dark moles. Since the age of 3, she has had focal seizures, 1-2 times a year, and is under the supervision of a neurologist, Carbamazepine was prescribed, which later was switched to Letiram. For hypocalcemia, she takes oral calcium daily, now 3000 mg. She also takes Calcitriol 2 tablets daily (since 10 years of age), and Vitamin D3 5000 IU daily. As the patient's complex presentation including phenotypic overlap, hormonal and metabolic abnormalities, multisystem involvement, and seizures requires multidisciplinary involvement, in 2022, a medical genetic consultation was performed followed by whole genome sequencing, which confirmed GNAS gene mutation likely PHP or pseudo-PHP.
Conclusions
This case highlights the diagnostic complexity of a patient with a rare genetic disorder, multiple developmental anomalies, endocrinopathies, and neurological symptoms. The overlapping phenotypic features and systemic involvement underscore the importance of a multidisciplinary approach to diagnosis and management.

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EP218

JOINT3702

Growth failure and chondrodysplasia following early hematopoietic stem cell transplantation for familial lymphohistiocytosis: a case report

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We report the case of a 3-year-old boy referred for short stature and growth failure, with a history of familial lymphohistiocytosis (FHL), for which he underwent allogenic hematopoietic stem cell transplantation (HSCT) at 3 months of age. The child was born at term with a birth weight of 4.010 kg and length of 51 cm. At 5 weeks, he was hospitalized for fever, leading to the diagnosis of FHL, confirmed by genetic analysis revealing a pathogenic variant in the PRF1 gene. Initial treatment with corticosteroids, cyclosporine, and alemtuzumab failed to induce remission, resulting in an HSCT. Following successful transplantation, growth was impaired. Family history revealed a target height of 176.5 cm (-0.58 SD), with both parents of Pakistani origin and first cousins, but no history of short stature or endocrine disorders. At the time of the HSCT, the height was 59 cm (-1.17 SD) and the weight was 6kg800 (0.7 SD). Clinical examination at 3 years 9 months revealed a height of 85.6 cm (-4.12 SD), weight of 14.8 kg (-0.86 SD), and a BMI of 20.2 kg/m^2 ($+2.91$ SD). He exhibited relative macrocephaly, rhizomelic shortening, but no other dysmorphic features. Growth velocity was measured at 4.3 cm/year. The differential diagnosis included growth hormone deficiency, skeletal dysplasia, and glucocorticoid-induced growth suppression. Hormonal evaluation showed IGF1 levels of 39 ng/ml, IGFBP3 at 1.8 mg/l, and normal thyroid function and cortisol levels. A normal glucagon test ruled out growth hormone deficiency. Radiographic imaging revealed dysplastic changes, including shortened humeral diaphyses, proximal epiphyseal dysplasia of the humerus, and iliac bone dysplasia. Despite a normal skeletal dysplasia panel, these findings were consistent with possible chondrodysplasia. At the follow-up visit at age 6 years 3 months, height was 96.5 cm (-4.52 SD), with a growth velocity of 3.3 cm/year. The diagnosis of probable chondrodysplasia and growth failure following early HSCT was made, based on the findings of Botto *et al.* (2020), who described a series of 7 children with similar growth failure and radiographic changes after HSCT for non-oncologic pediatric diseases, suggesting a new potential complication. This case highlights the importance of careful monitoring of growth and skeletal development in children undergoing HSCT for non-oncologic conditions, as they may be at risk for both endocrine and skeletal complications.

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EP219

JOINT2223

Case report and follow-up of juvenile paget's disease caused by TNFRSF11B mutations in sibling pair

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Background
Juvenile Paget's Disease (JPD; OMIM 239000) is a rare autosomal recessive disorder characterized by accelerated bone remodeling and elevated serum alkaline phosphatase (ALP) levels. Mutations in TNFRSF11B, which encodes osteoprotegerin (OPG), have been implicated in JPD.
Methods
This report describes two siblings with compound homozygous loss-of-function mutations in TNFRSF11B, leading to OPG deficiency and consequent typical symptoms of JPD. Case 1 (male, 7 years 3 months) presented with severe bone deformities with multiple fractures and hearing impairment. He cannot walk

indecently without any help. Case 2 (female, 4 months) presented with minor bone deformities and initial hearing impairment. Whole exon gene examination confirmed the homozygous mutation of TNFRSF11B gene c.412C>T (p. R138X). Their parents were non-consanguious. Traditional calcium and vitamin D treatments have limited effects on JPD patients. After alendronate sodium was administered, the symptoms of the siblings were alleviated, they could stand and walk without any help, and the serum total alkaline phosphatase (ALP) level was significantly decreased.
Results
After bisphosphonate treatment, ALP levels decreased significantly and skeletal symptoms improved in both cases.
Conclusions
Early identification and treatment of JPD caused by TNFRSF11B gene mutation can significantly improve the quality of life of patients. Bisphosphonates are effective therapeutic agents, and early intervention can prevent severe bone deformities and functional impairment.
Keywords
Juvenile Paget's Disease; Alkaline Phosphatase; Bone Remodeling; Bisphosphonates; TNFRSF11B.
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EP220

JOINT3353

Evaluation of the Impact of Therapeutic Patient Education (TPE) on Quality of Life Compared to Standard Care and Injectable Parathyroid Hormone Treatment in Chronic Hypoparathyroidism

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Background
This study assesses the impact of Therapeutic Patient Education (TPE) on quality of life in patients with chronic hypoparathyroidism.
Methods
We extracted Quality of Life results (assessed by SF36) on our cohort of patients with hypoparathyroidism (post-surgery or genetic), divided into three groups: (1) Standard Care (Control, $n = 10$), (2) included in our program of Therapeutic Patient Education (TPE, 6 online sessions co-animated with a patient expert and our referent center, $n = 28$), and (3) TPE + Teriparatide initiated before TPE (TPE + Teriparatide, $n = 11$). SF36 questionnaires were completed by the patients at Baseline (before TPE), 3 and 6 months later. Kruskal-Wallis tests were performed to assess group comparability at baseline and to analyze score evolution over time. A post-hoc Mann-Whitney test was applied to identify specific inter-group differences.
Results
Kruskal-Wallis tests indicated significant baseline differences in Physical Functioning ($P = 0.0058$), Role Physical ($P = 0.0013$), Role Emotional ($P = 0.0392$), Energy/Fatigue ($P = 0.0327$), and General Health Perception ($P = 0.0058$), indicating that groups were not comparable at baseline. At 3 months, no significant differences in score evolution were found among groups. At 6 months, Physical Functioning ($P = 0.0101$), Social Functioning ($P = 0.0023$), Pain ($P = 0.0043$), and General Health Perception ($P = 0.0039$) were significantly different between groups. The TPE and the TPE + Teriparatide groups showed significant improvement in Social Functioning compared to the Control group ($P = 0.0017$ and $P = 0.0077$, respectively). No significant difference was found between the TPE and TPE + Teriparatide groups. Regarding pain, both the TPE ($P = 0.0075$) and TPE + Teriparatide ($P = 0.0070$) groups showed significant improvement compared to the Control group.
Conclusions
SF-36 scores were significantly more impaired in the TPE and TPE + Teriparatide groups compared to the Control group, which is consistent with the fact that these treatments are preferentially targeted at more severe patients. Our findings suggest that TPE significantly improves social functioning and pain perception compared to standard care. The absence of a difference between TPE and TPE + Teriparatide indicates that TPE alone may provide substantial benefits. These results highlight the potential of TPE as a valuable intervention for enhancing the quality of life in patients with chronic hypoparathyroidism. The key role of patient support networks and the long-term effects of TPE should be further evaluated.
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EP221

JOINT1436

Osteopenic males PHPT patients: prevalence and clinical features

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PHPT is nowadays the third more common endocrine disease, with an estimated prevalence in the general population of 0.5%-1% that increase more than 2% with age in both sexes. PTX is the only definitive treatment for PHPT with very high cure rate and it is recommended for all PHPT patients with symptomatic disease and for asymptomatic patients meeting surgical criteria, updated over time in an inclusive way toward. To date osteoporosis is the surgical criteria more ofteen met while osteopenia is not taken into account as surgical indication. PTX improves bone mineral density and reduce bone remodeling biomarkers also in patients with milder PHPT forms, on the other hand whether PTX is linked to fracture risk reduction also in milder forms of PHPT is still debated. Recently, it has been reported that PTX was associated with a lower risk of fracture in older adults independently by frailty categories, presence of osteoporosis, and criteria for operative management suggested by guidelines. Our study aimed to evaluate the prevalence and clinical features of osteopenic males PHPT patients. From a consecutive series of 435 subjects with PHPT and densitometric data available on 3 sites (lumbar, femoral and radial) we selected 90 male subjects. In this subgroup, we focused on the 31 with osteopenia (34.4% of males). They were classified as symptomatic in 61.3% and asymptomatic in 38.7% of cases. Among the symptomatic, 94.7% have renal involvement. Among asymptomatics, the most frequently met criteria are age (100%) and 24-hour Urinary Calcium (80%). In conclusion, male PHPT subjects with osteopenia are almost 1/5 of PHPT patients with osteopenia and are symptomatic in the majority of cases, mostly due to renal involvement. Among asymptomatic subjects, 54.5% did not meet any criteria for surgery.
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EP222

JOINT1856

Prevention of rebound hypercalcemia in giant cell bone lesions treated with denosumab: a critical comparison of two different approaches

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Background
Denosumab is a monoclonal anti-RANK-L receptor antibody used to treat a wide range of bone lesions, including fibrous dysplasia, osteogenesis imperfecta, aneurysmal bone cysts, giant cell granuloma (GCG) and giant cell tumor of bone (GCTB) in both adults and children. The use of denosumab in pediatric patients is associated with a high risk of rebound hypercalcemia upon discontinuation. This condition often requires hospitalization and, in some cases, bisphosphonates to normalize calcium levels. Based on the clinical course of two patients with GCG treated with denosumab, we propose a preventive approach to rebound hypercalcemia.
Case presentation
Patient 1 was a 7-year-10-month-old boy who presented with maxillary swelling. MRI revealed a left maxillary mass (50x50x57mm), and pathology confirmed the diagnosis of GCG. Neoadjuvant treatment with denosumab (120 mg) was initiated with loading doses at T0, followed by doses at T15 and T45. T8 was not performed due to phosphaturia. Loading doses were followed by monthly doses of 100 mg for 8 months. The dose was gradually reduced to 20 mg over 6 months and discontinued after a total of 16 months of treatment. Follow-up MRI showed size reduction of the lesion to 45x54x37mm. Despite the tapering, the patient developed severe rebound hypercalcemia 2 months after discontinuation (total serum calcium increased to 15.8 mg/dl), requiring hospitalization and treatment with intravenous hydration, furosemide, oral glucocorticoids and endovenous zoledronate (dose 0.05 mg/kg/dose). Patient 2 was a 16-year-2-month-old boy referred for a costal lesion, which was diagnosed as GCTB after biopsy. Denosumab treatment was started with a dose of 120 mg at T0, followed by 100 mg (due to hypophosphatemia) at T8 (T15 was not performed due to hypophosphatemia) and T45. Monthly doses were then

administered and reduced to 40 mg within 3 months. One month after suspension, the patient received 2 mg (dose 0.03 mg/kg/dose) of intravenous zoledronate. Follow-up CT scan showed a stable size of the lesion with increased calcification. Six months after discontinuation, the patient successfully underwent surgical removal of the lesion, and his serum calcium levels remained within the normal range.
Discussion
Prevention of rebound hypercalcemia after suspension of denosumab may be challenging and tapering alone may not suffice. We propose a stepwise approach to the adverse events associated with denosumab involving strict monitoring for hypocalcemia and hypophosphatemia (which should be promptly corrected), and the administration of zoledronate at least one month after suspension to prevent rebound hypercalcemia.

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EP223

JOINT207

Bone-specific alkaline phosphatase as a complementary diagnostic marker for the assessment of children and adolescents with secondary osteoporosis

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Introduction
With increasing cases of osteoporosis in children and adolescents, the need for timely diagnosis, management, and follow-up has become important. In adults, the use of bone turnover markers (BTMs) to monitor anti-osteoporotic treatments has been studied and is being recommended. However, how BTMs can be used in children and adolescents with osteoporosis is not fully known, as well as its possible use as diagnostic criteria and/or as predictors of fracture risk. This study aimed to determine whether BTMs, particularly bone-specific alkaline phosphatase (BsALP) and C-telopeptide of collagen type 1 (CTx), accurately reflect bone mineral density (BMD).
Methods
In this retrospective study, 280 post puberty males, aged 12.5-18 years old, and females, aged 10.5-18 years old, who were previously diagnosed with hemato-oncologic, rheumatoid, gastrointestinal, and endocrinologic diseases at a single tertiary care center were reviewed. The association between the lumbar spine bone mineral density (LSBMD) Z-scores and BTMs, such as BsALP and CTx, were assessed.
Results
Of the 280 patients, 95 were male (33.9%), and the mean age was 15.4 ± 2.07 years. The mean LSBMD Z-score was -0.52 ± 1.23, with 61.4% being ≤ 0, 34.6% being $\leq$-1.0, 13.6% being $\leq$-2.0, and 3.2% being $\leq$-3.0. With multivariate regression analysis, LSBMD Z-scores and BsALP showed a negative correlation with $p < 0.007$, while CTx was not statistically significant. The logistic regression models showed that after adjusting for underlying diseases and sex, as BsALP increased, the probability of LSBMD Z-score being $\leq$-2 increased with an odd ratio of 1.043 ($p = 0.048$). When comparing BTMs with vertebral fracture while adjusting for underlying diseases and sex, as BsALP increased, the probability of vertebral fracture increased with an odd ratio of 1.035 ($p = 0.005$). When the same comparison was made with CTx, the odd ratios of LSBMD Z-score being $\leq$-2 and with the presence of vertebral fracture were 0.419 and 1.001, respectively ($p = 0.156$, 0.997), which were not statistically significant.
Conclusion
BTMs change during growth as a function of age and sex; thus, comparing BTMs directly with LSBMD without any adjustments will not give any correlation in children. This study suggest that BsALP can be used as a complementary tool to evaluate secondary osteoporosis in children and adolescents if adjustments for underlying disease and sex are made. However, further studies with a larger sample size are required to adjust for age, which will better reflect the characteristics of pediatric patients.

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EP224

JOINT1474

Novel allelic variants in Sanjad-Sakati and Kenny-Caffey syndromes identified by whole exome sequencing

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Introduction
Hypoparathyroidism-retardation-dysmorphia syndrome (HRD), also known as Sanjad-Sakati syndrome (SSS), is an autosomal recessive disorder characterized by permanent parathyroid hormone (PTH) deficiency, hypocalcemia, hyperphosphatemia, facial dysmorphism, and occasionally, psychomotor retardation. A similar syndrome, with additional features such as osteosclerosis and recurrent infections, is the autosomal recessive Kenny-Caffey syndrome (KCS1). Both syndromes have been associated with abnormalities in the gene encoding tubulin folding cofactor E (TBCE, 1q42.3). Mutations in *FAM111A* (11q12.1), which encodes a serine protease FAM111A, have also been described in a clinical variant of Kenny-Caffey syndrome (KCS2). We here-in describe a male patient with HRD, presenting previously unreported molecular abnormalities in both, the *TBCE* and *FAM111A* genes.
Methods
Whole exome sequencing was performed on peripheral blood genomic DNA of a 15-year-old male who sought medical care because of severe hypocalcemia and hyperphosphatemia, as well as facial dysmorphism. Born to non-consanguineous parents of Syrian-Jewish origin, he was found to have micrognathia, low ear implantation and retention of primary teeth. On the physical exam he was found in frank tetany with positive Trousseau and Chvostek signs, as well as bilateral cataracts. He has adult-like axillary and pubic hair and external genitalia were fully developed. Neuropsychological testing was normal, without evidence of mental retardation. Relevant laboratory results included a serum Ca of 4 mg/dL, P 7 mg/dL, intact PTH undetectable, 25-hydroxi-vitamin D3 10 ng/mL and mild eosinophilia. Renal and hepatic function tests, as well as thyroid function tests were all within normal limits. The ECG showed prolonged QT interval. Head CT revealed multiple bilateral calcifications, particularly in basal ganglia, thalami and cerebellum. He started on large doses of calcium carbonate, calcitriol and teriparatide with important symptomatic improvement.
Results and conclusions
The patient showed a highly polymorphic exome but none of the known mutations in *TBCE* and *FAM111A* genes. However, he harbored several compound heterozygous variants that have not been previously described. An insertion, two deletions and 5 single nucleotide changes in the intronic region of *TBCE* were identified (235372627insAG, 235380162_183delTGTGTGTGTGTGTGTGTG, 235412798_803delATTATT, 235427244G>A, 235430867A>G, 235435658C>T, 235438643G>T, 235439089G>A). An apparently non-pathogenic, synonymous variant in *FAM111A* (c.A672G p.Ala224Ala) was also found. HRD syndrome represents an overlapping spectrum, as illustrated by our patient, who despite having an unequivocal clinical and biochemical phenotype, he lacked the *TBCE* and *FAM111A* mutations known to be associated with SSS and KCS. Further research is needed to ascertain if the polymorphic intronic variants found in our patient are of pathogenic relevance.

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EP225

JOINT3979

Iatrogenic hypoparathyroidism revealed by amicrobial pustulosis following total thyroidectomy; a case report

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Introduction
Iatrogenic hypoparathyroidism is a well-documented complication of total thyroidectomy, often manifesting as hypocalcemia-related neuromuscular symptoms. However, atypical dermatologic presentations, such as amicrobial pustulosis, remain poorly recognized. This case highlights the importance of suspecting hypoparathyroidism in patients presenting with unusual post-surgical dermatologic manifestations [1,2].
Case Presentation
A 52-year-old female underwent total thyroidectomy in November 2021 for a multinodular goiter. She had no immediate postoperative complications and was not placed on calcium or vitamin D supplementation. In August 2022, she developed widespread pustular skin lesions consistent with amicrobial pustulosis. During her

dermatologic evaluation, severe hypocalcemia (34 mg/l) was incidentally discovered, prompting an endocrine assessment that confirmed iatrogenic hypoparathyroidism. Treatment with intravenous calcium and vitamin D supplementation led to the resolution of both her cutaneous and biochemical abnormalities within one month. However, four months after discontinuation of vitamin D due to supply issues, she presented again with similar pustular lesions associated with severe hypocalcemia, reaffirming the link between her skin manifestations and calcium metabolism disorder.

Discussion and Conclusions

This case illustrates an unusual presentation of iatrogenic hypoparathyroidism, where amicrobial pustulosis was the initial and predominant manifestation. The pathophysiological link between hypocalcemia and pustular dermatoses remains unclear, but calcium plays a critical role in keratinocyte differentiation and immune response regulation. Hypocalcemia-induced alterations in epidermal homeostasis may predispose to inflammatory skin conditions, such as pustulosis [3,4]. A major challenge in this case was the delayed diagnosis of hypoparathyroidism, as the patient had no classic neuromuscular symptoms like tetany or paresthesia. Instead, the recurrent pustular lesions were the primary indicator of underlying metabolic imbalance. This underscores the need for clinicians to consider calcium and parathyroid hormone (PTH) levels in cases of unexplained pustular eruptions, particularly in post-thyroidectomy patients [5]. In conclusion, this case emphasizes the necessity of maintaining a high index of suspicion for hypoparathyroidism in post-thyroidectomy patients with atypical dermatologic presentations.

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EP226

JOINT3452

Hypoparathyroidism: clinical and genetic characteristics with long-term outcomes

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Introduction

Hypoparathyroidism is a rare endocrine disorder in children which is mainly characterized by insufficiency or inefficiency of parathyroid hormone (PTH) leading to hypocalcemia and hyperphosphatemia. Hypoparathyroidism most commonly results from anterior neck surgery in adults while the most common cause is genetic abnormalities in children. In order to improve the diagnosis and expand the knowledge of the disease, we analyzed relevant data of clinical diagnoses, laboratory findings, molecular determination and long-term follow-up in 24 children with hypoparathyroidism in our center.

Method

A total of 24 patients with hypoparathyroidism, monitored and treated at Department of Pediatric Endocrinology in the SBU Izmir Dr. Behçet Uz Children's Hospital between 2010 and 2024 years, were retrospectively analyzed for the clinical, laboratory and genetic data. Genetic results of the patients were obtained by Next Generation Sequencing (NGS) or Sanger sequencing methods.

Results

This retrospective study included 24 patients (9 females and 15 males) with hypoparathyroidism. The most common initial presentation was convulsions (33.3%) and muscle spasms in hands (20.8%). Three of the patients were asymptomatic and diagnosed with incidental hypocalcemia. Parents were consanguineous in seven (35%) cases. The mean age of presentation was 6.7±5.9 (1 months-17.3 years). Twenty-three of the patients were followed up with a diagnosis of primary hypoparathyroidism and one patient with a diagnosis of secondary hypoparathyroidism due to thalassemia. Of the patients diagnosed with primary hypoparathyroidism, 12 had syndromic and 11 had isolated hypoparathyroidism. The most common cause of syndromic hypoparathyroidism was Di George syndrome (n:5), followed by *GATA3* mutations (n:3); two cases were diagnosed as pseudohypoparathyroidism and one case was diagnosed as Kenny-Caffey syndrome due to a variant in the *FAM111A* gene. The mean duration of follow-up was 6.9 ± 5.0 years (1.01-17.83). Ten patients had reached their final height at the time of the study and, for whom, long-term outcome data were analyzed. Their mean final height SDS was −1.98 ± 0.46 (Median: −1.85; min: −5.71; max: 0.78). No complications were observed in any of the patients during long-term follow-up.

Conclusions

In this study, clinical and genetic features and long-term follow-up of our patients with hypoparathyroidism were presented. Also, we presented a rare case of Kenny-Caffey syndrome, which presented with hypoparathyroidism. Reporting detailed features of the cases with hypoparathyroidism will increase the knowledge and awareness about the disease.

Keywords

Hypoparathyroidism, DiGeorge Syndrome, *GATA3*, *FAM111A, CASR*

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EP227

JOINT3675

Cinacalcet in primary hyperparathyroidism: QEHB audit

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Background

The first line treatment for primary hyperparathyroidism (pHPT) is parathyroidectomy, however, some patients are unfit for or do not accept surgery. In such cases, cinacalcet (a calcimimetic) can be initiated with the aim to normalise blood calcium levels and mitigate direct effects associated with hypercalcaemia. For patients who are not suitable for parathyroidectomy, the UK's national guidelines suggest use of cinacalcet if hypercalcaemia-related symptoms are present and serum aCa is 2.85-3.00mol/l or if aCa is > 3.00mmol/l, irrespective of symptoms.

Aims

To assess local practice against NICE guidance [NG132] for prescribing cinacalcet in patients with primary hyperparathyroidism. To evaluate treatment effect on adjusted calcium levels and investigate treatment duration required to achieve normocalcaemia, including any intolerances and reasons for discontinuing cinacalcet.

Method

A retrospective study of all patients initiated on cinacalcet from June 2011 to February 2024 at Queen Elizabeth Hospital, Birmingham. This includes collection of biochemical data, inpatient and outpatient records and prescribing data.

Results

Of the 61 patients started on cinacalcet, 40 were commenced following the release of the national guidance in May 2019. 37 of these 40 patients (92.5%) were prescribed cinacalcet according to the NICE guidance. Most outpatients had accompanying prescribing checklist forms (21/27) since local introduction. A significant reduction in serum aCa was seen in patients after cinacalcet treatment (mean 2.56, 95%CI 2.49-2.63 mmol/l) when compared to baseline figures (mean 3.06, 95%CI 3.00-3.11 mmol/l). Additionally, 45 patients (73.8%) achieved normocalcaemia after a median duration of 30 days and 120 days each for inpatients and outpatients respectively. 16/61 patients reported side effects, and of these, 3 patients stopped their medication (nausea, vomiting, worsened dyspepsia).

Conclusion

Local prescribing generally adhered to national NICE guidance. The specialist team initiation and input, as well as thorough prescribing checklists when starting the medication in outpatient endocrine clinics, greatly contributed to this. Although a small number of patients were started on cinacalcet outside the guidance, reasons for doing so included symptom control in those unfit for surgery, persistent hypercalcaemia following surgery and bridging therapy due to COVID-19 pandemic related delays for elective surgery. Despite being a long-term treatment, cinacalcet was generally well tolerated. The quantitative reduction seen in serum adjusted calcium correlates with existing literature and highlights the benefit of cinacalcet as the mainstay of medical management of hypercalcaemia of pHPT for those unable to have surgery.

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EP228

JOINT2188

Intravenous Bisphosphonates for Severe Hypercalcemia in Primary Hyperparathyroidism: Do We Need to Draw an Analogy From Osteoporosis Experience?

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Introduction
Intravenous (IV) bisphosphonates can effectively lower calcium levels in primary hyperparathyroidism (PHPT). However, in recurrent severe hypercalcemia, it may be used more frequently than what is ideal. Atypical femur fractures and osteonecrosis of the jaw are reported to be rare side effects from prolonged bisphosphonate use in osteoporosis and the risk is higher with IV compared to oral preparations. Local hospital guidelines recommend IV pamidronate for PHPT patients with severe hypercalcemia. According to the British National Formulary, IV pamidronate can be given at 4-weekly intervals in osteolytic bone metastases, but no similar guidelines exist regarding the number and frequency of infusions for PHPT patients with hypercalcemia. The aim of this single-centre study was to establish the frequency of IV bisphosphonate therapy in these patients and consider subsequent plans for monitoring.
Methods
Patients who had ≥ 3 pamidronate infusions per year, over the last 3 years ($n = 19$) were reviewed. Concurrent use of cinacalcet and clinical outcomes were analysed. Total infusions per patient was divided by their respective follow-up time (in months, from first IV treatment until surgery or till date) and multiplied by 12 to provide a comparative measure of the equivalent annualised frequency.
Results
All 19 patients were given IV pamidronate for severe hypercalcemia. The dose varied from 30-90mg per infusion. 63.2% ($n = 12$) were on concurrent cinacalcet treatment; 7 patients were completely intolerant to cinacalcet. In 14/19 patients, IV pamidronate was used to manage hypercalcemia whilst waiting for surgery. The other 5 patients opted for a conservative approach for various reasons: lack of localisation and reluctance for open surgery ($n = 2$), failed surgery ($n = 2$) and frailty ($n = 1$). These 5 patients were on cinacalcet but intolerant to higher doses. The mean follow-up time was 13 months (range 4-36 months). Pamidronate use ranged from 3-28 infusions during this time. The average equivalent annualised frequency of infusions was 7/year (range 2-12/year) in this cohort.
Discussion
A small but significant number of PHPT patients needed frequent IV bisphosphonate therapy. Reasons include longer waiting time for surgery (majority of patients), severity of hypercalcemia and intolerance to cinacalcet. The chronic use of pamidronate may increase the risk of atypical side effects in PHPT management too, which is well recognised from osteoporosis experience but less routinely perceived in endocrine clinical practice. This risk should therefore be emphasised (e.g. information leaflets, nurse-led clinics) as part of the counselling process when consenting PHPT patients for longer-term IV bisphosphonate therapy.

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EP229

JOINT1890

Bone mineral density alterations in primary hyperparathyroidism: clinical and diagnostic implications

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Background
Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by excessive parathyroid hormone (PTH) secretion, disrupting calcium and phosphorus metabolism. Among its systemic effects, bone health is particularly affected due to reduced bone mineral density (BMD) and an increased risk of skeletal fragility and fractures.
Objectives
1) To compare BMD and fracture risk (using the FRAX calculator) between PHPT patients and controls. 2) To analyze T and Z scores at different skeletal sites: spine, proximal femur, and distal one-third of the radius.
Methods
The study included PHPT patients diagnosed at the University Clinical Center's Endocrinology and Internal Medicine Department (2014–2024) who underwent densitometry using a Hologic device. The control group consisted of patients from the same period who also underwent densitometry but were not diagnosed with PHPT. Exclusion criteria included chronic kidney disease, antiresorptive or glucocorticoid therapy, rheumatoid arthritis, congenital bone fragility, diabetes mellitus type 1, hypogonadism, premature ovarian failure, malabsorption syndrome, and chronic liver disease.
Results
Among 441 patients evaluated for hypercalcemia, 237 met the inclusion criteria: 191 with PHPT and 46 controls. The study and control groups were matched for age, gender, and BMI. No significant differences in BMD were found between the PHPT and control groups in women ($P = 0.13$) or men ($P = 0.26$). Similarly, major osteoporotic and hip fracture risks did not significantly differ ($P = 0.28$ and $P = 0.19$, respectively). Notably, in the PHPT group, T-scores differed significantly among the lumbar spine, femoral neck, and radius ($P < 0.01$), while Z-scores did not (radius vs. femur: $P = 0.665$; radius vs. lumbar: $P = 0.14$). In the control group, no significant differences were observed in either T-scores ($P = 0.556$) or Z-scores ($P = 0.384$).
Conclusions
Consistent with prior research, our findings confirm a preferential loss of cortical bone in PHPT patients. However, femoral neck BMD and fracture risk were not significantly higher compared to controls.

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EP230

JOINT2043

Perspectives of patients and families on X-linked hypophosphatemic rickets (XLH) and its impact on quality of life: a qualitative study

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Background
X-linked hypophosphatemic rickets (XLH) is a rare genetic disorder causing chronic hypophosphatemia, impaired bone mineralization, and musculoskeletal complications. Despite advances in treatment, patients continue to experience a significant disease burden affecting their quality of life. This study explores the lived experiences of patients and caregivers to identify key challenges in disease management.
Methods
This qualitative study collected data through an open-ended survey distributed by the Spanish Association of Hereditary Rickets and Osteomalacia (AERyOH). A total of 11 responses (7 patients, 4 family members) were analyzed using MAXQDA software to identify key themes.
Results
Four major themes emerged. (1) Diagnostic delay: Many patients, especially adults, reported years of misdiagnosis, leading to delayed treatment and irreversible complications. (2) Treatment burden: The need for frequent phosphate and vitamin D intake, along with side effects, posed adherence challenges. (3) Physical limitations and chronic pain: Mobility issues and persistent pain significantly impact daily life. (4) Psychosocial impact: Participants experienced stigmatization, social isolation, and work-related challenges. Family members also reported emotional distress and caregiving burdens.
Conclusions
XLH affects not only physical health but also emotional and social well-being. Early diagnosis, optimized treatments, and psychosocial support are essential to improving patient outcomes. A multidisciplinary, patient-centered approach is needed to address these challenges and enhance the quality of life for individuals with XLH.

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EP231

JOINT2425

An exceptionally cause of fahr's syndrome: pseudohypoparathyroidism

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Introduction
Fahr's syndrome is a rare anatomo-clinical entity, characterised by bilateral and symmetrical intracerebral calcifications in the basal ganglia, most often associated with disorders of phosphocalcium metabolism. Hypoparathyroidism is the most common anomaly. Pseudohypoparathyroidism is exceptionally reported as a cause of Fahr's syndrome.
Observation
Patient aged 28, followed in psychiatry for delusional psychotic disorders evolving for 3 years, under neuroleptic treatment, without clear improvement. Complicated 1 day after her admission to the medical intensive care unit by the onset of confusion-type consciousness disorders evolving in a febrile and atraumatic context, and by the appearance of tetany crises involving the 4 limbs, the nape of the neck and the chest wall giving rise to respiratory disorders. On admission, the clinical examination revealed a confused patient with a Glasgow score of 13/15, a blood pressure of 100/70 mmhg and a heart rate of 102 bpm. The patient was polypnoeic and had an oxygen saturation of 99% on 4 litres of oxygen therapy, with a temperature of 38.5 C. The patient had a stiff neck and a soft abdomen, and the rest of the clinical examination was unremarkable. A lumbar puncture was performed, which returned normal. Cerebral CT revealed bilateral and symmetrical calcifications involving the basal ganglia. Biological tests showed hypocalcaemia at 61.76 mg/l (N:84-102), hyperphosphaemia at 49 mg/l (N:27-45), and a normal serum parathyroid hormone level of 12.8 pg/ml (N:12-80). Given this picture, the diagnosis of pseudohypoparathyroidism was accepted. Treatment consisted of calcium and vitamin D replacement therapy. Progress was favourable.
Discussion
The clinical manifestations of Fahr's syndrome include primarily neuropsychiatric signs: behavioural disorders, confusional or delusional syndrome. Other neurological manifestations are possible but less common. Fahr's syndrome is most often associated with dysparathyroidism: hypoparathyroidism is the most common anomaly. The association of Fahr's syndrome with hyperparathyroidism or pseudohypoparathyroidism, as in our patient's case, has rarely been described; a review of the literature found less than a dozen cases. Other pathologies can cause intracerebral calcifications, such as endocrinopathies, systemic diseases and infections, but with different sites and appearances. The diagnostic test of choice is computer tomography. The prognosis for Fahr's syndrome is good, as the clinical and neuropsychological signs regress once the phosphocalcic disturbances have been corrected.
Conclusion
Although Fahr's syndrome is a rare entity, this clinical case shows the importance of brain imaging and phosphocalcium assessment in the investigation of neuropsychiatric disorders, with a view to initiating appropriate therapeutic measures.

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EP232

JOINT294

Severe hypocalcemia and psoriasis: an intriging link

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Introduction
Down syndrome is a genetic disorder resulting from the presence of an extra copy of chromosome 21. The spectrum of this disorder is very broad, including endocrine and dermatological manifestations. Through this observation, we discuss an extremely rare cause of psoriasis: hypocalcemia. We demonstrate the improvement of skin lesions under prompt calcium treatment.
Observation
This is an 18-year-old patient who was hospitalized in the endocrinology department for the management of severe hypocalcemia at 0.9 mmol/l. The diagnosis of Down syndrome was made at birth due to typical dysmorphia. He has a history of seizures that have occurred for a year and have not been investigated. One month before his hospitalization, the appearance of well-defined, generalized erythemato-squamous plaques was noted, particularly on the scalp and extensor surfaces of the limbs, consistent with psoriasis. The patient was treated with topical corticosteroids without improvement, hence their discontinuation. An assessment revealed severe hypocalcemia at 0.9 mmol/l. The etiological investigation concluded to a vitamin D deficiency of less than 8 ng/ml and hypomagnesemia at 0.6 mmol/l. Vitamin and calcium supplementation, as well as magnesium, was initiated, leading to normalization of the phosphorocalcic balance and a spectacular improvement of the psoriatic lesions.
Discussion
Vitamin D deficiency is a known risk factor for psoriasis. Elsewhere, the association between hypocalcemia and psoriasis is not coincidental. Indeed, hypocalcemia can impair cell adhesion, thus favoring the onset of psoriasis. Moreover, psoriasis can cause extensive skin inflammation, resulting in extravasation of albumin and albumin-bound calcium into the interstitial space.

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EP233

JOINT1630

The potential (secondary) use of a calcilytic drug to prevent post-operative hypoparathyroidism

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Parathyroid gland insufficiency is a frequent complication following thyroid surgery (total/near-total thyroidectomy) and the leading cause of secondary hypoparathyroidism with its consequence, hypocalcaemia. Surgical precautions devised to protect parathyroid glands from traumatic injury have largely failed to eliminate the problem. We propose a mechanism behind postoperative hypoparathyroidism that may account for the high incidence rate and the transient course it takes in most of the instances. After its closure the surgical wound regularly fills with fluid bound to soak parathyroid gland parenchyma. Wound exudate differs from blood plasma by its low pH and because it is replete with products from ongoing enzymatic proteolysis. Hence contact with wound fluid may expose the calcium-sensing receptor on the parathyroid epithelial cells to potential activators such as protons, polyamines, amino acids and/or peptides. Wound fluid-mediated receptor activation would result in an inadvertent suppression of parathyroid hormone secretion. To explore this possibility, we assayed the levels of receptor-activating compounds in thyroid drainage fluid which comprises wound exudate. The human calcium-sensing receptor heterologously expressed in HEK293 cells was used as an experimental model to assay receptor activation, NPS-2143, a negative allosteric modulator to ascertain receptor specificity of the effects. In addition, we reviewed patient records collected during an uninterrupted case series of thyroidectomies, which was done to identify surgery-inherent variables that may impinge on the risk of hypoparathyroidism. The patient records showed that on day one after surgery the levels of both parathyroid hormone and serum calcium were lower than the respective preoperative values in 83 and 90% of the patients, respectively. Consistent with these rates we found that from a set of thyroid drainage fluid specimens the majority of the samples (some 80%) was capable of activating the calcium-sensing receptor. Receptor activation was attributable to a subfraction of drainage fluid with acidic pH and rich in hydrophilic amino acids. Probing the molecular mechanism, we observed that glutamate and aspartate at millimolar concentrations enhanced proton-dependent receptor activation (pH_{50} ~ 6.0) that was completely blocked by NPS-2143. The concentrations in drainage fluid of calcium ions and of spermine, the cognate agonists however were below the activation threshold. The data support the assumption that wound fluid can produce secretory insufficiency of the parathyroid glands. A clinical trial of a calcilytic drug to inhibit aberrant activation of the calcium-sensing receptor in thyroidectomy patients is called for to test the hypothesis and assess the option for a preventive treatment.

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EP234

JOINT357

Genetic skeletal disorders: phenotypic-genotypic characteristics and rhgh therapy responses of a pediatric cohort from a single center in china

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Objectives
The primary objectives of this study are to elucidate the genotype-phenotype correlations in individuals with Genetic Skeletal Disorders (GSD), evaluate the efficacy of recombinant human Growth Hormone (rhGH) therapy, and enhance clinical acumen among practitioners regarding GSD.

Methods
The retrospective analysis involved 80 pediatric GSD patients diagnosed from August 2019 to September 2024. Patients were diagnosed with GSD through whole-exome sequencing, and genetic variant information was systematically collected.
Results
The study included 80 GSD patients, diagnosed at a median age of 4.88 years, with a median height standard deviation score (HT-SDS) of -3.58. The most common clinical manifestations included skeletal deformities (87.5%), short stature (81.3%), and distinctive facial features (65.0%). Those with pathogenic genes linked to Fundamental Cellular Processes had more severe short stature and prenatal phenotypes. Thirty patients received rhGH treatment for a median of 2.25 years (0.33~8.92), showing HT-SDS increases of 0.66 ± 0.42 and 0.84 ± 0.52, after one and two years, respectively ($P < 0.001$). In contrast, eight untreated patients had an average HT-SDS decrease of -0.46 ± 0.55.
Conclusion
In this cohort, pediatric GSD patients predominantly presented with short stature, skeletal deformities, and distinctive facial features, indicating a genotype-phenotype correlation. Compared to untreated GSD patients, those receiving rhGH treatment demonstrated varying degrees of height improvement, however, the long-term efficacy of this treatment warrants further investigation.
Key words
Bone Diseases; Developmental; Genotype; Recombinant Human Growth Hormone; Growth Disorders
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EP235

JOINT524
Analysis of the therapeutic effect of burosumab in the treatment of 6 children with x-linked hypophosphatemia
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Objectives
To evaluate the effectiveness and safety of treatment with burosumab in pediatric X-linked hypophosphatemia (XLH) patients.
Methods
In this retrospective case study, six pediatric XLH patients treated with burosumab admitted to Beijing Children's Hospital, Capital Medical University from July 2022 to December 2024 were selected as the study objects. We colleceted clinical characteristics, biochemical indicators, imaging data of patients, treatment and follow-up (follow-up every three months until December 2024), and analyzed the clinical outcomes and adverse drug reactions after treatment.
Results
Among the 6 patients, there were 3 males and 3 female, aged 1.58 - 11.67 years. 4 patients had previously received treatment with phosphate supplements and active vitamins, but their wadding gait and lower limb deformities did not improve significantly, neither did their imaging changes of active richets. The initial dose of burosumab in 6 patients was 0.68 - 1.03 mg/kg, administered subcutaneously every two weeks, with a treatment period of 0.75 - 2.25 years. After treatment, gait abnormalities were improved in all 6 children, and the Knee width was reduced from 3.6 $\pm$ 2.5cm to 1.3 $\pm$ 1.5cm. The fasting serum phosphorus and TmP/GFR of 6 patients before treatment were 0.87 ± 0.10 mmol/l and 0.81 ± 0.11 mmol/l, respectively. After 3months of treatment with burosumab, both the fasting serum phosphorus and TmP/GFR levels increased (serum phosphorus 1.07 ± 0.11 mmol/l, TmP/GFR 1.02 ± 0.10 mmol/l). During the treatment, only 1patient reached the normal values of fasting serum phosphorus, while 3 patients had normal TmP/GFR). At the last follow-up, the serum phosphorus and TmP/GFR were 1.00 $\pm$ 0.14mmol/l and 0.90 $\pm$ 0.11mmol/l, respectively. After treatment, the alkaline phosphatase levels of all patients gradually decreased, from 574.83 $\pm$ 96.12U/l to 364.33 $\pm$ 107.69U/l. At the last visit, 4 patients returned normal level of ALP. At the last follow-up, only one child had elevated parathyroid hormone levels. The severity score of rickets decreased from 1.38 $\pm$ 1.47 points to 1.33 $\pm$ 1.21 points. One patients showed nephrocalcinosis, while the other patients did not experience any adverse drug reactions such as nephrocalcinosis, local skin injection reaction, hyperphosphatemia, or vitamin D deficiency were observed.
Conclusion
Treatment with brosuzumab can improve clinical symptoms in children with XLH, and no adverse drug reactions have been observed.
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EP236

JOINT163
utility of parathyroid index and calcium to phosphorous ratio in diagnosis of normocalcemic primary hyperparathyroidsm
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Normocalcaemic primary hyperparathyroidism(NCPHPT) is diagnosed as elevated parathyroid hormone(PTH), normal albumin-corrected serum calcium(sCa) and ionized calcium(iCa) after excluding secondary causes of PTH elevation. Parathyroid index(PF index) and calcium to phosphorous ratio(C/P ratio) are useful tools to differentiate NCPHPT from other causes of PTH elevation. We studied 40 consecutive patients with primary hyperparathyroidism(PHPT). Biochemically, serum albumin(S.Alb-gm/dl; N 3.5-5), creatinine(S.Cr-mg/dl; N 0.61-1.2), alkaline phosphatase(SAP-IU/l; 32-126), sCa(mg/dl;N 8.5-10.5), iCa(mmol/l;N 1.12-1.32), phosphorous(S.Phos- mg/dl;N 2.5-4.6), PTH(pg/ml; N 12-88), and 25 Hydroxy vitamin D (25OHD-ng/dl;N > 30) were evaluated. C/P ratio (N < 2.11) and PF index (N < 25.8) were calculated from these parameters. Mean $\pm$ SD was used to depict variables normally distributed, and median with interquartile range(IQR) for variables that do not conform to normality. The male-to-female ratio is 1:2(55 $\pm$ 16 years of age). Results for the whole group were S. Alb 4.2(3.9-4.48); S.Cr 0.86(0.64-1.26); SAP 88.5(73.75-121.5); sCa10.82 $\pm$ 1.58; iCa 1.42 $\pm$ 0.22;S.Phos 3.14 $\pm$ 0.83; S.PTH 206(140-316); 25OHD 32(25.73-43); C/P ratio3.74 $\pm$ 1.3;PF index 54.7(34.54-108.4). The data were analyzed as the normocalcaemic group(-NsCa)(sCa < 10.5) ($n = 19$) and the Hypercalcaemic group (HsCa)(sCa > 10.5)($n = 21$). The results for NsCa were 4.44 $\pm$ 0.43; 0.73(0.64-1.19); 78(71-89); 9.61 $\pm$ 0.62; 1.32 $\pm$ 0.19; 3.48 $\pm$ 0.74; 201 $\pm$ 117; 35.5(30-45); 2.89 $\pm$ 0.68; 44.75(26-55.4), respectively. In HsCa group 4.1(3.45-4.25); 1.06 $\pm$ 0.56; 102(85-160); 11.4(10.85-12.64); 1.51 $\pm$ 0.21; 2.83 $\pm$ 0.81; 284(178.4-352); 32.81 $\pm$ 16.5; 4.51 $\pm$ 1.26; 101(53-154), respectively. The sCa, iCa; SAP, S.Phos, PTH, C/P ratio, and PF index significantly differed between the groups(Mann Whitney $P < 0.005$). The data were analyzed based on 25OHD-low Vit D < 30($n = 16$) and Vit D > 30($n = 24$) the values of sCa11.5 $\pm$ 1.67*Vs*10.33 $\pm$ 1.34($P = 0.007$);iCa1.5 $\pm$ 0.25*Vs*1.38(1.23-1.43)($P = 0.25$); S.Phos 2.67 $\pm$ 0.62*Vs*3.45 $\pm$ 0.82($P < 0.002$) PTH 293 $\pm$ 205*Vs*196(127-281)(P = NS); 25OHD 21 $\pm$ 8.4*Vs*41.35(33.63-54.1)($P = < 0.0001$); C/P ratio 4.55 $\pm$ 1.26*Vs*3.2 $\pm$ 1.04($P = 0.01$);PF ratio112.43 $\pm$ 88.83*Vs*50.77(27.42-56)($P = 0.012$)(Mann Whitney P). The data were analyzed based on normal sCa, iCa, and 25OHD (rubric criteria for NCPHPT;$n = 8$), and the results were 4.41 $\pm$ 0.47; 83(74-92); 1.13 $\pm$ 0.44; 9.23 $\pm$ 0.52; 1.19 $\pm$ 0.07; 3.7 $\pm$ 0.65; 36.8(34-65); 2.57 $\pm$ 0.54; 40.67 $\pm$ 16.55, respectively. The data were grouped as NCPHT; normal 25OHD, calcium but elevated ionic calcium($n = 7$) and classic PHPT($n = 7$). The sCa, iCa, SAP, CP ratio, and PF index were statistically significant in all three groups(Kruskal Wallis H $P < 0.001$). The highest values were obtained for PHPT, and the lowest for the NCPHT category. Bone mineral density of the lumbar spine, hip, and, non-dominant forearm, were in the osteoporosis range among all categories and were not significantly different. All patients had parathyroid adenoma, which was confirmed histologically after surgery. The weight of the adenoma ranged from 26 mg to 15 gms. The C/P ratio and PF index were above the normal and predicted the hyperparathyroidism status across the spectrum; whole group, normocalcaemic and hypercalcaemic groups and normal Vs low vitamin D
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EP237

JOINT261
Effect of bisphosphonates on parathyroid adenoma in patients undergoing focused parathyroidectomy for primary hyperparathyroidism with hypercalcemic crisis
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Introduction
Patients with large adenoma and hyperparathyroidism induced hypercalcemic crisis are managed with bisphosphonates and mostly operated in the same sitting. The use of bisphosphonates provides the knife happy endocrine surgeon valuable time for imaging and protects the patient from cardiac effects of hypercalcemia. The effect of bisphosphonates on parathyroid gland is not clearly understood. In this study, we describe the texture of parathyroid gland after giving zoledronic acid.
Methodology
Prospectively maintained surgical data (October 2022 – October 2023). All patients who underwent focused parathyroidectomy for PHPT in hypercalcemic

crisis who received bisphosphonates preoperatively were included in the study and compared with no Zoledronic acid group. Patient demographics, Serum Calcium, PTH, Vitamin D, size and weight of the gland ex vivo and percentage fall in IOPTH value were noted. All patients received Zoledronic acid 4mg and the duration between administration of bisphosphonate and surgery recorded. Histopathology of all adenoma was reviewed by a single pathologist trained in Endocrine pathology. Data was statistically analysed using SPSS 15.
Results
Among 10 studied patients (mean age: 45.0 ± 15.02 years, M:F ratio 2:3), mean S.PTH was 75.60 ± 50.09 pmol/l, S.Calcium 14.28 ± 0.74 mg/dL, and ex vivo weight 5.14 ± 6.92 g. One patient had parathyroid carcinoma; most had parathyroid adenomas. Intraoperatively, adenomas showed reduced vascularity and increased peri-gland adhesions. HPE showed more fibrosis when compared to no zoledronic acid group
Conclusions
While the effect of bisphosphonates on spinal metastasis is documented, their mechanism in lowering hypercalcemia remains unproven. The observed reduced vascularity and increased adhesions suggest a potential direct impact on enlarged parathyroid glands. Notably, zoledronic acid rapidly lowered calcium levels within 48 hours, persisting over 2 weeks in some patients, with added cardioprotective benefits during anesthesia

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EP238

JOINT276

Body fat mass influences hip geometry in adult male diabetic patients: A community-based study from North India

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Introduction
Fat mass positively correlates with hip geometry and may influence fragility fractures. However, the impact in adult diabetic males is unexplored.
Objective
To evaluate the influence of body fat composition on hip geometry and predict fragility fracture.
Methods
83 urban-dwelling diabetic males, aged ≥60 years underwent dual-energy X-ray absorptiometry scan (DXA, HologicQDR-4500A/Bedford/MA). Hip structural analysis (HSA) at narrow neck (NN), inter-trochanteric region (IT), and femoral shaft (FS) sites were recorded. At these sites, cross-sectional area (CSA), cross-sectional moment of inertia (CSMI), section modulus (Z) and buckling ratio (BR) were analyzed. Also, fat composition at different sites from DXA were recorded. Pearson correlation coefficients (r) and reciprocator operating characteristic curves were calculated.
Results
Amongst the HSA variables, CSMI at NN showed significant positive correlation with total (r=0.52, $P = 0.005$), left (r=0.47, $P = 0.01$) and right (r=0.54, $P = 0.003$) arm, and trunk (0.53,$P = 0.004$) fat mass. CSMI at IT and FS also showed significant but weaker positive correlations with these fat variables. While CSA, Z and BR exhibited significant correlations with fewer fat sites, but were low. However, none of the fat mass sites predicted fracture on ROC curve analysis.
Conclusions
Fat mass positively influences hip geometry, particularly CSMI, primarily at femoral narrow neck followed by inter-trochanteric and femoral shaft sites in adult diabetic males. However, its limited predictive value for fragility fracture, suggesting additional factors like bone quality and metabolic changes may influence.

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Table 1. Pearson correlation coefficients between hip geometry variables and fat mass at different sites

	Cross-sectional area			Cross-sectional moment of inertia			Section modulus (Z)			Buckling ratio (BR)		
	NN	IT	FS	NN	IT	FS	NN	IT	FS	NN	IT	FS
Total	0.37*	0.29	0.19	0.52*	0.38*	0.35*	0.2	-0.05	0.21	0.06	0.10	0.21
Android	0.19	0.21	0.02	0.39*	0.33*	0.25	-0.01	-0.18	0.11	0.18	0.17	0.27
Gynoid	0.3	0.09	0.07	0.28	0.15	0.11	-0.06	-0.18	0.01	0.00	0.21	0.22
Trunk	0.35*	0.28	0.15	0.53*	0.39*	0.34*	0.20	-0.05	0.21	0.08	0.10	0.21
Arm												
Right	0.45*	0.49*	0.39*	0.54*	0.56*	0.49*	0.28	0.07	0.41*	-0.02	0.01	0.08
Left	0.36*	0.32*	0.25	0.47*	0.42*	0.30*	0.17	-0.03	0.19	0.06	0.09	0.16
Leg												
Right	0.34*	0.20	0.19	0.40*	0.24	0.31*	0.16	-0.09	0.17	0.03	0.13	0.25
Left	0.27	0.16	0.12	0.37*	0.22	0.23	0.11	-0.08	0.09	0.06	0.12	0.23

NN- Narrow neck, IT- Inter-trochanteric, FS- Femoral shaft; *$P<0.05$

EP239

JOINT1062

Familial hypocalciuric hypercalcemia due to a novel CASR mutation: diagnostic challenges and clinical implications

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Introduction
Familial hypocalciuric hypercalcemia (FHH) is a typically benign condition marked by elevated serum calcium levels alongside relatively low urinary calcium excretion. In most cases, FHH arises from loss-of-function mutations in the *CASR* gene, which encodes the calcium-sensing receptor (*CASR*), a G-protein coupled receptor predominantly expressed in the parathyroid glands and kidneys. The condition is often asymptomatic and generally does not require treatment. Identifying *CASR* mutations through genetic testing is crucial to distinguish FHH from primary hyperparathyroidism and prevent unnecessary parathyroidectomy.
Case Report
An 18-year-old male undergoing medical assessment as part of a job application was incidentally found to have elevated serum calcium. Repeat measurements of corrected calcium ranged from 2.9 to 3.0 mmol/l. He was asymptomatic with no evidence of end-organ damage. His medical history was unremarkable, and he took no regular medications. His family history was notable for his mother, who was diagnosed 15 years earlier with PTH-mediated hypercalcemia, presumed primary hyperparathyroidism. Her imaging was negative, and she had not required surgery or treatment. There was no family history of nephrolithiasis, pheochromocytoma, or pituitary disorders. Further biochemical evaluation showed a PTH level of 5.0 pmol/l (RR: 1.6–6.9) and a vitamin D level of 62 mmol/l. Urinary calcium excretion was low, with a calcium-to-creatinine clearance ratio of 0.012. A sestamibi scan suggested a possible right parathyroid adenoma; however, ultrasound did not confirm this finding. Genetic analysis identified a novel pathogenic *CASR* gene mutation, c.1793G>C (p.Cys598Ser) (chromosome 3: 122002594), confirming familial hypocalciuric hypercalcemia type 1 (FHH1). The patient was counselled on the benign nature and inheritance of FHH and and this confirmation allowed him to proceed with his intended career path without unnecessary medical restrictions. Given the family history of hypercalcemia, genetic testing of his mother is planned to determine if she carries the same mutation.
Discussion
This case expands the spectrum of pathogenic *CASR* mutations linked to FHH. The identified missense variant disrupts an intramolecular disulfide bond essential for receptor function. Although this specific mutation has not been reported before, similar mutations affecting this bond have been classified as pathogenic, supporting its pathogenicity. Distinguishing FHH from primary hyperparathyroidism can be challenging, especially when imaging suggests a parathyroid adenoma, increasing the risk of unnecessary surgery. In this case, genetic testing was crucial in confirming the diagnosis and avoiding unnecessary intervention.

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EP240

JOINT862

Severe hypercalcemia with persistent nausea and vomiting in a child with new-onset graves' disease

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Introduction
Graves' disease (GD) is the leading cause of hyperthyroidism in children and the most common etiology of thyrotoxicosis. Clinical manifestations resulting from

excessive thyroid hormone production affect multiple systems. Among these, disturbances of mineral homeostasis, particularly calcium, phosphorus, and magnesium, are often overlooked. Increased osteoclast numbers and activity driven by excess thyroid hormones contribute to these changes. Hypercalcemia occurs in approximately 20% of patients with hyperthyroidism and is usually mild and asymptomatic. Severe hypercalcemia is rare but requires immediate intervention to prevent serious complications, including nephrocalcinosis, cardiac dysfunction, and skeletal abnormalities.
Case
An 8 years and 11 months old girl was admitted to our hospital due to persistent nausea and vomiting for the past month. Seven months prior to admission, she visited the hospital due to 2 episodes of unprovoked seizure and started to take the antiseizure medication. After 1 month of medication, she was hospitalized for drug reaction with eosinophilia and systemic symptoms (DRESS) syndrom and was treated with intravenous (IV) corticosteroids. During the tapering period of steroid treatment, she developed new-onset facial palsy that progressed to bilateral lower extremity weakness, leading to re-admission and a diagnosis of acute inflammatory demyelinating polyneuropathy (AIDP). During admission, she was treated with IV immunoglobulin (IVIG) and IV corticosteroids, which was gradually tapered over 2 weeks. One month prior to admission, after discontinuation of corticosteroids, nausea and vomiting occurred. Both symptoms temporarily improved after IV hydration, but recurred and persisted for more than a month. Thyroid function tests revealed elevated T3 and free T4 levels with suppressed TSH. Thyroid autoantibody testing, thyroid ultrasonography, and scintigraphy showed results consistent with GD. Complete blood count, serum electrolytes, and liver function test results were all within normal limits. However, abnormalities of mineral metabolism, including hypercalcemia, hypophosphatemia, hypomagnesemia, and decreased serum alkaline phosphatase levels, have been identified. Intravenous hydration with diuretics and steroid therapy, and antithyroid medications led to rapid improvement in clinical symptoms and normalization of mineral and thyroid hormone levels. During the 7-month follow-up period, the patient continued to take antithyroid medications and remained in good condition.
Conclusion
This is a case of severe hypercalcemia manifested in a new-onset pediatric GD. This case demonstrates that severe hypercalcemia, although rare, has clinical significance in pediatric GD and highlights the importance of performing thyroid function tests in addition to calcium monitoring in patients with persistent nausea and vomiting.

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EP241

JOINT3059

Pseudohypoparathyroidism type 1c - a rare cause of obesity in children- a case report

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Introduction
Pseudohypoparathyroidism (PTH) represents a group of diseases characterized by by tissue resistance to parathormone and other endocrine disorders like hypothyroidism. Albright osteodystrophy phenotype consists of a number of symptoms concerning the patient's skeletal system and may often coexist with PTH. Patients in the majority are obese and with developmental delay.
Aim
We present the case of familial Albright osteodystrophy
Material and method
A 3-year-old male was admitted to Endocrinologic Ward with suspected hyperparathyroidism. He was originally referred to the Metabolic Disease Outpatient Clinic for obesity, but tests performed there showed elevated parathormone levels. A baby born from a second pregnancy, by cesarean section, on time, with a birth weight of 2920g. At birth, there was a disproportion in the size of the head and chest, a smooth philtrum, and a thin upper lip. Diagnosis performed for TORCH infection was negative. The boy had currently the following health problems: hypothyroidism, delayed psychomotor development, hypertrophy of the pharyngeal tonsil, frequent respiratory infections. Excessive weight gain has been observed since birth. Prader-Willi syndrome was ruled out. The patient's mother was diagnosed with short stature (finall height: 145 cm) as a child. The boy's older brother suffers from hypothyroidism, autism and elevated parathormone levels as well. The mother and brother have a body disproportions.
Results
Anthropometric measurement revealed patient's weight: 23.9 kg (>97 pc) and height: 91.5 cm (25-50 pc). The physical examination showed features of obesity, a large head, prominent forehead, bowed lower limbs, brachydactyly and enlarged palatal tonsils. Laboratory tests revealed hypertriglyceridemia, elevated parathormone and phosphate levels, slightly reduced vitamin D3 levels, normal total and ionized calcium levels. Thyroid ultrasound did not visualize parathyroid glands. Whole exome sequencing (WES) was performed and analysis of the detected variants. A known pathogenic heterozygous c.1006C>T variant (p.Arg336Trp) in the GNAS gene was detected. The older brother underwent genetic analysis which confirmed the presence of the same mutation. We are awaiting the results of genetic testing of the patient's mother anf father.
Conclusion
Although PHP is a rare condition, it should be considered in the diagnosis of obesity with concomitant skeletal problems and calcium-phosphate disorders. We emphasise the meaning of genetic investigation in confirming the etiology of hyperparathyroidism.

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EP242

JOINT2388

Pseudohypoparathyroidism type 1B and thyroid hemiagenesis: a case report

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Introduction
Pseudohypoparathyroidism (PHP) refers to a heterogeneous group of rare disorders characterized by resistance to parathyroid hormone (PTH). PHP type 1A is associated with Albright's osteodystrophy and resistance to multiple hormones (including TSH). In contrast, PHP type 1B develops PTH resistance over time, exhibiting mild clinical manifestations and low-level resistance to other hormones. The estimated prevalence of PHP is approximately 1 in 100,000 individuals. Thyroid agenesis, although rare, has been described in association with phospho-calcium metabolism disorders. However, its exact prevalence in patients with PHP remains unclear.
Case Report
A 21-year-old female has been followed since the age of 5 for hypothyroidism with positive antibody levels (antithyroid peroxidase > 2000mUI/mL and antithyroglobulin > 266mUI/mL), currently treated with levothyroxine (175 micrograms daily). Notably, neck ultrasound revealed thyroid agenesis of the right lobe. Her family history included hypothyroidism spanning three generations, but no other endocrinological disorders. At the time of hypothyroidism diagnosis, she also presented with markedly elevated PTH levels (296pg/mL), low serum calcium levels, phosphate in the upper limit of normal range and mildly increased urinary calcium excretion. She exhibited no clinical features or symptoms related to bone metabolism. After excluding more common causes for phospho-calcium abnormalities, genetic testing for PHP was performed. Methylation pattern analysis revealed changes across all differentially methylated regions (DMRs), a gain of methylation in NESP55 and loss of methylation in GNAS-AS1, GNASXL, and GNASAB, consistent with the diagnosis of PHP 1B. Subsequently, she has been treated with oral calcium, calcitriol and cholecalciferol, leading to normalization of both serum and urinary calcium and phosphate levels.
Discussion
Although PHP 1A is known to present with TSH resistance, PHP 1B is generally associated with minimal TSH resistance, which does not typically account for thyroid agenesis. Additionally, only a few cases of PHP 1B associated with Hashimoto's thyroiditis have been reported in the literature. Given the high prevalence of Hashimoto's thyroiditis, it has been assumed that its coexistence with PHP 1B is incidental.
Conclusions
This case highlights an unusual presentation of PHP 1B with concurrent thyroid agenesis and Hashimoto's thyroiditis. While the link between PHP and thyroid agenesis remains unclear, this case suggests the need for further investigation into potential shared pathomechanisms. Genetic testing remains crucial for diagnosis and management in atypical cases.

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EP243

JOINT3468

A case of resistant hypocalemia and hungry bone syndrome after parathyroidectomy

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Introduction

Hypocalcemia is a common problem after parathyroidectomy. When high-turnover bone disease is suddenly corrected by the reduction in parathyroid hormone (PTH) after surgery, reduced bone resorption and increased bone formation can cause insistent hypocalcemia.

Case

A 49-year-old female patient was admitted to our clinic with weakness, fatigue, polydipsia, polyuria, and constipation. She lost 5 kilos in the last 6 months. Her tongue was dry. She had elevated creatinine, alkaline phosphatase (ALP), and calcium (Ca) levels, and her phosphorus (P) level was decreased. She had serious hypercalcemia (Ca: 16,18 mg/dL) electrocardiography (EKG) was performed. There was no arrhythmia, but short QT was present (QTc:330 msn). Oral and İntravenous (iv) hydration was given. PTH, and 24-hour urinary Ca were elevated too. And 25 hydroxy vitamin D and glomerular filtration rate (GFR) was decreased. She had 9 to 29 liters of urine, and she had nephrogenic diabetes insipidus due to hypercalcemia. A 30*20*35 mm parathyroid adenoma was seen at ultrasonography and Tc-99 MIBI parathyroid scintigraphy also confirmed the parathyroid pathology. Subperiosteal bone resorptions, the 'salt and pepper' appearance, and brown tumors were seen in X-rays. Zoledronic acid 4 mg was administered, and surgery was. Her PTH was 12,5 ng/l, Ca was 7,13 mg/dl, P was 1,82 mg/dl, and Mg was 1,51mg/dl. Both Trousseau's and Chvostek's signs were positive. Iv and oral Ca replacement were initiated active vitamin D (calcitriol) was started and 25-OH vitamin D that started before the operation was continued. After 7 days of operation, she had hip pain. Bilaterally femur fracture was detected at radiography. And she underwent surgery. After 15 days, despite of 10 g oral calcium carbonate per day and 1,5 mg of oral calcitriol per day, the iv-calcium requirement continued. Calcitriol gradually increased to 4 mg per day and iv-calcium requirement decreased. After 54 days she was discharged. 6 months after surgery, oral calcium and calcitriol were still required.

Conclusion

Although the lack of well-defined clinical criteria for the diagnosis of hungry bone syndrome makes it difficult to determine its true incidence. It is an acute clinical condition characterized by hypocalcemia, hypophosphatemia and hypomagnesemia. Ca drops to its lowest level in 36 hours after operation. It is temporary and although it usually improves within a few weeks it can continue longer. It is important to closely monitor these patients during replacement therapy to avoid iatrogenic hypercalcemia and related complications.

Key words

Hypocalemia, parathyroidektomi

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EP244

JOINT280

Fahr's syndrome with hypoparathyroidism: a case report

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Introduction

Fahr's syndrome is a rare condition that was first described by German neurologist, Theodor Fahr, in 1930. It's characterized by the presence of symmetrical bilateral calcifications in the brain including the thalamus and the basal ganglia. Clinical features include neuropsychiatric symptoms like behavioural changes, cognitive impairment, seizures, extrapyramidal signs, etc. Fahr's syndrome is secondary to other conditions, most commonly hypoparathyroidism but it can also be associated with certain infections, neurodegenerative or mitochondrial disorders. Fahr's syndrome is not the same as Fahr's disease. The latter also causes intracranial calcifications but they are not associated with any abnormality in phosphate or calcium metabolism. We report a case of Fahr's syndrome and Hypoparathyroidism.

Case Report

This is a 57 years old gentleman who presented to the acute ambulatory unit reporting worsening headache, sleeping disturbances and non-specific tingling sensation in his arms. There was no weakness or visual field defects. He does not smoke or drink Alcohol. He reported his father had problems with his calcium that needed calcium supplements. His bloods showed significant hypocalcaemia with hypoparathyroidism. His adjusted calcium was 1.57 mmol/l, phosphate was 1.7 mmol/l, Parathyroid hormone was 0.3 pmol/l and his magnesium was 0.68 mmol/l. He was treated for his hypocalcaemia urgently. History included being involved in an explosion back in his home country where the bullet/Shrapnel scraped but did not penetrate his skull. CT head showed extensive bilateral symmetrical calcifications in the basal ganglia (caudate and lentiform nuclei), corona radiata pulvinar and dentate nuclei of the cerebellar hemispheres with no mass effect. These findings are consistent with Fahr's disease or Fahr's syndrome. Patient was started on Alfaclcidol 1 mg TDS and calcium 1 gm TDS aiming to prevent a calcium phosphate balance shift towards hyperphosphatemia which might trigger further calcifications. Patient's symptoms improved and has been stable on this dose of Calcium and Alfacalcidol. His bone profile is being checked every 2 months to ensure target levels achieved.

Conclusions

Fahr's syndrome is a rare but treatable condition that should be distinguished from Primary familial brain calcification (Fahr's disease) as the latter's etiology and management are unknown. Parathyroid abnormalities count are the most common causes of Fahr's syndrome, specially hypoparathyroidism. Management is with calcium and activated vitamin D which if given early, can prevent further calcifications.

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EP245

JOINT2001

Evaluation of cinacalcet prescribing and monitoring in primary hyperparathyroidism: a single-centre audit

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Primary hyperparathyroidism(PHPT) is a common endocrinological disorder causing hypercalcaemia, with potential complications affecting bones and kidneys. Diagnosis requires exclusion of secondary causes, and management typically involves parathyroidectomy. Cinacalcet is an alternative for a selected group of patients, necessitating careful patient selection and biochemical monitoring. This study evaluates the adequacy of PHPT diagnostic workup and the efficacy of Cinacalcet prescribing and monitoring in PHPT patients.

Methods

A retrospective audit was conducted in a single-centre endocrinology outpatient clinic, reviewing 42 patients with PHPT prescribed cinacalcet. Data on diagnostic work-up, cinacalcet initiation criteria, calcium monitoring, and treatment outcomes were analysed.

Results

While PHPT was confirmed in all patients ($n = 42$), diagnostic work-up revealed that urinary calcium assessment was performed in 61.9% of patients with clinical suspicion of familial hypocalciuric hypercalcaemia. Most patients ($n = 38$) had vitamin D measured as part of their assessment. Screening for end-organ damage using DEXA scan and ultrasound and/or CT KUB was performed in 93% of patients, with 40% showing evidence of complications. Regarding calcium levels, 47.6% of patients had serum calcium levels ≥ 2.85 mmol/l with symptoms, while 33.3% had levels > 3 mmol/l. A small proportion ($n = 8$) were started on cinacalcet for symptomatic PHPT despite having serum calcium < 2.85 mmol/l. Overall compliance with prescribing criteria was 66.7%. Importantly, none of the patients developed hypocalcaemia during treatment. At initiation, mean serum calcium was 2.93 mmol/l, decreasing to 2.69 mmol/l at one month following starting cinacalcet, with further reduction to 2.49 mmol/l in patients achieving normalisation. However, 23% had persistently elevated calcium despite treatment.A weak negative correlation was observed between cinacalcet starting dose and calcium levels at one month ($\rho = -0.30, P = 0.061$), and no significant correlation with final calcium normalisation ($\rho = 0.068, P = 0.58$). 35.7% of patients had serum calcium checked at one week after starting cinacalcet, while 61% had testing every 2-3 months. Overall compliance with BNF monitoring guidelines was 21.4%, with only 14.3% of patients meeting both prescribing and monitoring standards. No significant association was found between monitoring frequency and calcium normalisation ($P = 0.127$).

Conclusion

Our study shows that Cinacalcet effectively reduces serum calcium in PHPT. Monitoring of serum calcium during cinacalcet treatment could be more robust, to assess its efficacy and safety. The weak correlations between the starting dose of cinacalcet and serum calcium levels indicate that the current dosing strategy may

not fully account for the variability in response to treatment. Further research is needed to identify potential barriers to optimal prescribing and monitoring, and develop targeted interventions to improve adherence and patient safety. We would like to acknowledge Alexander Jones, Clinical Pharmacist, for their invaluable contribution to this audit by providing a list of patients who were dispensed Cinacalcet by the hospital pharmacy between 2017 and 2024, including the dates of dispensing, and quantities dispensed.

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EP246

JOINT1807

Experience of using cinacalcet for the treatment of secondary hyperparathyroidism in uzbekistan

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Aims
We decided to study the effectiveness of cinacalcet in dialysis patients in the Uzbek population.
Method
We randomly selected 50 patients (28 men and 22 women) on dialysis in our center. We divided the patients into two groups: group A consisted of 30 patients who were prescribed cinacalcet at a dose of 30 mg/day in addition to the treatment, and group B consisted of 20 patients who served as a control group. The patients were examined for 3 months, the control points were the 30th and 90th days. Both groups were similar in calcium, vitamin D and PTH levels, and ultrasound parameters.
Results
The indices of MBD improved in group A in relation to group B. The calcium level in patients of group A before treatment was 2.48 ± 0.47 mmol/l and significantlydecreased after treatment, amounting to 2.17 ± 0.38 mmol/l ($P < 0.05$). In group B, it was 2.51 ± 0.56 mmol/l and 2.49 ± 0.97 mmol/l ($P > 0.05$), respectively. Blood phosphorus in group A, according to the results of 90 days, decreased from2.83 ± 0.86 mmol/l to 1.72 ± 0.76 mmol/l, and in group B from 2.81 ± 0.91 mmol/l to 2.73 ± 0.65 mmol/l. Before the study, the PTH level in group A was 1132.3 ± 182.7 pg/ml, in group B – 1083.9 ± 169.3 pg/ml. After 30 days of the study, in group PTH decreased by 18% and was 928.5 ± 98.7 pg/ml ($P < 0.05$), while in group B it changed insignificantly – 1053.7 ± 158.6 pg/ml ($P > 0.05$). On the 90th day of treatment, the PTH level in group A decreased by another 16%, amounting to 779.9 ± 83.7 pg/ml ($P < 0.05$), thereby decreasing by 31.1% ($P < 0.05$) from the initial level. And in group B it remained at approximately the same level, amounting to 1032.1 ± 143.8 pg/ml. Also, in group A, the symptoms of hyperparathyroidism symptoms such as pain in bones and joints, muscle weakness, fatigue, decreased tone decreased in patientsand the well-being of patients improved, which was not observed in patients in group B. No patient experienced any side effects or intolerance to the drug, and there were no cases of overdose.
Conclusion
A single-center trial of cinacalcet in dialysis patients was found to be quite effective. In patients who received cinacalcet at a dose of 30 mg/day in addition to their current treatment, PTH levels decreased by more than 30% compared to the control group without cinacalcet. Patients taking cinacalcet showed improvement in MBD (calcium, phosphorus) indices. The subjective state of dialysis patients also improved, which confirms the safety of the drug.

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EP247

JOINT2201

Novel VDR gene mutation in a vitamin D-dependent rickets type 2A compound heterozygote:a case report

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Background
Vitamin D-dependent rickets type 2A (VDDR2A) is a rare autosomal recessive disorder caused by mutations in the vitamin D receptor gene (*VDR*), which is marked by end-organ resistance to 1,25-dihydroxy vitamin D ($1,25(OH)_2D$). The phenotype varies depending on the *VDR*'s domain affected, and alopecia is typically included.
Objective
To investigate the genotype and its correlation with alopecia in a VDDR2A case.
Methods
A consanguineous family of Chinese Han origin with one proband of VDDR2A was recruited. The patient was evaluated clinically, biochemically and radiographically. Gene sequencing was performed to all family members.
Results
The 3-year-old proband showed early-onset *al*opecia, rickets, hypocalcemia, hypophosphatemia, secondary hyperparathyroidism, elevated alkaline phosphatase and low level of 25-hydroxy vitamin D (25(OH)D). He had compound heterozygous variants of *VDR*. c.376G>T(p.E126*) was a novel mutation, mainly affecting Ligand-binding domain. The other variant, c.122G>A(p.C41Y), which was restricted to DNA-binding domain, had been identified to cause alopecia in homozygotes. The proband presented mild alopecia compared with homozygotes of c.122G>A mutation.
Conclusion
We identified a novel *VDR* mutation in a compound heterozygote. Though alopecia is the typical clinical feature of VDDR2A, this phenotype could be variable depending on the synergy of alleles.
Keywords
Rickets, VDDR2A, VDR, Alopecia

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EP248

JOINT3470

Evaluation of the effect of hypercortisolemia treatment on bone metabolism and structure in patients with endogenous cushing's syndrome- a single center experience

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Introduction
Cushing's syndrome is a very rare disorder characterised by a variety of clinical manifestations that result from cortisol excess, which can lead to multiple comorbidities such as diabetes mellitus, hypertension and bone disease. Prospective studies on large groups of patients with endogenous hypercortisolaemia assessing calcium-phosphate and bone metabolism over time are scarce.
The aim
Toevaluate the effect of hypercortisolaemia treatment on bone metabolism and structure in patients with endogenous Cushing's syndrome.
Patients and Methods
This is a controlled, prospective single-centre study involving a total of 30 consecutive patients diagnosed with endogenous Cushing's syndrome hospitalised at the Department of Endocrinology at Bielański Hospital in Warsaw. We evaluated patients' medical records, hormonal results (with special emphasis on calcium-phosphate and bone metabolism) at diagnosis and after implementation of surgical or pharmacological treatment. Bone turnover markers such as sclerostin, DKK-1, CTx, PINP will be assessed before and 3, 6, 12 months after achievement of normocortisolemia. A control group was matched based on sex, age and BMI, excluding hypercortisolemia.
Results
To date, we have enrolled 10 patients with endogenous Cushing's syndrome Male gender was predominant (M:F = 7:3). The mean age at diagnosis was 47.9 ± 16.6 years and ranged from 27 to 64 years. Nine out of 10 patients were diagnosed with ACTH-dependent hypercortisolemia (Cushing's disease). Average cortisol concentration at the diagnosis was 22.17 mg/dL. At follow-up at 3 months after achieving normocortisolemia, calcium-phosphate metabolism tests showed increase in total serum calcium (2.46.....2.53mmol/l), phosphorus (1.13....1.45mmol/l) and decrease in calciuria (4.78....3.64mmol/24h) and phosphaturia (23.18.... 16.95mmol/24h). There was a decrease in parathormone concentration (36,5…. 26,45pg/ml) and the active form of vitamin D [1,25(Oh2) D] (48,42……..35,92pg/ml). At baseline, mean bone mineral density was reduced L1-L4 T-score: -1.53 SD, femoral neck T-score: -1.28 SD, TBS T-score: -1.48

SD. The mean sclerostin concentration at the time of diagnosis of hypercortisolemia was 62,94 ng/ml, while Dkk-1 was 5078 ng/ml.
Conclusions
Our results confirmed that normocortisolemia improved calcium-phosphate metabolism. Further conclusions regarding changes in calcium-phosphate levels and bone turnover markers over time in normocortisolemic patients can be drawn when a larger study group has been enrolled.

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EP249

JOINT2355

PTH-independent hypercalcemia in a young adult due to a compound heterozygous CYP24A1 mutation

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CYP24A1, encoding the vitamin D-24-hydroxylase, regulates the catabolism of 1,25-(OH)2vitamin D. Inactivating biallelic mutations of the CYP24A1 gene are associated with elevated serum 1,25(OH)2vitamin D concentrations, hypercalcemia, hypercalciuria, nephrolithiasis and suppressed PTH concentrations. We describe the clinical and molecular basis of long-standing hypercalcemia and nephrocalcinosis in a young adult. The patient is a 19-year-old male presented for PTH-independent hypercalcemia (serum total calcium 11.6 mg/dl, serum PTH 2.6 pg/ml) and nephrocalcinosis. He had a history of recurrent episodes of vomiting and constipation in childhood, when he was supplemented with vitamin D. From the age of 13, annual blood tests have been performed, revealing mild hypercalcemia and 25OH vitamin D values between 39-56 ng/ml. Family history was relevant for high normal serum calcium (mother) and nephrolithiasis (grandmother). The patient's biochemistry in our clinic: serum calcium 11 mg/dl, urinary calcium 400 mg/24hrs, creatinine 1.22 mg/dl, PTH 2.4 pg/ml, 25OH-vitamin D 39 ng/ml, 1,25(OH)2vitamin D 66 pg/ml; serum phosphate 3.3 mg/dl, urinary phosphate 700 mg/24hrs, FGF23 224 pg/ml, normal PTHrP and ACE. Bone turnover markers were: cross laps 0.69 ng/ml, osteocalcin 50.4 ng/ml, P1NP 86.3ng/ml and he has a high bone mass (DXA): L1-L4 Z-score = 2.6 DS, femoral neck Z score = 3.8 DS, total hip Z-score = 4.2 DS. Analysis of whole exome sequence variants revealed that the patient is heterozygous for CYP24A1 c.1186C>T, p. (Arg396Trp) and c.428_430del, p(Glu143del), which are both pathogenic. With low-calcium diet, high water intake and limited sunlight exposure, after 3 months, the biochemistry improved: serum calcium 9.7 mg/dl, urinary calcium 360 mg/24hrs, creatinine 1.03 mg/dl, PTH 6.7 pg/ml, 25OHvitamin D 24 ng/ml, 1,25(OH)2vitamin D 62 pg/ml.
Conclusion
CYP24A1 mutations should be considered in the differential diagnosis of PTH-independent hypercalcemia in both children and adults.

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EP250

JOINT1809

An adolescent with spondyloepiphyseal dysplasia congenita and nephrocalcinosis: value of genetic testing in understanding complex clinical presentations

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Introduction
Spondyloepiphyseal dysplasia congenita (SEDC) is a rare autosomal dominant skeletal dysplasia (incidence 1:100,000 live births), caused by mutations in the COL2A1 gene, leading to abnormal type II collagen. Reported clinical manifestations include disproportionate short stature, cleft palate, scoliosis, kyphosis, hip deformities, atlantoaxial instability, hearing loss and visual abnormalities. Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is a rare autosomal recessive disorder (1:250,000) caused by mutations in the SLC4A3 gene, associated with urinary phosphate wasting. While homozygous mutations cause rickets, heterozygous mutations typically cause hypercalciuria without bone disease and potential treatment options include oral phosphate/fluconazole. We report the co-occurrence of SEDC with a heterozygous HHRH mutation in a Sri Lankan adolescent, where extended genetic testing helped clarify the complex clinical picture and guide management.
Case Presentation
A 14-year and 9-month-old boy, the fourth child of healthy non-consanguineous parents, was admitted with exertional dyspnoea and orthopnoea for 3 months. He had multiple congenital anomalies, including cleft palate (surgically repaired), atrial septal defect (spontaneous closure), and congenital talipes equinovarus, with poor growth, kyphoscoliosis, coxa vara, and flat feet. He had normal intelligence. On examination, he had extreme short stature (height age: 6 years) with low BMI, muscle wasting, joint deformities, upper motor neuron signs in upper and lower limbs, and no abnormalities in cardiovascular and respiratory systems. There were no features of rickets. He was peripubertal (Tanner III). His skeletal survey was suggestive of skeletal dysplasia, while cervical spine MRI showed odontoid hypoplasia and atlantoaxial instability. Sleep study showed nocturnal hypoventilation and pulmonary function tests indicated reduced vital capacity. He also had bilateral nephrocalcinosis with hypercalciuria, with normal serum calcium, phosphate, alkaline phosphatase, 25-OH-D and PTH levels. Whole exome sequencing confirmed SEDC, caused by a likely pathogenic heterozygous COL2A1 variant; however, this did not explain nephrocalcinosis. Further analysis revealed another heterozygous likely pathogenic variant in the SLC34A3 gene, with elevated serum 1,25-dihydroxy vitamin D levels, consistent with a mild phenotype of HHRH. He underwent neurosurgical stabilisation, leading to significant improvement in respiratory and neurological complications, while phosphate supplementation was commenced to reduce the hypercalciuria associated with HHRH. Genetic counselling was provided.
Conclusion
This case highlights the value of genetic testing in managing patients with complex clinical features not attributable to a single disorder. While genetic testing is not easily accessible in low-middle-income countries, it can be of great value in diagnosing and managing patients with complex manifestations where diagnosis remains elusive.

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EP251

JOINT1091

The outcome of parathyroidectomy for secondary hyperparathyroidism in hemodilaysis patients

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Objective
Secondary hyperparathyroidism (SHPT) is a complication of end stage renal disease. Parathyroidectomy is a surgical treatement option for hyperparathyroidism that is commonly performed. We aim in our study to evaluate the outcomes of PTX as a therapeutic strategy for SHPT in hemodilaysis patients.
Methods
We present a retrospective descriptive and monocentric study involving hemodiaysis patients with SHPT who underwent PTX in our ENT departement.
Results
We present 61 hemodialysis patients with dialysis duration ranging from 1 to 20 years who have SHPT. The mean age is 34 years, the sexe ratio is 1,54 and the most common cause of nephropathy is of indeterminate origin in about 50,81%. 52,46% presented with normocalcemia while 45,9% with hypercalcemia and 1,64% with hypocalcemia. The average level of PTH is 1808 pg/ml [334-3263]. the most frequent symptoms are bone pain in75,4%, pruritis in 32,7%, asthenia and weight loss in24,6%. 59 patients underwent cervical ultrasound that was normal in 52,42% while scintgraphy was performed in 60 patients that was pathologic in 98,33% with focal increased uptake in the 4 glands in 31,66%.87% of patients underwent a 7/8th PTX while 14,7% had a ¾ th PTX,1,63% a total PTX with autotransplantation and 1,63% total PTW without transplantation.85% experienced an hypocalcemia with an average of 1,76 on day 1 post operative and 86,66% presented a decrease of >80% of PTH level. the persistance of SHPT was observed in 8 patients and the recurrence in only 2 patients.
Conclusion
Parathyroidectomy is an effective surgical strategy for patients with SHPT that reduce PTH levels and improves the phosphocalcic metabolism, hence it it boost the quality of life and reduces the handicap index.

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EP252

JOINT3659

Pseudohypoparathyroidism revealed by bone pain: a case report

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Introduction
Pseudohypoparathyroidism (PHP) is a rare endocrine disorder of genetic origin, which can be either sporadic or hereditary. It results from target tissue resistance to parathyroid hormone (PTH), leading to clinical and biological abnormalities. Several forms exist, varying according to resistance to other hormones and the presence of dysmorphic syndromes, with heterogeneous clinical expression, even among patients carrying the same mutation. We report the case of a patient in whom pseudohypoparathyroidism was revealed by bone pain.
Case Report
A 15-year-old patient, born to non-consanguineous parents and without notable family history, presented to our department with bone pain. Physical examination was unremarkable. Laboratory tests revealed hypocalcemia (1.5 nmol/l), hyperphosphatemia (2.26 nmol/l), and elevated PTH (455 pg/mL). Further investigations showed no hypomagnesemia, vitamin D deficiency, or renal insufficiency. A follow-up assessment was conducted and revealed no abnormalities. The patient exhibited no cardiovascular, including QT prolongation, and no neuromuscular signs of hypocalcemia, such as cramps, paresthesias, or tetany. Additionally, there were no morphological anomalies like brachydactyly, rounded face, obesity, or growth retardation. The stomatological examination was normal, and no resistance to other hormones, particularly TSH or gonadal hormones, was identified. The diagnosis of PHP was established. Genetic testing was not performed due to its unavailability. The patient was treated with oral calcium carbonate and an alpha-hydroxylated vitamin D derivative, leading to significant improvement in bone pain.
Discussion and conclusion
PHP is characterized by elevated PTH, hypocalcemia, and hyperphosphatemia, in the absence of vitamin D deficiency, hypomagnesemia, or renal insufficiency. Its different subtypes are defined based on clinical criteria (Albright hereditary osteodystrophy, Progressive osseous heteroplasia, Acrodysostosis) and biological features, notably resistance to TSH and other hormones. In our patient, the absence of short stature, Albright's dysplasia, ectopic ossifications, hypothyroidism, and hypogonadism suggests PHP type 1B. Genetic testing would be necessary to confirm the diagnosis.

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EP253

JOINT2338

A rare parathyroid lipoadenoma in a patient with sporadic multiglandular primary hyperparathyroidism – pitfalls in preoperative localization and pathological diagnosis

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Sporadic primary hyperparathyroidism (PHPT) is usually caused by a single-gland adenoma, which on histopathology has a marked cellularity with a reduced amount of stromal fat. A 72-year-old woman was referred for evaluation of PHPT. Laboratory tests showed hypercalcemia (2.69 mmol/l, normal range 2.20-2.55) and elevated parathyroid hormone (14.40 pmol/l, normal range 1.58-6.03). She had been treated with alendronate for osteoporosis of the distal third of the radius, fulfilling an indication for parathyroidectomy in asymptomatic PHPT. Ultrasonography showed a 0.2 ml oval hypoechoic nodule inferior to the right lobe of the thyroid, which was confirmed by MIBI scintigraphy. However, an enlarged parathyroid below the right thyroid lobe was not found during the parathyroidectomy. The surgeon therefore extended the operation to include a right exploration and found an enlarged parathyroid behind the middle part of the right thyroid lobe. Although the blood calcium level normalized on the first postoperative day, two weeks after surgery it was at the same level as before the parathyroidectomy, consistent with persistent PHPT. The right upper parathyroid gland was initially described as an enlarged but normal parathyroid gland (13x5x7mm). After the second reading it was corrected to a parathyroid lipoadenoma due to the abnormal size and clinical context of PHPT. The patient has stable mild hypercalcemia with isolated osteoporosis in the radius. Reoperation for persistent PHPT is under consideration, the conservative approach may also be acceptable. Parathyroid lipoadenoma is a rare histological finding in PHPT with a prevalence of 0.2-1.0%. The presence of stromal fat in lipoadenoma resembles a normal parathyroid gland, which may confuse not only the pathology but also parathyroid imaging. While typical parathyroid adenomas are hypoechoic on ultrasound, lipoadenomas are hyperechoic due to the fat-rich content, which may contribute to the failure of both preoperative ultrasonography and scintigraphy. Both methods correctly localized only one of two pathological parathyroid glands in the present case, highlighting the fact that multiglandular PHPT is often associated with equivocal parathyroid imaging and a high rate of surgical failure. Supported by MH CZ - DRO (Institute of Endocrinology - EÚ, 00023761)

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EP254

JOINT757

A young case of hyperparathyroidism-jaw tumor syndrome carrying a large deletion of the CDC73 gene

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Hyperparathyroidism-Jaw Tumor Syndrome (HPT-JP) is a rare autosomal dominant syndrome with incomplete penetrance characterized by the combination of primary hyperparathyroidism (PHPT), renal lesions, jaw tumors and benign and malignant uterine lesions. Atypical parathyroid tumor and carcinoma are overrepresented in HPT-JT than in sporadic or other forms of familiar PHPT. The syndrome is caused by the germline mutation of *CDC73* encoding parafibromin. A 13-years old adolescent was referred to our outpatient clinic shortly after the surgical resection of the left inferior parathyroid gland which was diagnosed as atypical parathyroid tumor. The clinical history begun 2 months earlier with severe symptomatic PHPT (total serum calcium 16,6 mg/dl and PTH: 221 pg/mL). Neck ultrasound revealed a 1-cm lesion consistent with the left inferior parathyroid gland. This lesion was also detected by ^{18F}-Fluorocholina PET-CT but not by planar TC-sestamibi parathyroid scintigraphy. The family history was significant for PHPT affecting the patient's mother, three maternal first cousins and one maternal second cousin. Given the histology, the young age and the family history, genetic testing was performed, revealing a heterozygous germline deletion of all exons of the *CDC73* gene. This confirmed the diagnosis of HPT-JT. The patient's mother and one maternal first cousin carried the same deletion. Following this result, imaging of the jaw and kidney was performed, but no abnormalities were detected. After surgery, the patient developed hungry bone syndrome, which was managed with calcium carbonate and calcitriol. These treatments were gradually tapered over five months until they were discontinued. The patient has undergone regular biochemical and instrumental evaluation and remains in remission 16 months after surgery (total serum calcium level 10 mg/dl and PTH 17,20 ng/l). In conclusion, in young patient with PHPT, it is mandatory to thoroughly explore the family history and perform genetic testing to ensure an accurate diagnosis and to guide the appropriate follow up.

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EP255

JOINT2708

Is burosumab a good choice?: experience in adult X-linked hypophosphatemic rickets in a turkish patient

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Background
X-linked recessive hypophosphatemic rickets (XLH), also known as the Dent Disease, is a rare bone diasease which estimated prevalence is about 1 in 20.000 live births. It causes skeletal deformities, pain, stiffness and fatigue and impairs

quality of life. Burosumab, a fully human IgG1 monoclonal antibody directed against the fibroblast growth factor 23 (FGF 23), is a promising new drug in the treatment of hypophosphatemic rickets.

Case Report

A 26-year-old female patient was referred to the orthopedic clinic when she was 1 year old and noticed curvature in her legs. The patient with genu varum and coxa varum was consulted to the endocrinology department upon detection of hypophosphatemia and high alkaline phosphatase levels (Calcium:9,4, phosphorus: 2,1, Alkaline Phosphatase: 2440). Hypophosphatemic rickets was considered in the patient. And the patient received treatment with oral phosphate supplements and active vitamin D during childhood. In genetic analysis, PHEX mutation c.1645+1 G>A heterozygote was detected. No similar disease or mutation was detcted in her 3 sisters. The patient developed urinary incontinence when she was 4 years old. Urinary ultrasonography revealed that the right kidney was 65*23 mm, the left kidney was 70*27 mm, and type 3 nephrocalcinosis was detected in both kidneys. The 24-hour urine calcium, citrate and oxalate values of the patient were normal. After the age of 18, follow up began in the adult endocrinology department and conventional therapy was continued. Subcutaneous Burosumab treatment every 2 weeks was started in the patient whose phosphorus and vitamin D levels continued to be low despite conventional therapy and who developed hyperparathyroidism. There were no side affects releated to Burosumab treatment. At the followup 3 monts after the treatmet the patient report improvements in pain, mobility, physical function, energy, fatigue and mental wellbeing also there is improvement in laboratory values (f.e phosphorus levels increased from 2.1 to 3)(shown in Table 1 and Table2).

Conclusion

In our case we reported that a positive laboratory and clinical response with Burosumab treatment in the diagnosis of X-linked hypophosphatemic rickets, and observed no side effects developed in the short term. The lack of a significant improvement in 25-OH vitamin D and ALP values may be due to the early period. However, since Burosumab treatment is a new and promising option, its effectiveness and safety are unknown. We emphasize that there is a need for studies with more case reports and a larger number of patients to monitor long term effects.

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EP256

JOINT696

A curious case of trips and falls: pseudohypoparathyroidism

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We present a 7-year-old black African girl with no significant past medical history. The patient presented to the acute paediatric assessment unit following a fall whilst running for the bus. In the preceding week, she experienced multiple falls, several of which occurred where she had fallen from standing still without identifiable cause. The falls were preceded by a 2-month history of abnormal gait and arm positioning. No prodrome occurred prior to the falls, with no recollection of the fall itself. She was not post-ictal and become responsive immediately after. She denied any recent coryzal illness or fever. There was no birth, personal or family history of note. At initial assessment, her weight was 39.3kg (>99.6th centile), height 1.3m (>92.0nd centile) and BMI 23.18kg/m^2 (99.7th centile). She had a normal clinical examination, excluding difficulty performing heel-to-toe gait movements and left-sided dysdiadochokinesia. CT imaging of her head demonstrated symmetrical intra-axial calcifications predominantly involving subcortical white matter, basal ganglia and thalami. No evidence of intracranial haemorrhage or space-occupying lesions existed. Based on the distribution of calcifications, the imaging suggested a metabolic or genetic origin. X-ray of her hands showed normal contour and length of metacarpal bones. The appearance was within normal limits, with no bony exostosis or soft tissue calcifications. Laboratory investigations revealed significant hypocalcaemia, adjusted Ca^{2+} 1.43 mmol/l, high serum phosphate 3.25 nmol/l, low 25-hydroxy vitamin D 38 nmol/l and markedly elevated PTH 619 pmol/l. Further studies demonstrated a calcium:creatinine ratio of 0.04 and normal thyroid function. She responded to treatment with oral calcium, colecalciferol and alfacalcidol, with normalisation of bone biochemistry and resolution of gait/ coordination deficits. Methylation-specific MLPA demonstrated almost complete loss of the maternal methylation pattern at all four differentially methylated regions (DMRs) of the GNAS locus. No deletion was detected within GNAS or STX16. These findings confirmed a diagnosis of pseudohypoparathyroidism (PHP) type 1b. Pseudohypoparathyroidism is a rare heterogeneous group of disorders characterised by end-organ resistance to parathyroid hormone (PTH), in which other hormonal deficiencies, such as hypothyroidism and hypogonadism, may coexist. In PHP-1b, defective methylation leads to impaired Gsα expression, causing renal resistance to PTH. The basal ganglia are the most common sites of CNS calcification in PHP. This case highlights a rare but important cause of CNS calcifications. Early diagnosis and genetic confirmation are crucial for effective management, precise family counselling, and identifying at-risk relatives for early intervention.

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EP257

JOINT2025

Hypercalcaemia with unsuppressed parathyroid hormone level: a diagnostic dilemma; a case series

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Introduction

Hypercalcemia is a common disorder, with primary hyperparathyroidism (pHPT) and malignancy accounting for most of the cases. The parathyroid hormone level (PTH) is crucial in differentiating between the two conditions being raised in the former and suppressed in the latter. In a few instances, the picture can be clouded by additional factors that alter the hormonal level and can lead to misdiagnosis. **Case 1:**A 72-year-old male known dementia, diabetes and COPD presented with increasing confusion. Initial work up revealed corrected calcium 3.16nmol/l (2.20-2.60). PTH 3.2pmol/l (1.7-1.9). Vitamin D 21.3 nmol/l. The unsuppressed PTH raised the possibility of pHPT. It was, however, difficult to ascertain given that PTH is lower normal. Serum ACE and protein electrophoresis were unremarkable, eGFR> 90. The endocrinologist advised checking Magnesium which was low 0.4nmol/l (0.7-1.00). The patient received i.v fluids and Mg. A test following correction showed suppressed PTH of 1.5pmol/l with corrected calcium level 2.95nmol/l in keeping with hypercalcaemia of malignancy. A CT scan showed abdominal lymphadenopathy measuring 2cm. At the MDT, the impression was this is likely lymphoproliferative malignancy but given his co-morbidities, the plan was to manage palliatively. **Case 2:**A 56-year-old female patient with a recent history of subarachnoid haemorrhage due to ruptured aneurysm was undergoing rehabilitation under the care of the stroke team when she was noted to have raised corrected calcium 2.83nml/l(2.20-2.60). PTH 4.7pmol/l (1.7-1.9). Vitamin D 29.2nmol/l, eGFR>90. Similarly, it was not clear if this is pHPT given the unsuppressed PTH level. Magnesium level was subsequently checked and found to be low 0.35nmol/l (0.7-1.00). Correcting the magnesium revealed suppressed PTH 1.0pmol/l. A CT scan showed a mediastinal mass which is currently been evaluated by the chest physician for consideration of biopsy.

Discussion

Whilst hypercalcaemia with suppressed PTH typically raises concerns of malignancy, unsuppressed PTH in the context of hypercalcaemia usually indicates parathyroid pathology. This is commonly encountered in parathyroid adenomas/ hyperplasia but also in familial hypercalciuric hypercalcaemia and parathyroid malignancy. Nevertheless, many other factors could be contributing to the raised PTH level including magnesium or vitamin D deficiencies or chronic kidney disease. This could lead to confusion when trying to reach a diagnosis and formulate plans for further investigations. Our two cases are unusual as both demonstrate hypercalcaemia of malignancy in the presence of unsuppressed PTH due to unchecked hypomagnesaemia. It is of paramount importance to rule out these confounding factors prior to making a firm diagnosis.

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EP258

JOINT3708

The management of X-linked hypophosphatemia: oral phosphate and calcitriol supplementation vs. burosumab. a case report

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X-linked hypophosphatemia (XLH) is a rare genetic disorder caused by PHEX mutations, leading to excessive FGF23 activity, renal phosphate wasting, and chronic hypophosphatemia, resulting in rickets and skeletal deformities. Management has evolved from phosphate and calcitriol supplementation to burosumab, a targeted therapy blocking FGF23.
Case report
A 3 y 4 mo girl presents with mild facial dysmorphia (narrow forehead, low anterior hairline, bilateral epicanthus, short neck) and general rachitic signs (flaring thorax at the basis, rachitic rosary, thickened wrists and ankles, short stature and bilateral genu varum -intercondylar distance = 19 cm), with normal dental status. Blood tests showed normal serum Calcium, PTH, and 25-OH-Vitamin D, low serum phosphate and very high ALP. Normal renal and liver function. Lower limbs X-Ray show widened and cup-shaped with irregular margins distal femoral metaphysis. Delayed bone age: 2 y (-1.4 y delay). Thatcher score = 9. Normal 24-h urine analysis (particularly normal urinary phosphate and calcium) and normal TRP and TmP/GFR. The available Cento Metabolic panel excluded autosomal dominant and autosomal recessive hypophosphatemic rickets. Abdominal ultrasound, nephrology and neurology consult - normal. The suspicion of XLH was high, but genetic testing of the PHEX gene was lacking. We dosed FGF-23 (high) and 1,25-(OH)2-Vitamin D (low). We started conventional treatment, initially with Joulie solution (phosphate supplements are not available in Romania), 1 g of elemental phosphorus/day (divided in 5 doses) for a year, then managed to procure effervescent phosphate (2 × 500 mg/day, increasing adherence to therapy). Treatment also included Calcitriol (2 × 0.25 mg/day). Bilateral orthoses and physiotherapy were recommended. Over 2 years of conventional treatment, intercondylar distance worsened (19 cm to 20.5 cm). Phosphate levels were always low, ALP levels very high, Thatcher score still 9. At 5 yo, sequencing analysis discovered a nonsense variant in heterozygous status (NM_000444.5:c.264G > A) in the PHEX gene (Xp22.11), with a coverage of 339X at the variant site, confirming the XLH diagnosis. Burosumab treatment was initiated. Under the treatment, the intercondilar distance slowly decreased and the stature improved. Serum phosphate normalized and ALP levels decreased gradually. After 3.5 y of treatment with Burosumab (8 y 3 mo), the Thatcher score is 4.5, and intercondilar distance is 13 cm. No nephrocalcinosis and no other complications.
Conclusions
In severe XLH, conventional therapy often fails to correct hypophosphatemia and skeletal deformities. This case underscores Burosumab's superior efficacy, significantly improving phosphate homeostasis, bone health, and overall quality of life.

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EP259

JOINT3295

Family hypomagnesemia and hypercalciuric nephrocalcinosis: a case report and literature review

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Objective
To report the clinical features and management of a child with familial hypomagnesemia and hypercalciuric nephrocalcinosis (FHHNC) in order to enhance awareness of this condition. Methods: The medical history, laboratory tests, and treatment process of one FHHNC patient were analyzed, and genetic testing was performed on the proband, parents, and elder brother. Results: An 11-year-old girl presented with "growth retardation, polydipsia, and polyuria for over seven years." Seven years prior, she gradually exhibited growth retardation accompanied by excessive drinking, consuming 3-4 liters of water daily, polyuria, and nocturia, with two episodes of febrile convulsions (details unknown). On examination, her height was 117cm (-4.72SD), weight 21kg, presenting with disproportionate short stature, breast Tanner stage B1, no abnormalities in the heart or lungs, and bilateral X-shaped legs. Her parents were healthy, non-consanguineous, and there were no similar diseases reported in the family. Laboratory tests revealed serum calcium 1.5mmol/l↓, serum phosphorus 0.95mmol/l↓, alkaline phosphatase 1151u/l↑, parathyroid hormone 418pg/ml↑, 25-hydroxyvitamin D 17.97ng/ml↓, 1.25-hydroxyvitamin D 58.8pg/ml, serum magnesium 1.11mmol/l↓, urinary calcium 8.5mmol/24h↑, urinary phosphorus 3.6mmol/24h, serum creatinine 69.2umol/l↑, urinary alpha-1 microglobulin 39.8mg/l↑, urinary beta-2 microglobulin 29.3mg/l↑, urinalysis showing leukocytes 2+, renal ultrasound indicating nephrocalcinosis, cranial CT scan showing bilateral basal ganglia high-density shadows, and X-rays showing slight expansion and roughness at the distal metaphysis of the radius and ulna. Genetic testing identified a splice site mutation c.427+5G>A (homozygous) in the CLDN16 gene [Chr3(GRCh37):g.190120233G>A], which her parents and brother carried as heterozygous carriers without phenotypic expression. The diagnosis for the patient was 1. FHHNC; 2. Urinary tract infection.
Conclusion
FHHNC is a rare autosomal recessive disorder characterized by excessive renal excretion of magnesium and calcium, bilateral nephrocalcinosis, and progressive chronic renal failure. The disease often presents with severe renal impairment before diagnosis, with symptomatic treatment being the main approach, including low-dose hydrochlorothiazide, potassium citrate, and calcium-magnesium tablets to significantly improve hypomagnesemia and hypercalciuria. The prognosis is poor, with approximately one-third of patients presenting with chronic kidney disease at diagnosis, requiring renal transplantation for end-stage renal failure. Genetic testing can confirm the diagnosis. Routine magnesium blood tests are recommended for children with short stature. Clinicians should consider FHHNC in patients presenting with short stature, polyuria, hypocalcemia, hypomagnesemia, and nephrocalcinosis. This case reports a novel CLDN16 gene mutation site in China.

Keywords
Short Stature, Familial Hypomagnesemia and Hypercalciuric Nephrocalcinosis, CLDN16 Gene, Renal Failure, Hypocalcemia

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EP260

JOINT498

Association between bone turnover markers, bone mineral density, and serum osteoglycin in middle-aged men with Type 2 Diabetes mellitus

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Background
Patients with Type 2 diabetes mellitus (T2DM) have decreased bone health. We aimed to investigate serum levels of bone turnover markers (BTMs) (markers of bone formation and bone resorption) and bone mineral density (BMD) at three sites (lumbar, neck femur, and total femur) in middle-aged men with type 2 diabetes and to analyze the relationship between them. Also to evaluate serum osteoglycin as a novel marker and its relation to BTMs, BMD, and diabetic status.
Methods
We recruited seventy-eight patients with T2DM and thirteen non-diabetic, male volunteers as a control group. BMD was measured using a DEXA scan. BTMs (carboxy-terminal crosslinking telopeptide of type 1 collagen [CTX] and procollagen type 1 N propeptide [P1NP]), osteoglycin, PTH, and vitamin D were estimated. Data was compared among subjects and statistical analysis was performed.
Results
Most of the patients were having normal BMD with no significant difference between patients and the controls. BTMs and osteoglycin were significantly higher and vitamin D was significantly lower in the diabetic patients. Serum osteoglycin was positively correlated with DEXA Neck Femur ($r = 0.233$; p-value < 0.05).
Conclusion
Body mass index and Serum osteoglycin have a significant positive effect on BMD. Both markers of bone formation and bone resorption were increased indicating a state of increased bone turnover in T2DM.

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EP261

JOINT39

Clot twist: deep vein thrombosis uncovers primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by hypercalcemia, leading to various systemic complications. Recent evidence suggests a potential link between hypercalcemia and an increased risk of venous thromboembolism (VTE), an association warranting further exploration.
Case Presentation
We report the case of a 47-year-old male with a history of recurrent nephrolithiasis treated by extracorporeal shock wave lithotripsy in 2019. He was admitted for a deep vein thrombosis (DVT) of the right lower limb and initiated on anticoagulation therapy. Workup revealed PHPT with serum calcium of 107 mg/l, phosphorus of 18 mg/l, parathyroid hormone (PTH) levels 5.5 times the normal limit, and elevated 24-hour urinary calcium excretion. Complications included bilateral hydronephrosis secondary to renal calculi, osteolytic lesions, and osteoporosis in the lumbar spine and right femur. Cardiovascular evaluation was unremarkable. Cervical ultrasound identified a 20×14 mm left inferior parathyroid nodule, confirmed on MIBI scintigraphy. A multiple endocrine neoplasia (MEN) workup was negative. The patient was referred for surgical management.
Discussion
Recent studies, including large-scale investigations, highlight PHPT as an independent risk factor for acute VTE. Elevated calcium levels in PHPT patients may activate the coagulation cascade, increasing the propensity for thrombosis. In our case, the temporal association between PHPT and DVT reinforces this link. Early identification and treatment of PHPT can mitigate thrombotic risk, emphasizing the importance of integrating calcium-related disorders into VTE risk stratification models.
Conclusion
This case illustrates the multifaceted complications of PHPT, including its potential role in venous thromboembolism. Surgical intervention remains the cornerstone for resolving PHPT and reducing systemic complications. Further studies are needed to establish standardized guidelines for managing thrombotic risks in PHPT patients.

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EP262

JOINT143

Primary hyperparathyroidism and monoclonal gammopathy of undetermined significance: a misleading association? A case report

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Introduction
Primary hyperparathyroidism (PPH) and monoclonal gammopathy (MGUS) are two causes of hypercalcaemia. The association of the two is rare. Nevertheless, it has been reported in the literature, although the link has not yet been identified.
Case report
This is a 57-year-old patient who had been treated in internal medicine for MGUS for 6 months and had moderate hypercalcaemia. She presented to the emergency department with asthenia and worsening of her hypercalcaemia. A work-up showed confirmed HPP with hypophosphataemia, hyperpathormonemia and high 24-hour calciuria. A cervical ultrasound identified a parathyroid adenoma confirmed by MIBI scintigraphy.
Discussion
The association of MGUS or Multiple Myeloma (MM) and HPP is rare and may lead to diagnostic uncertainty as to the contribution of each aetiology to hypercalcaemia. In our patient, MGUS was diagnosed 6 months before HPP. One study showed that the prevalence of MGUS was 10% in patients presenting with HP. A recently published series of 5 cases (2020) reports 4 cases were diagnosed simultaneously for MM and HPP. The main hypothesis cited in the literature for this association is the induction of myeloma by high levels of PTH, which induces antiapoptotic effects on plasma cells.
Conclusion
The coexistence of two aetiologies of hypercalcaemia, MGUS and HHP, should encourage simultaneous diagnosis.
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EP263

JOINT251

Autoimmune polyglandular syndrome type 2: when calcium steps in

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Introduction
Autoimmune polyglandular syndrome type 2 (APS-2) is a rare endocrine disorder characterized by the coexistence of multiple autoimmune conditions, including type 1 diabetes, autoimmune thyroid disease, and others. Primary hyperparathyroidism (PHPT) is rarely associated with APS-2. This report discusses a complex case of APS-2 presenting with PHPT, illustrating the diagnostic challenges and therapeutic considerations.
Case Presentation
A 44-year-old female with a history of APS-2, including type 1 diabetes (diagnosed at age 10), autoimmune hypothyroidism, and premature ovarian insufficiency, presented for evaluation of hypercalcemia. Laboratory investigations revealed serum calcium at 111 mg/l, phosphorus at 27 mg/l, elevated parathyroid hormone (PTH) levels (twice the upper limit), and 24-hour urinary calcium excretion of 433 mg with fractional excretion of calcium exceeding 2%. Secondary causes were excluded through normal vitamin D levels and a 70 mL/min glomerular filtration rate. Imaging identified a right inferior parathyroid adenoma. Further evaluations ruled out multiple endocrine neoplasia (MEN) syndromes. Bone densitometry demonstrated femoral and lumbar osteoporosis, but there was no renal or cardiac damage. The patient was referred for surgical management of PHPT.
Discussion
PHPT in APS-2 is an uncommon finding, often masked by overlapping autoimmune conditions. This case emphasizes the importance of considering hypercalcemia and evaluating PTH in APS-2 patients presenting with osteoporosis or other metabolic bone diseases. The literature highlights the role of autoimmunity in parathyroid dysfunction, including potential contributions of anti-calcium-sensing receptor autoantibodies. While rare, PHPT should prompt careful screening to avoid misdiagnosis or delayed treatment.
Conclusion
This case underscores the complexity of diagnosing and managing APS-2 with PHPT. Multidisciplinary approaches are crucial to address the interplay of autoimmune conditions, ensuring timely diagnosis and optimal outcomes. Further research is needed to explore the prevalence and pathophysiological mechanisms linking PHPT and APS-2.

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EP264

JOINT1390

Alfacalcidol shortage in morocco and its impact on patient care: a retrospective study

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Introduction
The year 2024 was marked by a significant shortage of Alfacalcidol in our country, leading to notable challenges in daily medical practice. Alfacalcidol, a crucial vitamin D analog, plays a vital role in managing calcium homeostasis particularly in patients with hypoparathyroidism. The unavailability of this essential medication has had direct consequences on patient care, particularly an observed increase in hospital admissions for hypocalcemia.

Objectives
To evaluate the impact of the Alfacalcidol shortage on our routine clinical practice by analyzing hospitalization rates, patient outcomes, and alternative treatment strategies.
Patients and Methods
This is a retrospective study including 34 patients hospitalized in the Endocrinology and Diabetology Department of Ibn Rochd University Hospital in Casablanca for acute hypocalcemia in 2024. Data were analyzed using IBM SPSS Statistics 27.0.
Results
In 2024, hospitalizations for acute hypocalcemia saw a significant rise, reaching a peak of 34 cases. The mean age was 50.88 years with a female predominance of 85.9%. The average duration of symptoms was 13 days. Patients experienced tetany episodes, with 23% showing QT interval prolongation on ECG. The mean corrected calcium level at admission was 61 mg/l. Etiologies included 88.2% post-surgical hypoparathyroidism, 11.8% autoimmune hypoparathyroidism. Before hospitalization, all patients were on replacement therapy (calcium and alfacalcidol was replaced with cholecalciferol). Patients received intravenous calcium infusion with a good clinical and biological response.
Conclusions
The 2024 Alfacalcidol shortage had a significant impact on clinical practice, leading to a sharp increase in hospitalizations for acute hypocalcemia. This highlights the crucial role of Alfacalcidol in preventing severe complications and underscores the need for better strategies to mitigate the effects of future drug shortages.

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EP265

JOINT3714

Secondary hyperparathyroidism in patients with chronic renal failure

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Objectives
Identify the indications for parathyroidectomy (PTX) in secondary hyperparathyroidism (SHPT), report postoperative evolution, and describe early and late complications of PTX.
Materials and Methods
We carried out a retrospective study on patients with chronic renal failure who underwent parathyroidectomy (PTX) in our ENT department over a 13-year period, from January 2010 to December 2023. Clinical, biological, and radiological parameters were analyzed both preoperatively and postoperatively.
Results
Our study included a total of 70 patients with a mean age of 41 years. The median preoperative PTH and calcium levels were 1680 pg/mL [368,3742] and 2.2 mmol/l, respectively. The main clinical manifestation in our series was bone pain. In our study, 66 patients (94.28%) underwent cervical ultrasound, whereas parathyroid scintigraphy was performed in all cases. Cervicothoracic computed tomography was performed in only three patients (8.57%) to investigate ectopic parathyroid glands. No patient underwent magnetic resonance imaging (MRI). Surgical treatment consisted of subtotal parathyroidectomy in 66 patients, either 7/8th ($n = 56$) or 3/4th ($n = 10$). Three patients underwent total parathyroidectomy. The final histopathological examination revealed hyperplasia of the resected parathyroid glands in all patients. The cure rate was 78.57%. Persistent hyperparathyroidism was observed in 15 patients, including two cases associated with vitamin D deficiency. Three cases of recurrence were noted in our series.
Conclusion
Secondary hyperparathyroidism is a common and serious complication of chronic renal failure. Surgery is the treatment of choice when medical therapy fails.

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EP267

JOINT851

Suspected growth hormone deficiency as a mask of hypophosphatasia in a male patient with verified compound heterozygous variant in ALPL gene

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Introduction
Hypophosphatasia (HPP) is a rare inherited disease caused by mutations in the *ALPL* gene which encodes tissue-nonspecific alkaline phosphatase (ALP). The clinical presentation of HPP varies from lethal neonatal forms, severe skeletal dysplasia to minimal symptoms in adults.
Clinical case
We present a clinical case of a family with HPP, who were diagnosed after evaluation of a 20-year-old male patient due to complaints of short-statue. His height was 155 cm (SDS: -2.96), weight 52kg, no visual bone deformities. Hypopituitarism or any other endocrine abnormalities were excluded. Repeated tests showed low alkaline phosphatase (ALP -13 IU/l; ALP – 18IU/l reference range (40-150 IU/l) and elevated phosphate 1.76 mmol/l (0.74 - 1.52) along with all other parameters including calcium and bone remodeling markers within the reference range. On genetic evaluation we found a compound heterozygote variant *ALPL* c.1068C>A (p.Asp356Glu), c.1349G>A, (p.(Arg450His). At the moment of evaluation, short statue was the only clinical presentation of HPP, therefore no treatment was prescribed. His mother, sister, father (height 176cm) and both grandmothers (height 148cm) had low alkaline phosphatase levels. The patient's mother (age 43, height 149 cm, weight 54 kg) complained of pain in the spine and knee joints. Upon evaluation nephrocalcinosis was revealed. Her ALP levels were -19-24 IU/l (40.0-150.0) but all the other tests were within the reference range. DXA showed normal BMD at femur neck -1,1 SD, L1-L4 -0,2 SD Z-score. Exome sequencing showed the heterozygous variant in *ALPL* c.1068C>A (p.Asp356Glu). The patient's sister age 14 (height 146cm (SDS: -2.2), weight 41 kg) was diagnosed with primary hypothyroidism at the age of 6, since then she has taken Levothyroxine. The level of ALP was repeatedly low 19-24 IU/l (40.0-150.0) along with elevated phosphate 1.94- 2.1 mmol/l (0.74 - 1.52), all the other tests were within the reference range. Genetic testing revealed *ALPL* heterozygous variant c.1349G>A, (p.Arg450His). All three evaluated family members had excellent physical performance based on 6-minute walking, 10 second chair rise and grip strength tests.
Conclusion
This clinical case emphasizes a compound heterozygous variant in the ALPL gene as a plausible cause of short-statue. It is not clear if treatment with asfotase alfa would have improved this patient's height if it were given at a younger age.

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EP268

JOINT1039

Case of successful management of primary hyperparathyroidism and incidentally found micro PTC during pregnancy

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Introduction
Primary hyperparathyroidism in pregnancy is rare, with a reported incidence of 1%. Hunter and Turnbull documented the first case of hyperparathyroidism in pregnancy in 1931. Maternal and fetal/neonatal complications are estimated to occur in 67 and 80% of untreated cases respectively. Maternal complications include nephrolithiasis, pancreatitis, hyperemesis gravidarum, pre-eclampsia and hypercalcemic crises. Fetal complications include intrauterine growth restriction; preterm delivery and a three to five-fold increased risk of miscarriage, while neonatal complications include hypocalcaemia. We present a case of hyperparathyroidism successfully treated by surgery during second trimester.
Clinical case
41 y.o woman, with background of hyperparathyroidism diagnosed by combination of high adj Ca - 2.90 mmol/l(2.2-2.6), high PTH 12.6pmol/l(1.6-6.9) along with normal Vitamin D and high urine calcium/-creatinine ratio 0.035. US parathyroid and spect –CT scan confirmed diagnosis of left lower parathyroid adenoma. She found to be pregnant while awaiting surgery. During pregnancy her calcium level reached up to 2.97 mmol/l with PTH 117 ng/dl (15-65), which lead to the decision to perform surgery in second trimester. Post op histology was consistent with

parathyroid adenoma, but patient remained hypercalcaemic up to 2.91 mmmol/l despite of high fluid intake. Repeated US scan showed residual left inferior parathyroid lesion measuring 12 mm and small ill-defined subcentimetre thyroid nodule U2/U3. Subsequently, she had re-operative parathyroidectomy and left thyroid lobectomy with significant drop of PTH during surgery. Her PTH level normalised and adj Ca dropped to 2.5 and remained at this level until the end of pregnancy. Histology confirmed parathyroid adenoma tissue within scar tissue and 1 mm micro classical parathyroid carcinoma (pT1a). Had successful pregnancy without complications, apart from GDM, which ended up by elective caesarean section on time with normal baby. Her calcium level after pregnancy remains within normal limits.

Discussion

Parathyroidectomy is the definitive treatment for primary hyperparathyroidism and is recommended in pregnancy when serum calcium is greater than 2.75 mmol/l, particularly in patients with prior pregnancy loss. Retrospective data have demonstrated that patients treated with parathyroidectomy have lower rates of pre-eclampsia and preterm delivery compared to patients managed medically. Surgery is preferably performed in the second trimester due to incomplete organogenesis in the first trimester, and the risk of preterm delivery in the third trimester. Our case is also showing successful outcome of pregnancy treated with surgery, which allowed to avoid maternal and fetal complications. Concomitant finding of papillary thyroid cancer during pregnancy helped to avoid further thyroid surgery.

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EP269

JOINT3890

About a rare association: primary hyperparathyroidism and clear cell renal cell carcinoma

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Introduction

The association between primary hyperparathyroidism (PHPT) and neoplasia is well described in multiple endocrine neoplasia (MEN). However, its association with malignant solid tumors remains rarely reported. We present the case of a malignant renal tumor diagnosed simultaneously with PHPT

Case Report

A 58-year-old female patient with a history of diabetes and hypertension was hospitalized for management of severe hypercalcemia due to biologically confirmed PHPT, with a parathyroid hormone (PTH) level of 205 pg/mL, hypercalcemia at 3 mmol/l, hypophosphatemia at 0.56 mmol/l and vitamin D deficiency (11.2 ng/mL). She had no family history suggestive of multiple endocrine neoplasia. A cervical ultrasound revealed a 43 mm right superior parathyroid adenoma, along with two thyroid nodules classified as EU-TIRADS 2 and 3. Additionally, physical examination revealed abdominal collateral venous circulation and a left lumbar mass corresponding, on ultrasonography, to a solid-cystic lesion in the lower pole of the left kidney, measuring 11×10×12 cm, highly suspicious for malignancy. Plasma metanephrines and PTH-related peptide (PTHrP) levels were negative. The patient underwent a left lobisthmectomy and parathyroidectomy of the left inferior and right superior glands, leading to normalization of calcium-phosphorus balance postoperatively. Histopathological analysis confirmed hyperplasia of the left inferior and right superior parathyroid glands, as well as with two left vesicular thyroid adenomas. Subsequently, she underwent a left nephrectomy, and histopathological examination revealed a 13 cm clear cell renal cell carcinoma, classed pT2bNxM0 currently under supervising.

Discussion

It is possible that this association is a coincidence. However, that there might be an interaction between the two conditions, particularly due to the production of cytokines, growth factors, or other biologically active molecules that affect both the parathyroid glands and renal tissue. In the literature, there have been a few reported cases where patients with PHPT developed renal carcinoma, often after the treatment of hyperparathyroidism. It remains to be determined whether this association is coincidental or if there is an underlying relationship that has not yet been fully elucidated.

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EP270

JOINT1851

A young male patient presented with hypercalcemia due to familial hypocalceuric hypercalcemia type 1

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Familial hypocalciuric hypercalcemia is a genetic condition characterized by mild hypercalcemia, typically found in otherwise healthy and asymptomatic individuals. Differential diagnoses of hypercalcemia are usually based on the acuity and severity of presentation and concomitant level of serum parathyroid hormone. FHH arises from calcium-sensing receptor gene (CASR) mutations, leading to decreased receptor activity in response to serum calcium levels. This results in mild hypercalcemia, hypocalciuria, hypermagnesemia and hypophosphatemia, with normal or slightly elevated serum PTH levels. Here we describe a case of 19 yrs. old male referred by GP for having chronic fatigue for last few months. Initial investigations to find out the cause of fatigue, showed serum calcium level 2.71mmol/l (mildly higher than normal reference range) with normal phosphate of 1.14mmol/l and normal parathyroid level of 4.1 pmol/l. Subsequently, repeat blood test showed phosphate level of 0.77 mmol/l (low) with serum adjusted calcium level of 2.78 mmol/l. Family history includes father having high serum calcium level of 2.8 mmol/l which was not further investigated probably as he was asymptomatic. No other past medical history noted with no history of any current regular medications. He had low vitamin D previously which was treated with prophylactic dose of vitamin D only. His vital signs were stable with BP 118/68 mmhg, Pulse 70/min. Other systemic examination findings were unremarkable. His repeat blood test results in clinic showed Na 140 mmol/l, K 4.3 mmol/l, Creatinine 84 micromol/l, adjusted calcium level of 2.87 mmol/l, phosphate 0.86 mmol/l, 25 hydroxy vitamin D 50 nmol/l, PTH 3.6 pmol/l, TSH 1.6 mU/l, FT4 12.2 pmol/l. Urine test showed urinary calcium creatinine ratio of 0.08, with fasting urine calcium clearance of 0.0020. Considering his positive family history and presentation at an early age, genetic cause was suspected. Hence, a referral for a genetic test has been made. The genetic test results showed heterozygous for pathogenic CASR variant which can cause autosomal dominant familial hypocalciuric hypercalcemia type 1(FHH1). As he was otherwise healthy, reassurance given, and no further investigations or treatment have been offered. This case illustrates the importance of detailed history taking and appropriate clinical evaluation before deciding about further management for asymptomatic mild hypercalcemia. Appropriate clinical history and investigations including early referral for genetic test to diagnose Familial Hypocalciuric hypercalcemia will help to avoid unnecessary medical treatment or parathyroid surgery in selected cases.

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EP271

JOINT2296

Rare case of concomitant pseudohypoparathyroidism and bilateral ovarian teratoma

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Background

Pseudohypoparathyroidism (PHP) is a rare inherited disorder characterized by hypocalcemia and hyperphosphatemia due to end organ resistance to parathyroid hormone. This disorder is caused by mutations at the complex GNAS locus on chromosome 20 q13.3. The GNAS encodes alpha subunit of G protein stimulating the activity of adenylate cyclase, which is controlling the production of several hormones from different endocrine glands, such as: the thyroid, pituitary, ovaries, and testes. Ovarian teratomas are benign neoplasms that arise from pluripotent germ cells that differentiate into various tissues, including endocrine-related structures. Since GNAS mutations impact various tissues derived from the mesoderm and ectoderm, there could be a theoretical developmental link.

Case presentation

We present a rare case of concomitant pseudohypoparathyroidism and bilateral ovarian teratoma. A 35-year-old Caucasian female visited the clinic with complaints of carpal spasms, hand paresthesia, irritability and fatigue. Hypocalcemia detected from childhood was commenced with calcium supplements. A previous diagnosis of subclinical hypothyroidism due to thyroid hypoplasia, with negative anti-thyroid antibodies was reported and maintained on levothyroxine. At the age of 26, right ovarian cyst excision was performed (a histomorphological study confirmed a teratoma). Eight years later, a dermoid cyst was detected in the left ovary measuring 30x27x18mm, with no growth during regular follow-ups. No other clinically significant medical conditions in past medical history. She has a family history of

ovarian cancer and diabetes mellitus type 2. Physical examination was unremarkable, except for positive Chvostek and Trousseau signs, shortened 4th metacarpal and 4th metatarsal bones on both sides. Initial lab tests showed significantly low calcium level - 4.0mg/dl, increased PTH—241 pg/ml and Phosphorus- 5.2 mg/dl. DEXA scan and other laboratory results were within the reference range. A diagnosis of pseudohypoparathyroidism type 1a was made. Improvement of symptoms was achieved with combined calcitriol and calcium citrate supplementation.
Conclusion
This is a rare case of concomitant PHP and bilateral ovarian dermoid cysts. While there is no clinical evidence that these two disorders share any genetic or other pathophysiological properties, presence of both conditions in a single patient raises suspicion and remains an area of further investigations and research.

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EP272

JOINT784

Acute hypercalcemia after immune checkpoint inhibitor therapy with pembrolizumab. A case report

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Background.
Immune checkpoint inhibitors (ICIs) have dramatically changed cancer therapy by enhancing anti-tumor immunity. Their use, however, is potentially associated with a variety of immune-related adverse events (irAEs) that include rare cases of hypercalcemia. A single case of hypercalcemia induced by the programmed death-1 (PD-1) inhibitor pembrolizumab is currently reported. Severity, timing of occurrence, and pathophysiological mechanisms remain scarcely defined.
Case report
Seventy-year-old woman suffering from KRAS mutant, MSI-H colon adenocarcinoma with liver metastasis undergoing pembrolizumab as first line therapy. Shortly after its second administration, she developed severe, life-threatening, hypercalcemia (20 mg/dl) with acute kidney failure. Serum levels of intact parathyroid hormone (PTH), parathyroid hormone-related peptide (PTHrP), 25-OH vitamin D, and 1,25-OH vitamin D were suppressed, thus allowing the exclusion of primary hyperparathyroidism, ectopic PTHrP secretion and ectopic 25(OH)D-1-hydroxylase expression. Cross-sectional imaging ruled out the presence of osteolytic lesions or granulomatous disease. Immediate intravenous treatment included aggressive hydration and the infusion of zoledronic acid and high-dose glucocorticoids followed by pembrolizumab withdrawal. During the subsequent week, serum calcium levels gradually normalized and the patient's overall condition improved.
Discussion
The occurrence of hypercalcemia in cancer patients receiving ICIs requires a careful differential diagnosis between malignancy-associated and immune-mediated causes. Notably, the interference of pembrolizumab on the PD-1 pathway may enhance osteoclast differentiation and activity through a RANKL/OPG imbalance and the production of pro-inflammatory cytokines, like TNF-α and IL-6. Accordingly, experimental models of PD-1/PD-L1 inhibition have demonstrated increased bone resorption. Thus, based on the clinical and instrumental evidence, the immune-mediated PD-1 pathway disruption may be postulated as the main cause of this case of pembrolizumab-induced hypercalcemia.
Conclusions.
In patients receiving ICIs, monitoring of serum calcium and its assessment before each dose administration appear advisable. Early recognition and immediate management of hypercalcemia mitigate its morbidity and allow for the maintenance of immunotherapy. Further research into the interplay between PD-1 inhibition and bone homeostasis is warranted to improve the prevention and management of this rare but potentially critical irAE.

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EP273

JOINT979

Hyperphosphatemic familial tumoral calcinosis in an omani child: case report

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Hyperphosphatemic familial tumoral calcinosis (HFTC) is a rare autosomal recessive disorder characterized by progressive soft tissue calcifications due to a deficiency or resistance to intact fibroblast growth factor 23 (FGF23). The condition arises from pathogenic inactivating variants in the **FGF23**, **GALNT3**, or **KL**genes. We present the case of a 10-year-old Omani girl diagnosed with HFTC. She initially presented with a gluteal mass and persistently elevated serum phosphate levels. Radiological investigations, including radiographs, computed tomography (CT), and magnetic resonance imaging (MRI), revealed a large, lobulated, calcified mass within the gluteus maximus muscle. A CT-guided biopsy of the mass demonstrated fibrous tissue with extensive dystrophic calcifications, consistent with tumoral calcinosis. Genetic testing identified a homozygous pathogenic variant in the **GALNT3**gene (c.484C>T, p.(Arg162*)), confirming the diagnosis. Despite therapeutic interventions aimed at lowering serum phosphate levels, poor compliance led to persistent hyperphosphatemia. This case underscores the challenges associated with the diagnosis and management of HFTC and highlights the importance of early detection, patient education, and adherence to treatment protocols to mitigate disease progression.

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EP274

JOINT1437

Persistent hyperparathyroidism and bilateral oncocytic adrenocortical carcinoma: interplay of endocrine and oncologic challenges

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Introduction
Persistent hyperparathyroidism (PHPT) poses diagnostic and therapeutic challenges, particularly when coexisting with severe comorbidities. This case illustrates how PHPT influenced the treatment course of bilateral oncocytic adrenocortical carcinoma (ACC), underscoring the need for multidisciplinary management in addressing such complexities.
Case Description
A 60-year-old woman was diagnosed with oncocytic ACC in 2021, requiring left nephrectomy and adrenalectomy. Histopathological analysis confirmed oncocytic ACC with significant malignant potential (Ki67 18.5%, Weiss score 6). Despite initial surgical success with no evident metastases, severe hypercalcemia (>3 mmol/l) and renal impairment (eGFR 30–40 mL/min) revealed concurrent PHPT. Subtotal parathyroidectomy confirmed four-gland hyperplasia, yet hypercalcemia persisted postoperatively, delaying planned adjuvant mitotane therapy. In 2023; ^{18}F-Fluorocholine PET/CT localized an ectopic parathyroid adenoma at the sternocostal junction. A second surgery in May 2023, involving VATS exploration of the mediastinum and thymectomy, failed to locate the adenoma. A third surgery in October 2023, performed via sternotomy, successfully removed the ectopic adenoma, confirmed histopathologically. Intraoperative PTH monitoring demonstrated a significant decrease, indicating surgical success. During this period, a second ACC lesion was identified on the contralateral adrenal gland. In 2024, the patient underwent right adrenalectomy, with histopathology confirming an oncocytic ACC (Weiss score 4, Ki67 9%). Importantly, neither the initial nor the subsequent ACC exhibited functional activity at any postoperative stage. While it remains unclear whether the lesion represents a metachronous or metastatic process, delayed adjuvant therapy after the initial diagnosis likely influenced the clinical course. Postoperatively, hypoparathyroidism required intensive calcium and vitamin D supplementation. Subsequent DXA scans demonstrated improved bone mineral density, while renal function remained compromised due to solitary kidney calculosis and CKD (eGFR ~28–33 mL/min). Management of this case required close collaboration between endocrinologists, surgeons, nephrologists, and oncologists to address the overlapping challenges of PHPT and bilateral ACC. Multidisciplinary planning was crucial for integrating diagnostic imaging, surgical interventions, and long-term metabolic and oncologic care.
Conclusions
This case highlights the bidirectional impact of PHPT and ACC management, demonstrating how endocrine dysfunction may alter oncologic treatment strategies and outcomes. Advanced imaging modalities, repeated surgical

interventions, and close interdisciplinary collaboration are crucial in addressing such complex cases.

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EP275

JOINT1718

PROPEL: prospective observational registry for ENPP1 deficiency and early-onset ABCC6 deficiency

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ENPP1 Deficiency is a rare genetic disorder caused by inactivating mutations in the *ENPP1* (ectonucleotide pyrophosphatase/phosphodiesterase 1) gene (biallelic prevalence 1:64000). ENPP1 Deficiency is associated with low levels of plasma pyrophosphate (PPi) and AMP leading to ectopic (especially vascular) calcification (Generalized Arterial Calcification of Infancy [GACI] Type 1), pathologic skeletal mineralization (Autosomal Recessive Hypophosphatemic Rickets Type 2 [ARHR2]) and occlusive neo-intimal proliferation. Infants with ENPP1 Deficiency have 50% mortality in the first 6 months of life. Survivors typically develop hypophosphatemic rickets and experience bone deformities, hearing loss, impaired growth, pain and immobility leading to poor quality of life and function. Similarly, ABCC6 Deficiency, caused by biallelic mutations in the *ABCC6* (ATP-binding cassette transporter protein subfamily C member 6) gene, is a disorder of pathological mineralization and intimal proliferation manifesting in a spectrum of phenotypes, likely resulting from low PPi and adenosine due to reduced ATP, the substrate for ENPP1. The infantile-onset form (GACI Type 2) resembles ENPP1 Deficiency - infants present with widespread arterial calcification and severe cardiovascular complications. In both cases early genetic testing is key for apt treatment decision-making. Much of the current knowledge of ENPP1 and ABCC6 Deficiency is based on case reports or small retrospective studies. No targeted therapy exists for these diseases. This global, multicenter, prospective observational registry co-sponsored with GACI Global (PROPEL, NCT06302439) is designed to systematically collect clinical information to inform a comprehensive understanding of the burden of illness and progressive nature of these diseases. The key objectives are to determine the onset, variability and progression of pathological calcification and clinical complications and to assess the burden of disease on patients, including patient-reported outcomes (PROs). Except for optional PRO questionnaires, all data collected and recorded to the registry will be part of routine clinical exams. Patients will have an opportunity for optional blood draw to assess PPi levels. The registry is planned to open in 50 sites globally with the goal of recruiting up to 1,000 participants over the next 10 years, adding significant value to the existing body of evidence. Study updates and preliminary patient data will be presented.

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EP276

JOINT1794

Grading pseudofractures—the "breach – beak – bump – bridge" approach

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Pseudofractures are atraumatic radiolucencies resulting from compromised bone mineralization that are often associated with poor clinical outcomes in patients with metabolic bone disorders. The incidence, clinical course of healing, and risk of recurrence of pseudofractures are not well characterized, in no small part because pseudofractures and fractures are commonly reported under the general term "fractures" despite underlying pathophysiologic differences. Accordingly, this report proposes a grading scale to specifically assess pseudofractures. The grading scale was developed based on our clinical experience in treating femoral pseudofractures. The proposed circular taxonomy includes 4 radiographically distinct stages that include an unreactive initial Breach (Stage 1), appearance of a visible Beak (Stage 2) and a rounded Bump (Stage 3), and formation of a Bridge (Stage 4) across the interline. The loop closes at Stage 0, indicating absence of any radiographic hallmarks of a pseudofracture, either because a clinical suspicion does not have a radiologic correlate or because healing and remodeling are complete without residuals. These stages may correspond to a sequential transformation along the course of pseudofracture consolidation, although this requires scientific proof, and stagnation or relapse may occur at any stage. The stages should be further indicated by adding a "d" to the score for dislocation or an "s" for when the situation is clinically stable, meaning no pain and full weight-bearing because of surgical stabilization or sustainable cortical bridging (typically in Stage 4 or 0 [consolidation]). The scale may be used for any pseudofracture regardless of the anatomical site or underlying etiology. The proposed Breach–Beak–Bump–Bridge (4B) concept can be used as a tool in clinical practice to assess pseudofractures over time and to improve specificity and clarity in communication of these findings.

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EP277

JOINT1865

Radiofrequency ablation in primary hyperparathyroidism: a case study and literature review

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Primary Hyperparathyroidism (PHPT) is an endocrine disorder characterized by excessive production of parathyroid hormone (PTH), typically due to parathyroid adenomas, leading to hypercalcemia and its associated symptoms. Although surgery is a first-line treatment for PHPT, radiofrequency ablation (RFA) emerged as a minimally invasive alternative, especially for patients with comorbidities or those who want to avoid surgery. This poster presents a case study and a literature review of RFA in PHPT. A 78-year-old female patient with a history of breast cancer on aromatase inhibitors, type 2 diabetes mellitus, heart failure, atrial fibrillation with a pacemaker and atrophic gastritis was admitted to emergency department of our hospital with symptoms of hypercalcemia including weakness, anorexia, and nausea. Laboratory tests showed elevated serum calcium [corrected Ca^{2+}: 12.5 mg/dl (normal range: 8.4-10.5)] and PTH levels [PTH: 171.4 pg/ml (normal range: 55-65)] while imaging tests revealed a 23.5 mm parathyroid adenoma. After excluding other causes of hypercalcemia, the patient was diagnosed with PHPT. Considering the patient's comorbidities and her refusal to undergo surgery, RFA was chosen as a treatment option which was performed under ultrasound guidance and local anesthesia. The procedure involved hydro-dissection to protect surrounding structures. During the post-ablation period, patients improved clinically; subsequent follow-up confirmed a steady decline in calcium and PTH levels over 12 months and a 90% reduction in adenoma volume. A literature review was conducted for the efficacy of RFA in treatment of PHPT, based on recent studies. The RFA outcomes were promising as substantial reductions in PTH and calcium levels were noted, along with symptoms' relief and parathyroid adenoma volume rate reduction (VRR). Studies showed that the overall success rate was approximately 92%. Studies which compared RFA with parathyroidectomy found that surgery was more effective in lowering PTH levels since there is the risk of incomplete ablation in larger lesions and potential recurrence. However, RFA had lower rates of severe hypocalcemia, compared to patients undergoing parathyroidectomy, who experience a rapid drop in PTH levels and a rapid calcium influx into "the hungry bones" all resulting in decreased serum calcium levels. Other benefits of RFA are lower complication rate, faster recovery and lack of visible scarring making it an alternative option for patients with multiple comorbidities. In conclusion, RFA presents an effective alternative to parathyroidectomy for the treatment of PHPT. However, ongoing research is needed to optimize its role in clinical practice.

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EP278

JOINT10

Hypocalciuric hypercalcemia: navigating the diagnostic challenges

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Introduction
Familial hypocalciuric hypercalcemia (FHH) is a genetic disorder that causes lifelong hypercalcemia, often mimicking primary hyperparathyroidism (PHPT). FHH is primarily due to calcium-sensing receptor (CASR) gene mutations, leading to altered calcium homeostasis. This report discusses a case of FHH in a 68-year-old patient, highlighting the diagnostic challenges and clinical management strategies.
Case Presentation
A 68-year-old woman, Mrs. F.A, with a medical history of hypertension, type 2 diabetes mellitus complicated by chronic kidney disease, and gout, was referred for the evaluation of hypercalcemia. Initial laboratory tests revealed a corrected serum calcium level of 119 mg/l, hypophosphatemia (27 pg/l), and elevated parathyroid hormone (PTH) levels (five times the normal range). The 24-hour urinary calcium excretion was markedly low (<20 mg/l), suggesting hypocalciuria, with a fractional excretion of calcium less than 0.01. The patient's clinical examination showed an overweight status (BMI 28 kg/m^2) but was otherwise unremarkable. Cardiovascular and respiratory examinations were normal. The absence of endocrinopathies and a lack of familial history of hypercalcemia were noted. Imaging studies, including cervical ultrasound, MIBI scintigraphy, and MRI, did not reveal parathyroid adenomas.
Discussion
FHH is often misdiagnosed as PHPT due to overlapping clinical and biochemical features. Both conditions present with hypercalcemia and non-suppressed PTH levels. However, FHH is characterized by hypocalciuria, a key differentiating factor. Genetic testing, although not performed in this case due to cost constraints, can confirm the diagnosis by identifying mutations in the CASR gene. Management of FHH typically involves conservative measures, as most patients are asymptomatic and do not require surgical intervention. In contrast, PHPT often necessitates parathyroidectomy. In this case, the patient was managed with hydration and regular monitoring of calcium levels.
Conclusions
This case underscores the importance of considering FHH in the differential diagnosis of hypercalcemia, particularly in the presence of hypocalciuria. Accurate diagnosis is crucial to avoid unnecessary surgical procedures and to implement appropriate management strategies. Further genetic studies could enhance our understanding and diagnosis of FHH, ensuring better patient outcomes.

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EP279

JOINT44

Rocky road to diagnosis: uncovering primary hyperparathyroidism

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Introduction
Recurrent nephrolithiasis is a frequent pathology often associated with significant morbidity. Among its underlying causes, primary hyperparathyroidism (PHPT) is notable for its contribution to stone formation and nephrocalcinosis. However, PHPT remains an underdiagnosed yet treatable condition, necessitating heightened awareness for timely diagnosis.
Case Presentation
We report the case of a 47-year-old male with a history of recurrent nephrolithiasis treated by extracorporeal shock wave lithotripsy in 2019. The patient was admitted for a deep vein thrombosis (DVT) of the right lower limb and initiated on anticoagulation therapy. Etiological investigations revealed PHPT with serum calcium of 107 mg/l, phosphorus of 18 mg/l, parathyroid hormone (PTH) levels 5.5 times the normal limit, and elevated 24-hour urinary calcium excretion. Renal imaging showed bilateral hydronephrosis secondary to renal calculi. Localization studies identified a 20×14 mm left inferior parathyroid nodule, confirmed as pathological on MIBI scintigraphy. A surgical referral was made for definitive management.
Discussion
PHPT is a significant cause of recurrent nephrolithiasis, responsible for up to 7% of cases. Hypercalcemia and hypercalciuria, hallmark features of PHPT, promote calcium stone formation. Evidence suggests that delayed diagnosis of PHPT, often exceeding six years from the onset of symptoms, exacerbates renal damage. Studies underline the importance of metabolic assessments in patients with recurrent urolithiasis to identify PHPT early. Surgical intervention, typically parathyroidectomy, is curative, with a marked reduction in stone recurrence postoperatively. In our case, the presence of bilateral hydronephrosis further emphasizes the burden of undiagnosed PHPT. Regular follow-up and management of residual risk factors, such as vitamin D deficiency or low urinary citrate levels, are critical for long-term outcomes.
Conclusion
This case highlights the strong association between PHPT and recurrent nephrolithiasis. Comprehensive metabolic workups in patients with urolithiasis are crucial to prevent delayed diagnoses and their complications. Early surgical management remains the cornerstone of treatment, reducing recurrence and preserving renal function.

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EP280

JOINT2034

Pregnancy and lactation-associated osteoporosis with multiple spinal fragility fractures

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We present a case of a 31-year-old woman who was admitted to the Department of Endocrinology, Diabetes, and Isotope Therapy due to multiple vertebral fractures 6 months after delivery of her first child. The patient had been diagnosed with autoimmune thyroid disease with normal thyroid function before pregnancy. Treatment with levothyroxine was started in the 22nd week of gestation and continued until 6 weeks after delivery. She received vitamin D, iodine, and folic acid supplementation during pregnancy and lactation. She breastfed on demand. The patient does not smoke or abuse alcohol. Three months after delivery, the patient had a strong thoracolumbar pain while she was lifting a baby. On X-ray, scoliosis, L3-L4 discopathy, bone atrophy, and multiple vertebral fractures were depicted. Densitometry at the lumbar spine revealed osteoporosis Z-score (-) 4.8. Chest X-ray, ultrasound of breast, abdomen with pelvis, and bone scintigraphy did not reveal abnormalities. Thoracic and lumbar spine magnetic resonance imaging revealed fractures (Th4, Th7, Th9, Th12 and L1). The patient was treated with vitamin D (2000 IU a day) and calcium (1.5 g a day). A spine corset and rehabilitation were recommended but did not decrease thoracolumbar pain. On admission, the patient's BMI was 18.75 kg/m2. Osteoporosis at the lumbar spine (Z-score (-) 4.8) and femoral neck (Z-score (-) 2.9) was confirmed. During hospitalization, laboratory tests revealed normal levels of calcium, phosphates, parathormone, vitamin D, and bone turnover markers. There were no hormonal disturbances. Non-endocrine causes for secondary osteoporosis were also excluded. Finally, the patient was diagnosed with pregnancy and lactation-associated osteoporosis (PLO). Treatment with higher doses of vitamin D (4000 IU a day) and calcium (2.0 g a day) was initiated. After 8 months bone density parameters improved and the patient reported back pain relief.

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EP281

JOINT3821

Ectopic parathyroid adenoma associated with a thymoma: a case report

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Introduction
The combination of a parathyroid adenoma and thymoma is rare, with only few cases documented in the literature. This association may be explained by the shared embryological origin of the parathyroid glands and the thymus. We present here the case of a patient with primary hyperparathyroidism who was also found to have a thymoma in the anterior mediastinum.

Case presentation
A 60-year-old female patient was diagnosed with primary hyperparathyroidism based on hypercalcemia of 3.1 mmol/l, hypophosphatemia of 0.6 mmol/l, and inappropriate PTH level of 128 pg/ml. During the initial localization workup, a SPECT-CT scan showed an ectopic, hyperfunctional parathyroid gland located behind the manubrium of sternum. A chest CT scan revealed a calcified anterior mediastinal nodule in contact with the anterior surface of the ascending aorta, measuring 21 mm and a second lesion measuring 15 mm behind the manubrium sterni, corresponding to the hyperfixation area seen on the SPECT-CT. The patient underwent surgery with resection of the two masses. The histopathological report confirmed the diagnosis of thymoma (type AB1) and ectopic parathyroid adenoma.
Discussion
Primary hyperparathyroidism is a common endocrine disorder, with parathyroid adenomas accounting for 85% of cases. In about 10% of cases, the adenoma is ectopic due to abnormal embryological migration of the parathyroid glands. Despite their distinct primary functions, the parathyroid glands and thymus share a close relationship during organogenesis, as both are derived from the third branchial pouch. The association of a parathyroid adenoma with a thymoma is a rare clinical occurrence, with only a few cases documented in the literature. Patients may only present with the clinical signs and symptoms of primary hyperparathyroidism, making it difficult to suspect the presence of a thymoma. This association can be linked to familial syndromes, such as multiple endocrine neoplasia type 1.
Conclusion
Due to the close developmental link between the parathyroid and thymus glands, it is important to investigate the presence of thymic lesions when managing patients with primary hyperparathyroidism.
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EP282

JOINT3639
Assessment of bone mineral density and it's determinants in children with precocious puberty
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Background
Precocious puberty (PP) is defined as the early onset of pubertal development, often leading to accelerated bone maturation and potential alterations in mineral metabolism. Understanding the interplay between bone mineral density (BMD) and calcium-phosphate homeostasis in this population is crucial for assessing long-term skeletal health. This study aims to evaluate factors influencing BMD and differences in calcium-phosphate metabolism among children with PP.
Methods
A cohort of 34 children (30 girls and 4 boys) diagnosed with PP underwent a comprehensive assessment, including dual-energy X-ray absorptiometry (DXA) to measure BMD at the spine (BMD Spine) and Total Body Less Head (BMD TBLH). Height-adjusted Z-scores (HAZ) were also analyzed. In addition, hormonal levels (IGF-1, androgens such as DHEAS, androstenedione, testosterone, 17-OH progesterone, and estradiol) and responses to an LHRH stimulation test at three time points were evaluated. Markers of calcium-phosphate metabolism—including total calcium, parathyroid hormone (PTH), alkaline phosphatase, inorganic phosphates, urinary calcium excretion, and vitamin D levels—were also analyzed. Statistical tests assessed correlations between these parameters and BMD.
Results
Decreased BMD was found in 10 out of 34 children, defined as HAZ $<$-1 (among which all 10 patients had reduced HAZ TBLH, and 5 of them had also reduced HAZ Spine). A significant positive correlation was observed between bone age, calendar age, body mass, PTH, and BMD Spine. Additionally, BMD TBLH showed strong positive correlations with bone age, testosterone, and IGF-1 levels. Children with reduced HAZ TBLH had higher levels of DHEAS compared to those with normal HAZ TBLH. However, no statistically significant differences were found in IGF-1, PTH, vitamin D levels, or other hormonal markers between children with reduced BMD and those with normal BMD. Furthermore, no significant impact of vitamin D insufficiency ($<$20 ng/ml) on bone mineralization parameters was observed ($P>0.05$).
Conclusion
Bone age, testosterone, and IGF-1 levels were strongly correlated with BMD in children with PP, highlighting their potential role in skeletal development. While vitamin D levels did not significantly affect BMD, distinct hormonal differences, particularly in DHEAS, were observed in children with lower BMD, indicating complex regulatory mechanisms in bone health in PP. These findings underscore the need for further longitudinal studies to assess the long-term impact of metabolic alterations on skeletal integrity.
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EP283

JOINT1527
Cystic angiomatosis. a diagnostic challenge - case report
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Introduction
Cystic Angiomatosis (CA) is a rare condition with several dozen cases reported in the literature. It is characterized by multifocal skeletal and visceral angiomatous lesions. The aetiology of the condition remains unclear and the exact pathological background has not been determined so far, similarly as the diagnostic and therapeutic procedures.
Case report
We report the case of a 26-year-old male patient with a 5-year history of severe bone pain located in pelvis, spine, ribs and limping. CT scan showed osteolytic lesions with osteosclerotic rim in the capitula of humerus, pelvis, spine and several lesions in the right acetabulum. It also revealed gross splenomegaly with multiple heterogenous lesions and multiple hepatic lesions. Next, PET-CT was performed showing low FDG uptake in overmentioned lesions. It was followed by bone scintigraphy that showed hyperconcentration of the tracer in the same skeletal locations. Based on the obtained results, the main suspected diagnosis was malignant sarcoma with multiple bone metastases. The US-guided biopsy of the hepatic lesion was performed showing haemangioma. Next, the patient underwent splenectomy and histological examination revealed multiple small haemangiomas. Finally, the biopsy of the left ilium was performed that revealed spaces of bone tissue replaced with fibrous tissue with multiple, thin-walled blood vessels and the absence of myeloid neoplasia, lymphoma or carcinoma. The histological features were characteristic for systemic CA.
Conclusion
Whereas CA is a condition of mostly benign course, routinely performed radiological examination usually suggests more aggressive disorders, including malignant neoplasia, which should be excluded in the differential diagnosis. Therefore, the biopsy of the bone should be performed in the early stages of the diagnostic process to prevent patients from unnecessary stress. To our knowledge this is the first report on a patient with CA in Poland.
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EP284

JOINT81
A rare case of primary hyperparathyroidism caused by a giant parathyroid adenoma: a case report
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Background
Giant parathyroid adenomas (GPAs) are a rare cause of primary hyperparathyroidism, and are characterized by adenomas that weigh $>$3.5g. The large size and higher calcium levels of GPA may mimic parathyroid carcinomas.
Clinical Case
A 43-year-old female was referred to the Endocrinology for hypercalcemia, detected after evaluation for recurrent calculi was performed. Initial laboratory findings revealed adjusted serum calcium of 3.34mmol/l, albumin of 41g/l, and phosphate 0.5 mmol/l. On systems query, she denied polyuria, polydipsia, dysuria nor loin-to-groin pain. She had no bone pain, jaw pain, abdominal pain, dyspepsia, and constipation, constitutional symptoms or mood changes. She was not on calcium supplements, lithium or thiazide. Of note, she had a history of bilateral recurrent renal calculi treated with medical expulsive therapy. On examination, she was well hydrated, and did not have neck masses, or palpable lymph nodes. Systemic examination was unremarkable. Inpatient management of severe hypercalcemia included aggressive intravenous hydration, subcutaneous calcitonin and intravenous pamidronate. A

diagnosis of primary hyperparathyroidism was made, complicated by renal calculi, low bone density, and stage 3A CKD. Parathyroid carcinoma was initially considered in view of her significantly elevated PTH levels. Due to her young age of onset, familial PHPT was considered. A screen for symptoms associated with multiple endocrine neoplasia (MEN) syndrome was negative. Neck ultrasound demonstrated a large, lobulated, hypoechoic mass posterior to the left hemi-thyroid (5.1 × 1.7 × 1.7 cm). Technetium-99m labelled sestamibi localized the left hyperfunctioning parathyroid tissue. Early definitive left parathyroidectomy was performed, and histology revealed a parathyroid adenoma with no features of malignancy. She did not have hypocalcemia post-operatively. During follow-up over 3 years, she has remained normocalcemic, with improvements in bone density.

Conclusions

GPA appears to be a genetically distinct entity compared to parathyroid adenomas and carcinoma. (1) While no malignant transformation has been noted in the literature, patients with atypical adenomas should be followed up because of the molecular resemblance to carcinomas. (2) As it is difficult to differentiate parathyroid carcinomas from giant parathyroid adenomas pre-surgically, a strong clinical index of suspicion of malignancy is important to avoid a misdiagnosis.

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EP285

JOINT2597

Renaltú, a web page to satisfy the information needs on primary tubulopathies for patients and care provider

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Introduction

Primary tubulopathies are a group of hereditary disorders affecting renal tubular function, leading to electrolyte imbalances and mineral homeostasis alterations. Among them, X-linked hypophosphatemic rickets (XLH) is the most common hereditary form of rickets, characterized by persistent hypophosphatemia due to excessive FGF23 activity, resulting in impaired bone mineralization and growth retardation. Renaltube has established itself as a key scientific platform in the study of these disorders, while the development of RenalTú, a web page designed to satisfy the information needs of patients and care providers, represents a significant step toward improving access to specialized knowledge and resources.

Objectives

To describe the development and functionality of RenalTú as an interactive digital tool for patients with primary tubulopathies.

Methods

The development of RenalTú was structured into two key areas: technological development and educational content creation. The platform was designed as a responsive and user-friendly website, ensuring accessibility across multiple devices. Interactive features, such as structured disease information, educational videos, patient testimonials, and forums for community engagement, were integrated to enhance user experience. The educational content was developed in collaboration with nephrologists, geneticists, and patient advocacy groups to ensure accuracy and relevance. Additionally, clinical guidelines and ongoing clinical trials were included to facilitate informed decision-making by patients and healthcare providers.

Results

RenalTú (www.renaltu.com) was developed as a patient-centered digital resource, providing reliable information on primary tubulopathies in an accessible and interactive format. It enhances disease awareness, treatment adherence, and patient-provider communication.

Conclusions

RenalTú serves as an essential resource to bridge the knowledge gap for patients and caregivers dealing with primary tubulopathies, facilitating self-management and specialist interactions.

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EP286

JOINT465

Profound hyponatremia in acute heart failure with a good outcome

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We report on a male with severe hyponatremia secondary to congestive cardiac failure from dilated cardiomyopathy who was managed with fluid restriction, diuresis, and Tolvaptan before proceeding to emergency cardiac transplantation.

Case synopsis

This 54-year-old gentleman had a preceding history of the viral flu 2 months before coming in with progressive shortness of breath and swelling of his legs. He had seen a cardiologist 1 month before his attendance and an outpatient echocardiogram had revealed severely impaired left ventricular function (ejection fraction of less than 35%) he was commenced on diuretics along with Bisoprolol, spironolactone, and Ramipril. He subsequently presented to ED 2 weeks later with symptoms of progressive heart failure. Electrolyte estimation revealed severe hyponatremia (sodium of 121 mmol/l) and acute kidney injury. His serum osmolality was 262mmol/kg, urine osmolality 644mmol/kg, urine sodium of 23 mmol/l. Liver functions were deranged in keeping with hepatic congestion secondary to severe heart failure while thyroid and adrenal function were normal. Oral Bumetanide had worsened his sodium levels (sodium of 114mmol/l) and renal function with a further dropping in his urine sodium levels to 11 mmol/l, and an endocrine opinion was sought for his deteriorating sodium levels. Tolvaptan was introduced at 15 mg daily with strict monitoring of his renal function and fluid status. His sodium improved to 126 mmol/l over 2 days though he remained profoundly volume overloaded with clinical heart failure. Intravenous diuresis was commenced with stabilization of his renal function and the patient was transferred to the cardiac unit for close observation. He continued to receive regular tolvaptan with subsequent stabilization of his sodium levels to the low 120's and improvement in his renal failure proving that he had cardiorenal syndrome which responded to judicious management of his heart failure. Given persistent very poor cardiac function with an ejection fraction of under 15%, the patient was transferred to a tertiary hospital following discussion, for emergency orthoptic cardiac transplantation with a good outcome.

Discussion

This case highlights the importance of managing significant hyponatremia with a multi-disciplinary approach. Persistent low urine sodium in the setting of ongoing diuretics in our patient with severe hyponatremia suggested diuretic unresponsive heart failure and increasing risk of mortality and a poor outcome hence the key factor in management involved the judicious use of Tolvaptan and diuretics in optimizing heart failure as a bridge to eventual cardiac transplantation.

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EP287

JOINT1791

Design of 3 multicenter, phase 3, randomized trials to evaluate efficacy and safety of the enzyme replacement therapy efzimfotase alfa in patients with hypophosphatasia (HICKORY, MULBERRY, CHESTNUT)

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Introduction

Hypophosphatasia (HPP) is a rare inherited, metabolic disease caused by deficient tissue-nonspecific alkaline phosphatase (ALP) activity and characterized by skeletal and nonskeletal manifestations, including rickets/osteomalacia, fracture-s/pseudofractures, muscle weakness, and pain, which significantly impact quality of life. HPP was previously classified into subtypes by age at onset; however, manifestations can change and accumulate over time, suggesting that HPP is a continuous, progressive disease. The objective of the ongoing HICKORY (NCT06079281) and MULBERRY (NCT06079359) trials is to determine the efficacy and safety of efzimfotase alfa, an investigational next-generation ALP enzyme replacement therapy (ERT) for HPP in treatment-naive patients. The objective of the ongoing CHESTNUT (NCT06079372) trial is to determine the safety and tolerability of efzimfotase alfa in patients who initiate treatment after prior treatment with asfotase alfa, a first-generation ERT.

Study Design
HICKORY, MULBERRY, and CHESTNUT are ongoing multicenter, phase 3, randomized, parallel arm trials in patients ≥2 years of age (HICKORY: ≥12 years) with HPP (**Table**). Each study includes a 24-week randomized period followed by an open-label extension of up to 2.5 years. Weight-based doses of 20, 35, or 50 mg efzimfotase alfa will be administered subcutaneously biweekly. Approximately 184 patients will be recruited globally. This clinical program is the first to evaluate a broad HPP patient population across ages, ages at onset, manifestation types (including no overt skeletal manifestations), and functional endpoints such as the 6-Minute Walk Test (6MWT) and the 30-second Sit-to-Stand Test (STS).

Table

	HICKORY	MULBERRY	CHESTNUT
Design	Randomized, double-blind, parallel arm, placebo-controlled	Randomized, double-blind, parallel arm, placebo-controlled	Randomized, open-label, parallel arm, active-controlled
Treatment groups; allocation	Efzimfotase alfa vs placebo; 2:1	Efzimfotase alfa vs placebo; 2:1	Efzimfotase alfa vs asfotase alfa; 1:1
N (approximate)	~114	~30	~40
Age, y	≥12	2 to <12	2 to <12
Treatment naive[a]	Yes	Yes	No
Primary endpoint	6MWT after 24 wk	RGI-C score after 24 wk	Incidence of TEAEs
Secondary endpoints	STS, LEFS, TUG, 6MWT, RGI-C, RSS	RSS, 6MWT, BOT2, PDMS-3,	RGI-C, RSS, 6MWT, BOT-2, PDMS-3

[a]Patients in the CHESTNUT trial must have been treated with 6 mg/kg per week asfotase alfa for at least the 6 months before study initiation. Treatment-naive patients have no prior exposure to asfotase alfa.BOT-2, Bruininks Oseretsky Test of Motor Proficiency, Second Edition; LEFS, Lower Extremity Functional Scale; PDMS-3, Peabody Developmental Motor Scales, Third Edition; RGI-C, Radiographic Global Impression of Change; RSS, Rickets Severity Scale; TEAE, treatment-emergent adverse event; TUG, Timed Up-and-Go.

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EP288

JOINT1644

Interest of the bone scintigraphy in the diagnosis and monitoring of enchondroma, about a case

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Introduction
Enchondroma or central chondroma is a benign cartilaginous tumor with development intramedullary characterized by the proliferation of mature hyaline cartilaginous tissue. A tumour of the subject fasting (30-40 years), very common, usually discovered by chance. Solitary enchondroma accounts for nearly 3% of all bone tumors and between 12 and 24% of benign bone tumors. Generally asymptomatic. The scintigraphic aspect of enchondroma lacks specificity and may be a false positive aspect on planar images in a context of searching for secondary bone locations. Objective: The interest of bone scintigraphy in the localization and diagnostic orientation of benign bone tumors and its role in the monitoring of any malignant degeneration.
Materials and Methods
We report the case of a patient referred for an extension assessment of a mammary neoplasia. A bone scan completed with SPECT/CT was performed with a GE NM/ CT DISCOVERY 670 Gamma camera.
Results
Standard radiography showed a clear (osteolysis) of the upper end of the tibia (left tibial plate). On the planar scintigraphic imaging, there was a focal hyperfixation focus in the upper epiphyso-metaphyseal region of the left tibia. SPECT/CT slices showed a mixed osteocondensing lesion with osteolysis of the left epiphyseal cartilaginous matrix without periosteal reaction or rupture of the cortical, evoking an enchondrome of the left tibial plateau.
Discussion
The described appearance suggests enchondroma. However, a differential diagnosis with bone infarction cannot be ruled out. Interest of an MRI to establish the diagnosis and eliminate differential diagnoses (bone infarction). In addition, a subsequent scintigraphic check-up is recommended for the follow-up of any sarcomatous transformation
Conclusion
SPECT/CT has allowed a morphological characterization and the anatomical localization of enchondroma and elimination of false diagnosis of secondary bone localization. Bone scintigraphy is of interest during enchondroma where it allows to map the lesions and serves as an initial follow-up examination of any sarcomatous transformation.

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EP289

JOINT833

Mass effect revealing a sphenoidal brown tumor: a case report

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Introduction
Brown tumour or fibrocystic osteitis is a rare benign bone lesion secondary to hyperparathyroidism. It can affect the entire bony skeleton, including the pelvis, ribs, clavicles and limbs. However some infrequent localisations are possible such as cranial and facial bone damage. we present a case of a sphenoidal brown tumour associated with tertiary hyperparathyroidism.
Case presentation
The patient was 33 years old and had been on haemodialysis for more than 8 years for chronic renal failure in a single polycystic kidney complicated by tertiary hyperparathyroidism with major hyperparathormonemia at 1398 ng/ml. The patient presented with a pituitary tumour syndrome consisting of headaches with decreased visual acuity, especially on the left side, associated with a galactorrhoea amenorrhoea syndrome that had been evolving for 1 year. Cerebral MRI revealed a 51*35*33 mm process involving the base of the skull, displacing the pituitary gland and centred on the sphenoid bone, initially suggesting a brown tumour, which was confirmed by CT scan with the presence of calcifications and a clear blowing aspect of the sphenoid cortex. Hormonally, she was complicated by anteropituitary insufficiency, which we substituted, in particular corticotropic, thyrotropic and gonadotropic insufficiency, associated with hyperprolactinaemia of probable disconnection. Finally, the patient was scheduled for neurosurgery in view of her visual prognosis.
Discussion
First described in 1891, the brown tumour is a fibrocystic bone lesion caused by hyperactivity of osteoclasts, as a result of hyperparathyroidism. It is an uncommon complication that can affect the entire bony skeleton, including pelvis, ribs, clavicles and extremities. Involvement of the sphenoidal bone is considered rare, hence the particularity of our case. The brown tumours may be completely asymptomatic or manifest as bone pain or pathological fractures, which was the case of our patient, mimicking a pituitary adenoma.
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EP290

JOINT2242

Familial hyperparathyroidism due to gcm2 gene alteration: a case report

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Introduction
Primary hyperparathyroidism (PHPT) is a common cause of hypercalcemia, often linked to parathyroid adenomas, hyperplasia, or, in rare cases, genetic mutations. Lithium therapy, frequently used in bipolar disorder, has been associated with PHPT due to its effects on calcium metabolism. However, distinguishing lithium-induced hyperparathyroidism from primary forms remains challenging. We present a case of PHPT in a lithium-treated patient with an underlying genetic mutation.
Case Report
A 48-year-old woman was referred to our clinic due to an incidental finding of hypercalcemia. She had a medical history of bipolar disorder, treated with lithium for over 10 years. Laboratory tests revealed a corrected calcium level of 11.4 mg/dL (8.3-10.6), phosphorus at 3.7 mg/dL (2.7-4.5), vitamin D at 30.3 ng/mL (20-60), parathyroid hormone (PTH) at 109.5 pg/mL (18.5-88), and 24-hour urinary calcium at 45.9 mg/24h (100-300), with a calcium/creatinine clearance ratio of 0.01. Given the suspicion of PHPT, repeat tests confirmed similar findings. Parathyroid scintigraphy indicated hyperplasia of the left superior and inferior parathyroid glands. Additional tests, including bone densitometry and renal ultrasound, showed no pathological findings. Considering these results, the mental health team evaluated

the feasibility of discontinuing lithium therapy, and genetic testing was performed for potential hereditary causes of PHPT. Despite lithium discontinuation, hypercalcemia persisted. Genetic analysis identified a heterozygous variant in the GCM2 gene, associated with familial PHPT. The patient underwent selective parathyroidectomy of the left superior and inferior glands, leading to normalization of calcium and PTH levels postoperatively.
Discussion
Between 10% and 20% of lithium-treated patients develop hypercalcemia with hypocalciuria and elevated PTH due to reduced parathyroid gland sensitivity to calcium. Typically, calcium levels normalize within months of discontinuing lithium. However, in this case, persistent hypercalcemia suggested an alternative etiology. The identification of a GCM2 gene mutation, a rare cause of familial PHPT, explained the continued hypercalcemia despite lithium cessation. This highlights the importance of genetic testing in cases where standard etiologies do not fully account for clinical findings. Few cases of GCM2-related familial PHPT have been documented, underscoring the need for further research into its pathophysiology and optimal management. This case emphasizes the necessity of a comprehensive approach in evaluating hypercalcemia, particularly in patients on long-term lithium therapy, to differentiate between drug-induced and primary hyperparathyroidism and to consider potential genetic contributions when the clinical course is atypical.

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EP291

JOINT2856

Geriatric patient presenting with severe hypercalcemia due to suspicious parathyroid carcinoma

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Introduction
Primary hyperparathyroidism is a common endocrine disorder of calcium metabolism characterized by hypercalcemia and elevated or inappropriately normal concentrations of parathyroid hormone. Almost always, primary hyperparathyroidism is due to a benign overgrowth of parathyroid tissue either as a single gland (80% of cases) or as a multiple gland disorder (15–20% of cases). Most of patients with PHPT are asymptomatic, but the symptoms and signs could include nephrolithiasis, osteitis fibrosa cystica, osteoporosis, fractures, bone pain, myopathy, and neuropsychiatric impairment. Primary hyperparathyroidism can be cured by removal of the parathyroid gland or glands but identification of patients who are best advised to have surgery requires consideration of the guidelines that are regularly updated. 1.
Case Report
77 y/o female was hospitalized in our clinic. During hospitalization, performed lab tests revealed significantly elevated serum calcium (x2 ULN) and elevated PTH 20-fold. Thyroid US demonstrated parathyroid tumor suspicious for Cr measuring up to 4 cm and multinodular goiter with total thyroid volume of 25 cm3. During physical examination patient was demonstrating spasticity, lethargy, anxiety, confusion. Patient had a history of ischemic stroke – 2018, PE Arterial hypertension was diagnosed 10 years ago. Patient admitted to have increasing blood pressure findings, renal insufficiency was also diagnosed couple months ago, but no further diagnostic or treatment interventions were initiated. 10 days leading up to hospitalization patient admitted to have had lower and upper extremity tremors. She admits to having these symptoms occasionally. Decreased appetite, severe constipation were also noted. Patient had trouble moving around and was brought in by her family members. Laboratory findings also revealed sublinical hyperthyroidism, suspicious for toxic multinodular goiter. Parathyroidectomy was planned along with the total thyroidectomy. Surgery used intraoperative recurrent laryngeal nerve monitoring device, which revealed low impulse during surgical exploration of parathyroid tumor, instead of additional total thyroidectomy, only subtotal parathyreidectomy was performed considering potential risks associated with recurrent laryngeal nerve compromise.
Conclusion
High level of clinical suspicion and routine laboratory work-up for screening purposes is required for timely diagnosis of hyperparathyroidism. The evaluation and management of patients with parathyroid disease remains challenging, and surgical treatment requires experience and expertise. It's important to perform vertebral and renal imaging in addition to bone desitomety followed by corresponding treatment if required.
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EP292

JOINT3617

A case of primary hyperparathyroidism due to an oxyphil cell adenoma

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Introduction
Oxyphil cell parathyroid adenoma were defined as parathyroid tumours containing >75% oxyphilic. They are considered to be an uncommon cause of primary hyperparathyroidism, and were historically thought to be clinically silent cells because they were believed to involuted. Recently these adenomas present more often than previously thought and may manifest a more severe form of primary hyperparathyroidism than classical adenoma. We report the case of a parathyroid adenoma with oxyphilic cells responsible of primary hyperparathyroidism
Observation
This is a 57-year-old patient with a history of fracture of the left foot, who presented with incidentally discovered hypercalcaemia at 2.71 mmol/l. The work-up showed hypophosphaemia at 0.7 mmol/l, hypercalciuria at 7.3 mmol/24h, associated with PTH at 186 pg/ml, with no detectable repercussions. The indication for surgery was based on the presence of a fracture and hypercalciuria. The localised work-up showed a left lower parathyroid adenoma fixed on sestamibi scintigraphy, not visualised on cervical ultrasound. The patient underwent a simple post-operative course, and the patho-anatomical examination concluded that it was an oxyphilic cell adenoma of the left lower parathyroid gland. Post-operative serum calcium was 2.32 mmol/l and serum phosphorus 1 mmol/l.
Conclusion
Oxyphil cell parathyroid are an uncommon cause of primary hyperparathyroidism. Functional oxyphil adenomas occur more frequently than is usually appreciated. Their role still remains controversial, Nevertherless, they could play an important role in hormone secretion.

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EP293

JOINT2611

Imaging in X-linked hypophosphataemia (XLH)

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Summary
X-linked hypophosphataemia (XLH) is a rare metabolic bone disorder where mutations in the PHEX gene lead to increase circulation of hormone fibroblast growth factor 23 (FGFR23), causing a series of clinical manifestations including rickets, lower-limb deformity, short stature, craniosynostosis, Chiari 1 malformations, spinal stenosis, pseudo fractures and osteoarthritis, among others, with significant impact to the patient's quality of life. Imaging plays an important role in XLH from diagnosis to treatment response, early detection and management of complications. We present a comprehensive pictorial review of different imaging modalities used in our cohort of patients including x-rays, ultrasound, CT, MRI, bone scan and SPECT. We illustrate the most common findings seen at different stages of the disease and explain the advantages vs disadvantages of each imaging modality dependent on the clinical question posed for children and adults.
Methods
We searched the imaging database in our institution and found 42 patients with ages ranging from 3 to 78-years (20 under 16y) reviewed their imaging and selected the ones which best illustrate the findings seen at different stages of the disease including at diagnosis, during treatment response, and evidence of compilations. For some of the abnormalities we provide companion images depicting both normal appearances and the range of specific manifestations seen in non-XLH patients (e.g. grades of nephrocalcinosis) to facilitate a better understanding of the imaging findings.
Objectives
Know the available imaging toolbox and how to use it in XLH, from diagnosis to treatment response, including identification of complications, both in children and adults.

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EP294

JOINT2026

Primary hyperparathyroidism: from diagnosis to treatment

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Introduction
Primary hyperparathyroidism (PHPT) is the leading cause of hypercalcemia. It is secondary to hypersecretion of parathyroid hormone (PTH) by the parathyroid glands. Today, PHTP is asymptomatic in 80–90% of cases. The aim of this work is to analyze the clinical, paraclinical and therapeutic profile of primary hyperparathyroidism (PHTP).
Materials and Methods
This is a retrospective study that collected 49 patient files followed for PHTP in our department, over a period of 5 years from 2016 to 2023.
Results
There were 16 men and 33 women (sex ratio = 2.3), the average age was 58 years (27 and 88 years). The circumstances of discovery were: bone pain in 83% of cases, hypercalcemia in 69% of cases and asthenia in 11% of patients. Biology showed a mean calcemia at 2.66 mmol/l (2.5 – 3.4). The mean value of parathyroid hormone was 386 pg/l. Vitamin D was measured in 16 patients; 71% of them had hypovitaminosis D. Imaging (cervical ultrasound and MIBI scintigraphy) showed a hypoechoic mass opposite the thyroid pole with a lower left location in 67% of cases. Symptomatic treatment of hypercalcemia was associated with surgical treatment in all cases. The mean value of postoperative calcemia was 2 mmol/l with a mean PTH value of 20 pg/l. The anatomopathological study concluded a parathyroid adenoma in 83%, parathyroid hyperplasia and an atypical adenoma in 10% of cases and a parathyroid carcinoma in 6% of cases.
Conclusion
Surgical management of the hyperfunctioning parathyroid gland(s) is the only curative treatment for HPTP. Medical management concerns patients for whom surgery is not indicated, who present a surgical contraindication or who refuse surgery. The diagnosis of HPTP warrants contact with an endocrinologist to ensure its management.

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EP295

JOINT2353

Demystifying an unusual culprit and analyzing implications for management: a case of lithium-induced parathyroid hyperplasia presenting as severe symptomatic hypercalcemia

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Background
Lithium remains one of the most effective treatments for bipolar disorder and has been associated with the development of hyperparathyroidism. Even experienced physicians can be perplexed when caring for such patients since there is a paucity of data regarding the management of lithium-induced hyperparathyroidism.
Case presentation
A 33-year-old female with bipolar disorder who is on long-term Lithium treatment presented to the hospital with a three-day history of tremors, nausea, vomiting, and constipation. She denied any fever, vision changes, hematuria, abdominal or flank pain. Vital signs were normal. Physical examination was only remarkable for fine tremors. Laboratory tests showed a serum Creatinine of 1.7mg/dL (baseline 0.5mg/dL), corrected Calcium 12.6 mg/dL (ref 8.5-10mg/dL), PTH 153 pg/mL (ref 15-65pg/mL), Phosphate 0.8 mmol/l (ref 0.8-1. 45mmol.L), 1,25 dihydroxy Vitamin D 83pg/mL (ref 18-78 pg/mL), 24-hour urinary calcium 410 mg/day (ref 100-300mg/d), Lithium level 3.1mmol/l (ref 0.5-1.2mmol/l), EKG showed a normal QTc. The endocrinology team was consulted, and the patient was started on fluids, calcitonin, cinacalcet, and pamidronate, which lowered her calcium level. Lithium was discontinued, and Valproic acid was started as an alternative. However, she had a relapse of mania during hospitalization. Psychiatry suggested restarting Lithium while continuing medical treatment for hypercalcemia. Parathyroid technetium 99m Sestamibi-CT scan showed findings of parathyroid hyperplasia and the patient deferred surgery. She was later discharged with strict outpatient Endocrinology and Psychiatry follow-up.
Discussion
Lithium alters the set point of calcium-sensing receptors in the parathyroid cells, causing increased PTH release and elevation of the calcium threshold required to suppress PTH. It affects the Wnt/B catenin pathway, causing parathyroid growth. A trial of Lithium dose reduction, discontinuation, or switching to other mood stabilizers can be attempted; however, it is associated with relapse of the mood disorder in patients on chronic lithium. Cinacalcet, which sensitizes calcium-sensing receptors, can be used while on Lithium with close monitoring of calcium levels. Parathyroidectomy can be considered for non-responders and the treatment of choice for patients who develop parathyroid adenoma.
Conclusion
Lithium-induced hyperparathyroidism is a rare complication of long-term lithium therapy. Individualized patient education regarding the risks and benefits of Lithium continuation, medical and surgical options, and the importance of a multidisciplinary follow-up with regular calcium and PTH monitoring at least every 6 months.
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EP296

JOINT1169

Two different causes of hypercalcemia

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Hypercalcemia is not common among children, actual incidence in children is unknown. Although vitamin D intoxication is rare, the health effects can be serious if it is not promptly identified.

1st patient:

Blood tests	Results	Reference interval
Ca (mmol/l)	**4.43**	2.2-2.7
P (mmol/l)	1.46	0.95-1.75
25(OH)vit D (ng/ml)	**525**	30-50
PTH (pg/ml)	**1.8**	15-68
Hb (g/dl)	10.7	10.7-13.4
Creatinine umol/l	**43**	21-36

A 2 years old boy – previously healthy, presented with 2 week history of nonspecific symptoms: fatigue, poor apetite, weight gain, constipation. 1st child, 41.g.w., 3.7kg. Weight 9.4kg (-2.5SD), height 86cm (-1SD), HR 150x/min, BR 26x/min, BP 85/60 mmHg.

- Additional examination: ECG- short QTc complex, ST segment depression, Echocardiogram- normal, Kidney ultrasound – normal.
- Upon detailed questioning, the mother admitted that child receives 1000-2000 units of vitamin D daily, additionally consumes 200ml of adapted formula, as well 200-400ml of sweetened milk with added vitamin D. Total dose of vitamin D – 2600 IU/daily, long term.
- Treatment: i/v hydration + loop diuretics for 10 days, + p/o prednisolone (from 7th-10th day).

After 3 month with low calcium diet, discontinuation of vitamin D supplementation - Ca 2.38 mmol/l (N), 25(OH)D 87.3 ng/ml (N).

2nd patient:

Blood tests	Results	Reference interval
Ca (mmol/l)	**3.43**	2.2-2.7
P (mmol/l)	1.26	0.95-1.75
25(OH)vitaminD (ng/ml)	**154.2**	30-50
PTH (pg/ml)	**13.1**	15-68
Hb (g/dl)	11.2	10.7-13.4
Creatinine (umol/l)	**83**	21-36

A 2 years 2 month old boy – previously healthy, complains about ataxia, vomiting (5x), fatigue. 1st child, 41.g.w. 3.8kg. Weight 14.3 kg (+0.5SD), height 90.8cm (0SD) HR 125x/min, BR 24x/min, BP 94/58-**143/93mmHg**

- Additional examination: Fundus oculi – normal CT, MR cerebellum – normal Kidney ultrasound – **nephrocalcinosis.**ECG, echocardiogram- normal.
- Patient receives 400-800 units of vitamin D daily.
- Genetic testing: CYP24A1 gene biallelic mutation.
- Treatment: i/v hydration + loop diuretics 8 days, hydrocortison 7 days. ACE inhibitor- long-term.

The presence of CYP24A1 mutation explains the increased sensitivity to vitamin D in patients with idiopathic infantile hypercalcemia, it is genetic risk factor for development of symptomatic hypercalcemia that may be triggered by vitamin D prophylaxis in otherwise healthy infants.
Conclusions
Nonspecific symptoms like vomiting, constipation, hypertension may be sign of hypercalcemia in children. Symptomatic hypercalcemia is rare in children and requires extensive investigation.

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EP297

JOINT470

Osteoporosis at a young age: an issue for endocrinologists – a case report

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Introduction
Bone loss in younger gynecologic cancer survivors occurs prematurely, sometimes decades before routine age-based osteoporosis screening in the general population. Data regarding bone loss management in this group of patients are generally lacking, especially in ovarian cancer survivors.
Case
A 31-year-old female was referred to an endocrinologist regarding the treatment strategy for osteoporosis. The medical history was clarified: in 2014, she was diagnosed with stage 3 ovarian cancer (G1 serous carcinoma). Laparotomy, total hysterectomy with adnexectomy, omentectomy, peritonectomy in the minor pelvic region and diaphragm, and paraaortic lymphadenectomy were performed, followed by six cycles of Paclitaxel/Carboplatin chemotherapy in the same year. Due to a BRCA2 gene mutation revealed by genetic testing, the usual choice of hormone replacement therapy (HRT) was not applied. She was monitored for oncologic recurrence and osteoporosis development. The patient was regularly followed up by the endocrinologist, with observation of Ca-P metabolism tests, bone markers (BAP, CTX), and DXA changes. DXA results presented progression from osteopenia in 2015 (spine: T-1,22; 1,033 g/cm2) to osteoporosis in 2023 (T-3,6; 0,741 g/cm2). The patient was discussed in the Reproductive Health MDT: there are no clear contraindications for prescribing HRT in the presence of a previous oncological disease and the BRCA2 gene mutation. The BRCA2 gene mutation increases the risk of breast cancer in postmenopausal women; however, there is no data indicating an increased risk at a younger age. At this stage, was recommended to prescribe HRT for at least one year, and if osteoporosis continues to progress or osteoporotic fractures occur earlier, bisphosphonates should be prescribed.
Conclusion
This case highlights the challenging management of osteoporosis in young cancer survivor and the necessity of MDT when facing a clinical situation with no strong clinical evidence and treatment guidelines.

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EP298

JOINT1211

Adrenal glands, pancreas, and urinary catheter calcifications in a 59-year-old woman with primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism is endocrine disease defined by increased calcium levels and excessive level of parathyroid hormone, associated with diverse systemic complications. Most common are urinary lithiasis and osteoporosis, but calcification of soft tissue are more rarely found.
Case Presentation
A 59-year-old woman, was admitted to the hospital for surgical treatment of primary hyperparathyroidism revealed by pathologic fracture. The diagnosis of primary hyperparathyroidism was confirmed based on calcium level of 3.53 mmol/l, inappropriate PTH level of3708 ng/dL, and hypercalciuria at a level of0.15 mmol/kg/24h, complicated by severe osteoporosis with a T-score of -6.6. A right 22mm parathyroid adenoma was found by neck ultrasound and parathyroid scintigraphy. Kidney scan showed calculi in the urinary tract, along with pancreatic and adrenal calcifications, which are known and uncommon soft-tissue calcification associated with hyperparathyroidism. She didn't have adrenal insufficiency, and there was no sign of tuberculosis. During her hospital stay, the patient's urinary catheter was found to have calcified deposits which was relatedwith significant hypercalciuria. This is a rare but notable manifestation of PHPT, highlighting the impact of prolonged elevated calcium levels on the urinary system.
Disscussion and conclusion
This particular case demonstrates the variety of complications that primary hyperparathyroidism can cause, some of which may be unexpected. While hypercalcemia and osteoporotic fractures are common manifestations of PHPT, calcifications in the adrenal glands, pancreas, and urinary catheter are less prevalent but nonetheless important to recognize. In some cases of PHPT, calcifications have been observed, particularly in the pancreas and adrenal glands. These calcifications are the result of the long-term impact of high calcium and PTH levels on various organs. Urinary catheter calcification is uncommon but can happen as a result of high calcium levels in the urine, particularly when hypercalciuria is present. To avoid serious problems, early surgical intervention and calcium metabolism monitoring are essential. Additionally, since PHPT can present with a variety of clinical symptoms, such as fractures and unusual calcifications, it highlights the importance of being vigilant in the diagnosis process.

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EP299

JOINT2016

An intrathyroidal parathyroid adenoma: a location not to be ignored!

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Introduction
Primary hyperparathyroidism is a common endocrine pathology, explained in the majority of cases by the presence of a parathyroid adenoma, located in the cervical region. Intrathyroid localization of the parathyroid adenoma is rare and can be a cause of failure of surgical treatment. We report a case of intrathyroid parathyroid adenoma.
Observation
This is a 72-year-old patient, diabetic hypertensive, admitted for management of hypercalcemia discovered during the exploration of diffuse joint and bone pain. The etiological and impact assessment showed corrected calcemia at 2.8 mmol/l, hypophosphatemia, hypovitaminosis D at 14.2, and parathyroid hormone at 494 pg/ml. The cervical ultrasound showed a thyroid nodule of 33x17 mm classified EUTIRADS III. SPECT-CT objectified an intralobar nodule intensely fixing the MIBI. An *in situ* PTH dosage was performed returning 9698 pg/ml. The patient had oral hydration, and a right loboisthmectomy. The intraoperative frozen section and final histological examination confirmed the intrathyroidal localization of a parathyroid adenoma. The evolution was favorable with normalization of calcemia and PTH in the postoperative period.
Conclusion
Parathyroid ectopia is one of the causes of failure of surgical treatment of hyperparathyroidism. Intrathyroid localization must not be overlooked in order to successfully perform surgery for hyperparathyroidism. The current therapeutic strategy aims at preoperative identification of pathological parathyroid glands that combines data from cervical ultrasound, MIBI-Tc99m scintigraphy and exploratory cervicotomy.

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EP300

JOINT3823

Palopegteriparatide use for severe postoperative hypocalcemia

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Introduction
Hypocalcemia can occur as a complication of total thyroidectomy. In this context, postoperative hypoparathyroidism is due to accidental removal, damage or devascularization of the parathyroid glands. Hypocalcemia can also occur as part of hungry bone syndrome (HBS) in patients who have previously had long-standing hyperthyroidism, as it causes increased bone turnover with overall bone resorption, which then transitions to osteoblastic activity once the excess hormone is eliminated.
Case report
A 26-year-old woman underwent total thyroidectomy for long-standing Graves' disease with concomitant orbitopathy. Postoperatively, she developed hypocalcemia. She was discharged from the ENT department with calcium carbonate 6 g daily and calcitriol 3 mg daily. She did not show up for endocrinology follow-up

as scheduled. One month after surgery, she was hospitalized because of severe symptomatic hypocalcemia (paresthesias, abdominal cramps, positive Trousseau's and Chvostek's signs). Laboratory findings revealed an unmeasurably low PTH level, severe hypocalcemia (total calcium 1.3 mmol/l, ionized 0.47 mmol/l), hypomagnesemia (0.54 mmol/l) and hyperphosphatemia (2.4 mmol/l). These findings were primarily suggestive of iatrogenic (postoperative) hypoparathyroidism, but likely with concomitant HBS aggravating hypocalcemia, as the patient had severe long-standing hyperthyroidism prior to surgery. Persistent symptomatic hypocalcemia despite treatment necessitated transfer to the ICU, where she received intravenous calcium chloride as a continuous infusion, magnesium sulfate, and further dose adjustments of calcitriol, calcium carbonate and cholecalciferol were made. The targeted calcium levels could not be achieved, so teriparatide was initiated in two daily doses together with other medications. A short time later she was switched to palopegteriparatide 18 mg subcutaneously daily. Satisfactory calcium levels were maintained and the patient was discharged on the following daily doses: calcitriol 3 mg, calcium carbonate 12 g and palopegteriparatide 18 mg. Over the next few months, calcium levels were maintained with only minor adjustments to the above therapy. The patient stopped coming for regular check-ups and stopped taking the medications regularly. Inadequate adherence to therapy led to severe hypocalcemia (this time asymptomatic) and she was hospitalized. Satisfactory calcium levels were achieved and maintained by adjusting calcium and vitamin D supplementation alone, without PTH replacement therapy.

Conclusion

Palopegteriparatide can serve as a bridging therapy in patients with severe hypocalcemia due to hypoparathyroidism and HBS after total thyroidectomy for Graves' disease in the period when satisfactory serum calcium levels cannot be maintained with high doses of calcium and vitamin D supplementation.

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EP301

JOINT823

Dermatological disorders associated with hypocalcaemia: a case report

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Introduction

Chronic hypocalcaemia is associated with several dermatological disorders, which may take a variety of symptomatic forms. Our case report illustrates this association.

Case report

A 68 years old women who underwent thyroidectomy 10 years ago, was admitted for aetiological assessment of hyperkeratotic, scaly generalized lesions on an erythematous background evolving for 6 months in a context of altered general condition. The anamnesis reported constipation with frilosity and generalised paresthesias, with no other signs. Clinical examination revealed a fever of 38°C and the dermatological lesions described above, associated with diffuse pachyonychia, with positive schvostek more marked on the right side. The work-up revealed a neutrophil cells increase correlated with a rise in the CRP up to 300 mg/l and the sedimentation rate up to 113 mm/h, associated with severe hypocalcaemia to 54 mg/l. The suspicion of psoriasis was strongly supported on the basis of the above, and confirmed by biopsy. Patient was under levothyroxine with adjustement, associated with intravenous and oral correction of blood calcium levels. Dermatologically, a local emollient treatment was initiated. The course was marked by remarkable clinico-biological improvement.

Discussion

The acute response of the keratinocyte to calcium resembles that of the parathyroid cell. Overall, hypocalcaemia will affect keratocyte differentiation and give rise to a binding defect that can be seen in most desquamative and hyperkeratotic dermatological diseases such as psoriasis and pustulosis. As in our patient's case, it can lead to new or worsening conditions. However, what characterises the dermatological lesions associated with hypocalcaemia is their remarkable evolution after correction of the triggering or aggravating hypocalcaemia. The majority of studies note the beneficial effect of calcium and vitamin D supplementation in the healing process, even in cases of normocalcaemia.

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EP302

JOINT3872

A falsely labeled primary hyperparathyroidism: about a case report

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Introduction

Primary hyperparathyroidism is a common pathology, with diagnosis based mainly on biological parameters alone. Localization should only be performed if surgery is indicated. We report a case of MAX syndrome mistaken for primary hyperparathyroidism in the presence of a parathyroid adenoma.

Case report

A 64-year-old postmenopausal woman with 7 years' postmenopausal history, no personal or family history of lithium or thiazide diuretic use, consulted an endocrinologist for a parathyroid incidentaloma. The initial work-up revealed a biological profile of elevated calcemia (108 mg/l), elevated PTH (2 times normal) and hypophosphatemia, raising the initial suspicion of primary hyperparathyroidism without prior measurement of 24-hour calciuria. Given the presence of osteoporosis at bone mineral density, surgery was indicated. Subsequently, a 24 h calciuria was performed, which came back collapsed with a urinary calcium fraction lower than 0.01, thus rectifying the diagnosis of familial hypocalciuric hypercalcemia.

Discussion and conclusion

Marx syndrome or familial hypocalciuric hypercalcemia (FHH) is a genetic disorder caused by mutation of the calcium-sensitive receptor (CASR) gene, resulting in decreased receptor activity in response to serum calcium levels. This pathology is the first differential diagnosis to be ruled out before considering primary hyperthyroidism. The decisive biological element between these two entities is urinary calcium excretion over 24 h, with a ratio of calcium clearance to creatinine clearance of less than 0.01, indicating FHH. The coexistence of FHH and a parathyroid incidentaloma is possible, as in our case, and this is why imaging should always come last after establishing a diagnosis of primary hyperpathyroidism.

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EP303

JOINT288

Primary hyperparathyroidism meets fibromyalgia: a crossroads of symptoms

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Background

Fibromyalgia is a chronic diffuse pain syndrome characterized by widespread musculoskeletal pain, chronic fatigue, and sleep disturbances. These symptoms overlap with those commonly observed in hyperparathyroidism, a condition that may also present with neuropsychiatric and musculoskeletal complaints. Understanding the interplay between these two conditions could provide valuable insights into their pathophysiological mechanisms and diagnostic challenges.

Case Report

We present the case of a 49-year-old woman with a history of treated breast carcinoma, admitted to the endocrinology department for evaluation of hypercalciuria. The patient exhibited anxiety, irritability, and a focus on multiple somatic complaints, including asthenia, headaches affecting sleep quality, diffuse muscle pain, fatigue, and morning stiffness. She reported an exacerbation of pain with heat and stress, although her appetite remained intact. Symptoms persisted despite treatment with non-steroidal anti-inflammatory drugs and antidepressants. The patient underwent multiple specialist consultations, and a brain MRI revealed nonspecific white matter hyperintensities. Clinical examination identified 11 tender points out of 18 according to the American College of Rheumatology (ACR) criteria, leading to a diagnosis of fibromyalgia. Further investigations suggested a likely diagnosis of normocalcemic primary hyperparathyroidism, supported by a serum calcium level of 2.44 mmol/l, a phosphate level of 0.7 mmol/l, an inappropriately elevated parathyroid hormone (PTH) level of 166.60 pg/mL and a urinary calcium excretion of 11.22 mmol/24h. Neck ultrasound revealed a left parathyroid nodule measuring 10 × 7 × 2 mm, and bone densitometry confirmed osteoporosis. Other potential causes of hypercalciuria, such as granulomatous diseases, were ruled out.

Conclusion

The diagnosis of fibromyalgia is frequently delayed, leading to a significant socio-economic burden due to prolonged symptomatology and repeated medical consultations. In this case, the coexistence of fibromyalgia and hyperparathyroidism underscores the importance of a thorough diagnostic approach to unexplained chronic symptoms. Further research is essential to clarify the potential pathophysiological connections between these two conditions and optimize patient management.

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EP304

JOINT3719

ENT manifestations of the relapsing polychondritis (RP) in diabetic patients

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Introduction
Relapsing polychondritis (RP) is a rare inflammatory systemic disease mainly affects cartilage, and describes several ENT manifestations.
Aim
To describe the clinical and evolutionary particularities, in diabetic patients with autoimmune polychondritis, and their therapeutic management.
Objectives
The patient was 80 years old, with a history of diabetes. He presented to our emergency department with a swelling of the right auricle that had been evolving for 3 days in a context of apyrexia, associated with vertiginous attacks, bilateral hypoacusis evolving for years, and chronic dysphonia. Examination revealed swelling, warmth, redness and pain over the right auricle. The external auditory canal was well calibrated, with a free mastoid region. A peripheral vestibular syndrome was noted, and the nasofibroscopy showed a laryngeal pseudomyxoma. A biological inflammatory syndrome was noted. the patient was initially put on intravenous antibiotic therapy for 15 days without any improvement, with worsening of the affected area and fistulization to the skin. A microbiological sample showed the presence of pseudomonas aeruginosa and antibiotic therapy was set according to the antibiogram. A cervicothoracic CT was performed in search of respiratory tract chondritis, which came back normal. The progression was complicated by sepsis, followed by infectious endocarditis, requiring a transfer to cardiology, for further treatment. During hospitalization in the cardiology department, The patient developed perichondritis of the contralateral ear, internal medicine was consulted to investigate a possible RP in a diabetic patient, with a series of additional exams enabling us to confirm RP.
Conclusion
It's important to know how to recognize RP, because a delay can lead to severe complications. Diagnosis is clinical and may be supported by biopsy and response to treatment.

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EP305

JOINT3760

The phantom hormone: decoding bone loss in a breast cancer patient

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Background
Women who have had breast cancer treatment may have an increased risk of osteoporosis and fracture. Moreover, breast cancer might have complications like distant metastases accompanied by hypercalcemia and high alkaline phosphatase levels, but hyperparathyroidism is not commonly considered in the differential diagnosis.
Case Presentation
We present the case of a 62-year-old female, with medical history of breast cancer (2013, right breast conservatory surgery, subsequent radiotherapy and 5 years of hormonal treatment with Tamoxifen), with no tumor recurrence detectable at yearly oncology assessments, is referred to an endocrinology consult due to persistent elevated alkaline phosphatase and severe osteoporosis with lowest bone mineral density (BMD) at distal radius level (T-score of -4 SD), compared to lumbar spine (T-score L1-L4 of -2.7 SD) and hip (T-score femoral neck of -2.7 SD). Causes of secondary osteoporosis were investigated detecting elevated PTH (104 pg/ml, N:10-69), normal 25-OH-vitamin D (64.1 ng/ml, N > 30, under adequate vitamin D supplementation 4000-5000IU/day), mild hypercalcemia (10.33mg/dl, N:8.5-10.3), hypercalciuria (398.4 mg/24h, N < 250), normal phosphatemia (3.67 mg/dl, N:2.6-4.5). Considering vitamin D was above 40-50ng/ml, and PTH is its end-activator (by renal hydroxylation) potentially increasing hypercalcemia, we decided to stop vitamin D supplementation until investigations were completed. Cervical ultrasound identified normal thyroid gland, but a small hypochoic nodule 6.3 mm localized in the lower pole of the left thyroid lobe confirmed a parathyroid adenoma by parathyroid scintigraphy. The functional and imaging data confirmed the diagnosis of primary hyperparathyroidism, and a 3-month biological follow-up spontaneous improvement was observed: PTH of 83.32 pg/ml, 25-OH-vitamin D maintained within normal range 31.56 ng/ml, normal calcium levels (total calcium of 9.8mg/dl), normal phosphatemia.
Conclusions
We presented the case of a woman diagnosed with severe osteoporosis seven years after a breast cancer diagnosis, associating persistent elevated alkaline phosphatase levels in the absence of detectable local or distal tumor recurrence, which proved to be in the context of primary hyperparathyroidism.

Keywords
osteoporosis, breast cancer, primary hyperparathyroidism
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EP306

JOINT3289

Pseudohypoparathyroidism 1b diagnosed in middle adulthood with an atypical presentation: a case report

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Introduction
Pseudohypoparathyroidism (PHP) refers to a group of heterogeneous disorders defined by targeted organ unresponsiveness to PTH characterized by endocrine abnormalities (hypocalcemia, hyperphosphatemia and elevated PTH concentrations), abnormal physical characteristics and neurocognitive deficits. The are several types: type 1 PHP (1a, 1b, 1c), type 2, pseudo-pseudohypoparathyroidism, and other forms (acrodysostosis)
Case report
A 45-year-old man was referred to the endocrinology department from orthopaedic department due to an elevated PTH concentration in the blood test (1,385 pg/mL) with normocalcaemia, normophosphatemia, normal creatinine, and low 25-(OH) vitamin D after a fall with damage in the right forearm.. The x-ray showed a lytic lesion in the epiphysis of radius, another in the metacarpus of the third finger and brachydactyly. The biospy showed a benign lesion with giant cells (giant cell granuloma). A bone gammagraphy showed other lesions in the knees, shinbone and tarsus suggestive of brown tumors. A bone densitometry showed a Z-score -2.8 at the spine and -2 at the hip. The 24-hour urine calcium was normal. He had hypothyroidism diagnosed ten years ago and suffered a fracture of his left ankle fifteen years ago. He was taking levothyroxine and 25-(OH) vitamin D supplements. His height was 173 cm and his weight 82 Kg. He had peculiar facial features and hands. He did not have children. Therefore, we suspected a PHP and we requested a genetic test, a complete hormonal test and started treatment with calcitriol. The genetic test was compatible with PHP type 1b, with a loss of methylation in GNAS A/B located within the differentially methylated region (DMR1) in the GNAS complex locus. No other hormonal abnormalities were found A bone densitometry performed nine months later showed an improvement in the Z-score: Z-score -1 at the spine and -1.7 at the hip. The dose of calcitriol was increased up to two micrograms/day to maintained the PTH levels (111 pg/mL) at the upper level of normal range (28-115 pg/mL)
Conclusions
It is important an early diagnose and treatment in patients with PHP to avoid long-term bone damage and perform genetic counseling Calcitriol is an effective and safe treatment in normocalcaemic patients with PHP like ours

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EP307

JOINT3722

Hypercalcemia as the initial manifestation of sarcoidosis: a case series

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Introduction
Sarcoidosis is a multi-system granulomatous disorder that can present with hypercalcemia, renal impairment, and other systemic manifestations. Hypercalcemia in sarcoidosis results from the overproduction of 1,25-dihydroxyvitamin D by activated macrophages within the granulomas. Here we present a case series on three patients diagnosed with sarcoidosis over the past 10 years in our trust.
Case Presentations
Case 1:A 37-year-old male presented with weight loss, fatigue, nausea, polyuria. Initial investigations revealed hypercalcemia (4.06mmol/l) and acute kidney injury (AKI) with elevated creatinine (315µmol/l). Computer tomography (CT) imaging was suggestive of sarcoidosis, and an elevated ACE level (220 IU/l) supported the diagnosis. Biopsy of left inguinal lymph nodes confirmed non-necrotizing granulomas. The patient was treated with intravenous fluids, bisphosphonates, and prednisolone, leading to improvement in hypercalcemia (2.45mmol/l) and renal function (creatinine 105µmol/l). **Case 2:**A 38-year-old male with sarcoidosis presented with hypercalcemia (3.4mmol/l) and AKI while on long-term prednisolone. Whilst CT-imaging showed bilateral mediastinal and hilar lymphadenopathy consistent with sarcoidosis, biopsies of these did not show granulomatous changes. ACE levels (92.8 IU/l) were elevated, supporting the diagnosis of sarcoidosis, despite the lack of granuloma formation on biopsy. Treatment with intravenous fluids and pamidronate, followed by prednisolone therapy, resulted in clinical and biochemical improvement. **Case 3:**A 63-year-old female with a 19-year history of sarcoidosis presented with persistent hypercalcemia (3.46mmol/l), muscle weakness, and polyuria, despite ongoing steroid therapy. CT-imaging showed no active granulomatous disease or malignancy, and the patient's complex medical history, including chronic kidney disease and atrial fibrillation, complicated the management. The patient's recurrent hypercalcemia was managed with bisphosphonates, which showed slight improvement in calcium levels.
Discussion
Sarcoidosis remains an important differential for hypercalcaemia and all patients should receive full body CT-imaging to guide further investigations and management including site for tissue biopsy. Whilst corticosteroids remain the cornerstone of treatment for sarcoidosis, these cases highlight the role of adjunct therapy including bisphosphonates in the management of the hypercalcaemia. These were sufficient to resolve associated complications including impaired renal function secondary to nephrocalcinosis and interstitial nephritis.
Conclusion
This case series highlights the complexities in diagnosing and managing sarcoidosis-related hypercalcemia. Clinicians should maintain a high index of suspicion for sarcoidosis in patients presenting with unexplained hypercalcemia and renal dysfunction, particularly when other causes such as malignancy have been excluded. It also reinforces the importance of early recognition and a multidisciplinary approach involving nephrology, endocrinology, and respiratory medicine to optimize patient outcomes.

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EP308

JOINT2721

A case report: COL1A1 mutation with albright hereditary osteodystrophy (AHO) features

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This case report outlines the clinical presentation, diagnostic journey, and treatment response of a 21-year-old female initially referred at age 6 with recurrent fractures. Genetic testing confirmed a COL1A1 mutation commonly associated with osteogenesis imperfecta (OI), but the patient also exhibited features suggestive of Albright Hereditary Osteodystrophy (AHO). Whole genome sequencing ruled out GNAS mutation, prompting a discussion on the phenotypic spectrum of COL1A1 mutations.

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EP309

JOINT2432

Waddling gait and parathyroid adenoma: what to have in mind for a quick diagnosis?

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Parathyroid adenoma often remains undiagnosed for a relatively long time, due to the fact that bone pains and disorders of the osteomuscular system, patients seek to be resolved in other non-endocrinological problems. Case presentation: The case describes a primary thyroid adenoma in a 46-year-old patient with a two-year history of upper and lower limb pain, treated by a rheumatologist as polyathralgia without signs of improvement from therapy! In the meantime, the patient is also diagnosed with severe osteoporosis. The neurologist who was consulted for a headache during the neck examination noticed a mass in the lower part of the neck and in the ultrasound a nodule was seen for which he was referred to the endocrinologist (Figure 1). After the corresponding laboratory and imaging examinations, the patient is diagnosed with very high PTH, high calcium(Table 1) bilateral nephrocalcinosis (Figure 2), marked osteoporosis (Figure 3), fractures of the lumbar vertebrae (Figure 4), bones with diffuse osteolytic foci (Figure 5) and parathyroid adenoma, together with the expressed and characteristic clinical waddling gait from lumbar fractures and myopathy lead to primary hyperparathyroidism from parathyroid adenoma. The patient is referred for surgery and for a short time he was being fully recovered and normal gait of walking.

Key Words
Parathyroid adenoma, parathyroid hormone, hypercalcemia, bone pain

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EP310

JOINT3483

Extremely rare association of primary hyperparathyroidism and familial hypocalciuric hypercalcemia

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Introduction
Familial hypocalciuric hypercalcemia (FHH) is a rare benign hypercalcemia that is sometimes difficult to distinguish from moderate primary hyperparathyroidism (HPT1). Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominantly inherited disorder of calcium metabolism. Its main feature is mild to moderate hypercalcemia, mostly persistent and non-progressive, hypocalciuria, with normal or slightly elevated serum PTH levels. It is typically found in otherwise healthy and asymptomatic individuals. The coexistence of familial hypocalciuric hypercalcemia (FHH) and primary hyperparathyroidism (PHPT) is extremely rare.
Case Report
We report the case of a 56-year-old female patient with hypercalcaemia associated with hyperparathyroidism. The corrected calcaemia was elevated to 109 mg/l (reference values [RV] 86-100) with a PTH 1-84 at 240 pg/ml (RV 9.20-44.6) and a low calciuria at 75 mg/24h (RV 100-320), associated with a scintigraphy showing a 12*9 mm parathyroid adenoma on the lower left parathyroid, the patient did not adhere to the criteria for surgery of a HPT1. Strict monitoring of blood calcium levels and urinary and bone clinical signs was indicated. The hypocalciuria was controlled two times, then a diagnosis of an association of a HHF and a HPT1 was suspected.

Discussion
The diagnostic usually includes family history, clinical assessment, laboratory studies, 24-hour urine calcium excretion measurement. Genetic testing for *CASR* mutations is recommended in ambiguous cases revealing a heterozygous mutation in exon 4 of the calcium sensor gene. In our case it was not yet tested. Treatment mainly involves patient education and reassurance, with calcimimetic medications like Cinacalcet-HCL used in more symptomatic cases, despite not being FDA-approved for FHH.
Conclusion
Diagnosing FHH can be challenging due to its overlap with primary hyperparathyroidism (PHPT). The association of the two pathologies is rare. The possibility of Marx syndrome was raised by the hypocalciuria.

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EP311

JOINT3398

Sjögren's syndrome revealing familial hypocalciuric hypercalcemia: a case report

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Introduction
Familial hypocalciuric hypercalcemia (FHH), also known as Marx syndrome, is a benign hereditary condition with autosomal dominant transmission. Here, we describe a case of FHH diagnosed in the context of the management of Sjögren's syndrome.
Case Report
A 41-year-old female patient with no significant medical history presented with ocular and oral dryness. The diagnosis of Sjögren's syndrome was confirmed based on a Grade 4 Chisholm lymphocytic sialadenitis found on labial biopsy and the presence of positive anti-SSA antibodies. A phosphocalcium assessment repeatedly showed hypercalcemia (2.7–2.83 mmol/l) with normal phosphatemia and alkaline phosphatases, along with hypocalciuria confirmed on multiple occasions (0.45–1.3 mmol/24h). Given this moderate and asymptomatic hypercalcemia, an etiological investigation was conducted, ruling out:Primary hyperparathyroidism (normal PTH, unremarkable ultrasound), Multiple myeloma (normal serum immunoelectrophoresis), Sarcoidosis (normal angiotensin-converting enzyme levels), Drug-induced hypercalcemia (no relevant medication history) The presence of hypocalciuria further supported the diagnosis of familial hypocalciuric hypercalcemia (FHH).
Discussion
Renal involvement in Sjögren's syndrome can lead to hypercalciuria due to tubular dysfunction. The uniqueness of this case lies in the unexpected finding of hypocalciuria, which, after an extensive workup, was attributed to FHH. FHH is associated with an inactivating mutation of the calcium-sensing receptor (CaSR) gene, located on chromosome 3, necessitating screening of other family members

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EP312

JOINT1121

Osteoporotic fractures in hypogonadotropic hypogonadism linked to PROKR2 gene mutation

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Congenital Hypogonadotropic Hypogonadism is caused by conditions affecting the hypothalamus or pituitary gland, leading to altered or absent secretion of *GnRH* (gonadotropin-releasing hormone) or inadequate biosynthesis of pituitary gonadotropins (*FSH* and *LH*). The disease can be categorized into two groups: two-thirds of patients present with hypogonadotropic hypogonadism associated with anosmia, defined as "Kallmann syndrome," while the remaining one-third exhibit congenital hypogonadotropic hypogonadism with normal olfactory function, termed "idiopathic." An alteration in the prokineticin system (*PROK1* and *PROK2*) is among the various causes of hypogonadotropic hypogonadism. Specifically, PROK2 is predominantly expressed in the central nervous system, where it prompts the migration of *GnRH*-secreting neurons. Loss-of-function mutations in this protein or its receptor (*PROKR2*) have been associated in literature with the onset of hypogonadotropic hypogonadism, even in the absence of olfactory dysfunction. A 44-year-old male patient was referred to our outpatient clinic following recent pathological rib fractures, without a family history of fragility fractures or osteoporosis. Blood tests revealed normal phosphate-calcium metabolism, however the gonadal profile showed low levels of testosterone and gonadotropins, documenting hypogonadotropic hypogonadism. The patient reported no symptoms commonly associated with hypogonadism such as difficulties with ejaculation or nocturnal/morning erections). Despite this, a scrotal ultrasound revealed testicles smaller than expected for his age and a physical examination detected mild gynecomastia. The patient reported no change in his sense of smell. The densitometry scan revealed the presence of osteoporosis at the radial site (Z-score -2.4) and reduced bone mass at the lumbar vertebral site (Z-score -1.7). The Trabecular Bone Score (TBS) showed a markedly reduced value (TBS L1-L4: 1.012). X-rays of the dorsal and lumbar spine revealed osteoporotic fractures in the D11 and D12 vertebrae. An MRI of the pituitary gland with contrast showed no abnormalities. Genetic analysis identified a heterozygous mutation in exon 3 of the *PROKR2* gene, classified as a variant of uncertain significance for hypogonadotropic hypogonadism. After confirming normal haematocrit and PSA levels, therapy with testosterone gel was initiated for hypogonadotropic hypogonadism resulting in a progressive normalization of testosterone levels. For osteoporosis associated with fragility fractures, intravenous infusion of zoledronic acid was administered and vitamin D supplementation therapy was started. In conclusion, hypogonadism should be considered in the evaluation of male patients presenting with osteoporosis, especially at a young age, to ensure accurate diagnosis and management of the condition and its associated complications.

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EP313

JOINT1252

Pitfalls and challenges in the management of secondary hyperparathyroidism and mineral and bone disorders associated with CKD

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Mineral and bone disorders (MBD) associated with chronic kidney disease (CKD), known as CKD-MBD, involve key alterations including hyperphosphatemia, low vitamin D levels, hypocalcemia, and secondary hyperparathyroidism (SHPT). These changes disrupt bone and mineral metabolism, leading to renal osteodystrophy and increased fracture risk. The management of CKD-MBD and associated osteoporosis is often a challenge in current practice. We report the challenges encountered in managing a series of dialysis patients under the care of our Endocrinology Department. The first case involves a 75-year-old male undergoing peritoneal dialysis with SHPT and osteoporosis (forearm T-score of -5.8). His parathyroid hormone (PTH) level was 1063 pg/mL, prompting a 99mTc-MIBI scintigraphy, which revealed a right inferior parathyroid adenoma and left inferior hyperplastic parathyroid gland. Treatment with cinacalcet was initiated but proved inadequate, as PTH levels increased to 1138 pg/mL two years later, with a corrected calcium level of 11.1 mg/dL. Parathyroidectomy (PTx) was advised but deferred due to his fragility, opting for conservative treatment. The second case involves a 55-year-old woman on hemodialysis (HD) with a history of subtotal PTx, with persistent SPTH (levels of 1655 pg/mL), with a corrected calcium level of 9 mg/dL. Post-PTx 99mTc-MIBI scintigraphy identified a left inferior parathyroid adenoma, and she subsequently underwent total PTx. Postoperatively, her PTH level decreased to 300.9 pg/mL, while her corrected calcium level dropped to 7.8 mg/dL despite supplementation with 1800 mg of calcium and 1.5 µg of alfacalcidol daily. Osteoporosis (forearm T-score of -4.5) treatment with denosumab was postponed due to hypocalcemia risks. The third case pertains to a 47-year-old woman on HD with SHPT (PTH levels of 2544 pg/mL) who underwent total PTx. However, PTH remained elevated at 2891 pg/mL, with a corrected calcium level of 7.7 mg/dL. A subsequent 99mTc-MIBI scintigraphy identified two additional hyperplastic parathyroid glands, indicating a total of six parathyroid glands. Due to marked improvement in her general symptoms and bone mineral density after the first PTx, conservative management was decided until further evaluations. The final case concerns a 74-year-old woman on HD with osteoporosis (femoral neck T-score of -3.5). She presented

with a PTH level of 434 pg/mL and a corrected calcium level of 9.5 mg/dL. Treatment with denosumab, in combination with alfacalcidol, was initiated, resulting in a significant and prolonged drop in calcium levels to 6.86 mg/dL one month after denosumab administration. These cases highlight the complexity of managing CKD-MBD in dialysis patients.

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EP314

JOINT1793

Giant parathyroid adenoma revealed by severe hypercalcemia and disabling bone pain: case report

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Parathyroid adenomas are a common cause of primary hyperparathyroidism; however, giant parathyroid adenomas (GPA), defined as weighing more than 3.5 grams, are rare.

Case Presentation

We report the case of a 53-year-old woman who presented with severe, disabling bone pain, prompting medical evaluation. Laboratory tests revealed severe malignant hypercalcemia (146 mg/l), hypophosphatemia (24 mg/l), and markedly elevated parathyroid hormone (PTH) levels (1898 pg/mL). Initial management consisted of intravenous hydration (2–4 L/24h). Due to persistent hypercalcemia, treatment with zoledronic acid (4 mg) was initiated. Electrocardiography showed a bundle branch block without QT interval shortening. Neck ultrasound identified a large, well-defined, hypoechoic, hypervascularized parathyroid adenoma at the inferior pole of the right thyroid lobe, measuring 2.67 $\times$ 2.02 $\times$ 4 cm. Once calcium levels were stabilized, the patient underwent a successful parathyroidectomy. The excised adenoma weighed 6 g, and histopathological examination confirmed a benign parathyroid adenoma. Postoperatively, PTH levels significantly decreased (100 pg/mL), with notable clinical and biochemical improvement.

Discussion/ Conclusion

This case highlights the importance of recognizing severe hypercalcemia as a potential indicator of GPA and underscores the essential role of surgical intervention in achieving favorable patient outcomes.

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EP315

JOINT1342

Method for increasing the ultrasonic conductivity of skull bone tissue in patients who are planned to be treated with magnetic resonance imaging-guided focused ultrasonic imaging

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The invention relates to medicine, namely to endocrinology and neurosurgery, and can be used to treat patients with altered ultrasound conductivity of bone tissue who are planned to be treated with magnetic resonance imaging-guided focused ultrasound (MR-FUS) The MR-FUS method is most often used to treat movement disorders such as Parkinson's disease, dystonia, and essential tremor. The method is based on two technologies – high-intensity focused ultrasound (HIFU) and MRI. Using heating or cavitation at a variable distance from the sensor, HIFU can cause selective thermal coagulation in a clearly defined volume. The error in the destruction of brain tissue with this method is extremely small and averages 0.50–0.75 mm, varying depending on the technical characteristics of the selected equipment. The arsenal of solutions to the problem associated with low CUPT is very limited, which in turn leads to numerous refusals to perform operations using focused ultrasound. The objective of the invention is to develop a method for increasing the ultrasound conductivity of the bone tissue of the skull for further surgical interventions in patients using MR-FUS in a short time and with a safer method. The technical result of using the invention is a significant increase in the skull UCCT in patients with an initial UCCT of less than 0.35, achieving the threshold value necessary for thalamotomy with MR-FUS. The proposed method for increasing the ultrasound conductivity of the cranial bone tissue is carried out as follows. The patient for whom MR-FUS is planned undergoes CT of the cranial bones to determine the UPCCT, as well as laboratory tests for ionized calcium and vitamin D. If the coefficient is less than 0.35, the patient is administered Bonviva (Ibandronic acid) 3 mg intravenously by bolus over 15-30 seconds once every 3 months, Aquadetrim (Cholecalciferol) at a dose of 1500-5500 IU per day and Calcium D3 Nycomed (Calcium carbonate + Cholecalciferol) at a dose of 500 mg + 200 IU 2 times a day. The course of treatment is 3-6 months. After 3 months, the patient undergoes a repeat CT of the cranial bones on the same device and with the same program to assess the ultrasound conductivity coefficient of bone tissue, and laboratory tests for vitamin D and ionized calcium. If the cranial CUPCT increases by more than 0.35, the patient is referred for surgery using focused ultrasound. If there is no effect after 3 months.

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Diabetes and Insulin

EP316

JOINT2706

Blood sugar profiles in children receiving high doses of systemic glucocorticoids

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Backround

Glucocorticoids (GC) are still the first-line treatment of many autoimmune, inflammatory and allergic conditions. The prevalence of glucocorticoid induced hyperglycemia is not well known in the paediatric population. Specific recommendations for timing and frequency of blood glucose monitoring are lacking in children receiving high doses of glucocorticoids.

Objective

To describe the blood sugar profiles measured with continuous glucose monitoring (CGM) in children receiving systemic glucocorticoid treatment.

Methods

Children who received glucocorticoid treatment due to an underlying condition at a dose of at least 1 mg/kg/day prednisolone-equivalent were monitored with a iPro 2 or a Guardian 4 continuos glucose monitor during their GC treatment course. CGM data and blood sugar profiles were analyzed retrospectively. Time above range and time in range (TAR - percentage of glucose values above 10 mmol/l, TIR - precentage of glucose values in the range 3.9- 10 mmol/l) were measured and diurnal glucose variations were analyzed.

Results

Blood sugar profiles were measured in 10 patients (2 boys, 8 girls) aged 4 to 17 years (mean age 10,5 years $\pm$ 0.7 years) over the mean period of 5 days. Six patients received oral prednisolone and 4 received intravenous methylprednisolone. Seven patients experienced episodes of hyperglycemia. The average TIR of the partcipants during the GC treartment was 93.0 $\pm$ 36.9%, the average recorded TAR was 6.1 $\pm$ 9.1%. The average sensor glucose (SG) at 08:00 AM was 5.0 $\pm$ 1.6 mmol/l, at 08:00 PM 8.3 $\pm$ 3.0 mmol/l and at midnight 7.6 $\pm$ 2.6 mmol/l. Hyperglycemic episodes occured predomonitatly between 18:00-21:00PM and presented mainly as a single prolonged postprandial episode after dinner or late evening snack.

Discussion and conclusion

Two thirds of the investigated subjects experienced GC-induced hyperglycemia. Participants experienced episodes of hyperglycemia regardless of the route of GC administration. Higher SG measurements were registered during evening hours compared to early morning and this should be taken into account, when screening for GC-induced hyperglycemia.

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EP317

JOINT2075

The role of muscular fitness on bone mineral content and areal bone mineral density in children and adolescents with type 1 diabetes: a 2-year longitudinal analysis of the diactive-1 cohort study

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Background
The incidence of type 1 diabetes (T1D) among youth is on the rise. Poor glycemic control can contribute to comorbidities, including compromised bone health. In growing populations, muscular fitness has been associated with improved bone health.
Aim
To explore the relationship between muscular fitness and bone health in children and adolescents living with T1D.
Methods
A total of 83 youth with T1D (ages 6–18 years; 44.6% girls; mean glycosylated hemoglobin [HbA1c]: 7.5 ± 1.0%) from the Diactive-1 Cohort Study were monitored over two years. Bone mineral content (BMC) and areal bone mineral density (aBMD) were assessed using dual-energy X-ray absorptiometry (DXA) whole-body scans for the total body less head (TBLH), arms, legs, pelvis, and spine. Muscular fitness metrics, including handgrip strength, one-repetition maximum (RM), and muscle power, were evaluated with a dynamometer and eGYM devices. Handgrip strength and TBLH bone parameters were standardized for age and sex using reference data from the BMD Childhood Study and the FitBack Project. The statistical analyses were computed via R studio program.
Results
Generalized linear mixed models showed longitudinal associations of handgrip strength with TBLH-BMC (unstandardized beta coefficient [B]= 17.18, 95% confidence interval [CI] 12.47–21.90) and TBLH-aBMD (B= 0.004, 95%CI 0.002–0.006); RM with TBLH-BMC (B= 20.09, 95%CI 10.88–29.31) and TBLH-aBMD (B= 0.007, 95%CI 0.004–0.011); and power with TBLH-BMC (B= 26.80, 95%CI: 17.31–36.28) and TBLH-aBMD (B= 0.009, 95%CI 0.005–0.012). Comparable results were observed across the other regions ($p<0.05$). Additionally, analyses with standardized data confirmed the relationships of handgrip z-scores with TBLH-BMC z-scores (B= 0.19, 95%CI 0.08–0.30) and TBLH-aBMD z-scores (B= 0.350, 95%CI: 0.210–0.490).
Conclusions
Strengthening programs aimed at improving muscle strength could play a crucial role in preventing bone health complications in youth with T1D. These findings emphasize the importance of incorporating muscular fitness into therapeutic strategies for this population.

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EP318

JOINT667

Impact of emergency admission on glycemic control in hospitalized diabetic patients

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Introduction
Emergency admissions are stressful situations that can disrupt glycemic control in diabetic patients. These disruptions are often caused by multiple factors, such as the severity of the underlying condition, the physiological stress response involving cortisol and adrenaline secretion, and sometimes inadequate therapeutic adjustments in the hospital setting. Few studies have explored the impact of emergency admissions on glycemic control in diabetic patients, despite their potential implications for management and prevention of acute complications. This study aims to evaluate the impact of emergency admissions on glycemic control in hospitalized diabetic patients.
Patients and methods
We conducted a multicenter cross-sectional study between February and March 2024 in three Tunisian university hospitals: Hedi Chaker University Hospital in Sfax, Habib Bourguiba University Hospital in Sfax, and Taher Sfar University Hospital in Mahdia. The study included diabetic patients hospitalized in cardiology, pneumology, urology, general surgery, and orthopedic departments. Data collected included the reason for admission (emergency or elective), the occurrence of acute hyperglycemic complicaton or hypoglycemia, and the evaluation of glycemic control. Glycemic control was classified as insufficient if less than 50% of blood glucose readings (BGR) were within the intra-hospital glycemic target (defined by the ADA as 1–1.8 g/l), moderate if 50–70% of BGR were within the target, and satisfactory if more than 70% of BGR met the target.
Results
A total of 315 patients were included, two-thirds of whom were men. The median age was 65 years, and the median diabetes duration was 8 years. The majority (87%) had type 2 diabetes. Most patients (75.9%) were admitted via emergency departments. Acute hyperglycemic decompensation was diagnosed in 21% of patients, and hypoglycemia was observed in 20.6%. Among patients who underwent glycemic monitoring, 50.7% had insufficient glycemic control, while only 21.6% achieved satisfactory control. Emergency admissions did not significantly increase the risk of hyperglycemic decompensation (P = 0.631), although 78.5% of patients with decompensation had been admitted through emergency departments. The frequency of hypoglycemia was also comparable between emergency and elective admissions (P = 0.211). Similarly, emergency admission was not significantly associated with insufficient glycemic control (P=0.396).
Conclusion
This study demonstrates that while the majority of hospitalized diabetic patients were admitted through emergency departments, these admissions did not significantly influence the risk of hyperglycemic decompensation, hypoglycemia, or insufficient glycemic control.

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EP319

JOINT2570

Screening for prenatal depression in women with gestational diabetes: the relationship with self-esteem and social support

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Introduction
Pregnancy is a period of particular vulnerability, with prenatal depression being the most commonly observed psychopathological disorder. This study aims to assess the presence of depressive symptoms and associated psychosocial disorders in a sample of pregnant women followed for gestational diabetes.
Patients and Method
A cross-sectional study was conducted over a seven-month period in the National Institute of Nutrition. Prenatal depression, self-esteem, and social support were assessed using the Edinburgh Depression Scale (EPDS), Rosenberg Self-Esteem scale, and Social Support Questionnaire (SSQ6), respectively. An EPDS score greater than 12/30 indicates the presence of depressive symptoms.
Results
One hundred sixty-three women took part in the study, with a mean age of 33.21 ± 4.82 years, ranging from 22 to 48 years. Half of the participants were beyond 28 weeks of gestation at the time of the interview. The median Edinburgh depression score was 10 ± [6; 14] and depressive symptoms were observed in 61 participants, representing 37.4% of the sample. The mean Rosenberg self-esteem score was 32.94 ± 5 and a low to very low self-esteem level was detected in 26.4% of the women. The SSQ6 perceived social support scale revealed two scores: availability of support (12 ± [9; 16]) and patient satisfaction with the received support (28 ± [20; 31]). The presence of depressive symptoms was significantly associated with low to very low self-esteem levels (47.5% vs. 13.7%, $P< 10^{-3}$), lower availability scores (10 ± [8; 13.5] vs. 13 ± [10; 17], P = 0.001), and lower satisfaction scores (26 ± [18; 30] vs. 29 ± [21.75; 32], P = 0.02). Similarly, significant correlations were found between a decrease in the depression score and an increase in self-esteem (r = -0.55; $P< 10^{-3}$), availability, and satisfaction scores (r = -0.28; $P<10^{-3}$).
Conclusion
Early screening and appropriate management of psychosocial difficulties during pregnancy, particularly low self-esteem and lack of social support, could play a crucial role in reducing depressive symptoms in this population.

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EP320

JOINT2325

Identification of cardiometabolic phenotypes and key indicators in patients with arterial hypertension, type 2 diabetes mellitus, and obesity

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Cardiovascular diseases (CVDs) remain a major global health concern, contributing to one-third of global mortality. Recent research highlights the role of cardiometabolic phenotypes in determining cardiovascular risk, particularly in patients with arterial hypertension (AH), type 2 diabetes mellitus (T2DM), and obesity (OB). The interplay between these conditions results in complex pathophysiological mechanisms that require further investigation to optimize risk stratification and management strategies.
The study **aimed**to identify specific cardiometabolic phenotypes in patients with AH, T2DM, and OB and to determine early markers of cardiovascular and renal dysfunction. The study further sought to explore correlations between these conditions and biomarkers, including cardiotrophin-1 (CTF-1), neutrophil gelatinase-associated lipocalin (NGAL), N-terminal pro-brain natriuretic peptide (NT-proBNP), leptin, and cystatin C.
Materials and methods
A total of 211 patients were included in the study, divided into four groups based on comorbid conditions: 1. Group 1 (AH only) – 49 patients. 2. Group 2 (AH and OB) – 54 patients. 3. Group 3 (AH and T2DM) – 57 patients. 4. Group 4 (AH, OB, and T2DM) – 51 patients. Clinical, laboratory, and instrumental assessments were conducted, including lipid and carbohydrate profiles, renal function tests, and echocardiography. Biomarkers such as NGAL, NT-proBNP, and CTF-1 were measured using enzyme-linked immunosorbent assays (ELISA).
Results
The study identified three distinct cardiometabolic phenotypes: phenotype 1 (AH and OB, $n = 54$): Characterized by progressive cardiac remodeling, increased leptin levels, and a moderate risk of renal impairment. Phenotype 2 (AH and T2DM, $n = 57$): Associated with significant renal dysfunction, as evidenced by elevated NGAL and cystatin C levels, indicating early nephropathy. Phenotype 3 (AH, OB, and T2DM, $n = 51$): Displayed the most severe metabolic disturbances, with high NT-proBNP levels reflecting heart failure progression and increased NGAL levels predicting renal complications. Lipid metabolism disturbances were more pronounced in groups with OB and T2DM, with significantly higher total cholesterol and triglycerides. Carbohydrate metabolism markers (insulin and HbA1c) were significantly elevated in patients with T2DM. Echocardiographic data showed increased left ventricular mass and reduced ejection fraction in patients with multiple comorbidities.
Conclusions
The findings highlight the importance of early detection of cardiometabolic phenotypes to prevent cardiovascular and renal complications. NGAL emerges as a strong predictor of nephropathy, while NT-proBNP serves as a marker for heart failure progression. The combination of AH, OB, and T2DM significantly worsens cardiometabolic status, necessitating personalized therapeutic strategies.
Key words
type 2 diabetes mellitus, obesity, arterial hypertension, cardiometabolic phenotypes.
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EP321

JOINT901

Correlation of hypoglycemic episodes and cognitive functions in people with diabetes mellitus

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Introduction
People with Diabetes Mellitus (DM) often face episodes of hypoglycemia with a serious impact on their daily life. Newer data suggests that severe episodes of hypoglycemia, experienced either recently or throughout life, cause cognitive decline.
Aim
To investigate the relationship between hypoglycemic episodes and cognitive functions among people with DM.
Material – Methods
A quantitative non-randomized cross-sectional study was performed with a sample of 104 individuals with type 1 and type 2 DM aged between 18 and 65 years. Subjects included were experiencing episodes of hypoglycemia and had not been diagnosed with any disease causing cognitive impairment. The study was conducted in two public hospitals of Athens within one year. A demographic questionnaire, the Hypoglycemia Patient Questionnaire and the Clarke's Hypoglycemia Awareness Questionnaire were administered while the Montreal Cognitive Assessment (MoCA) was also conducted. For the statistical analysis of the data, the t-test criterion for independent samples, the analysis of variance for one factor (One-way ANOVA) and the multiple regression analysis were applied.
Results
At the MoCA test the mean score was 26.16 ± 2.69 while the lowest score was 18 and the highest was 30. More than half of the participants had a normal score (equal to or higher than 26) (59.6%) while the 40.4% presented possible mental impairment. Participants who showed reduced awareness of hypoglycemia had a lower MoCA test score than those with high awareness to a statistically significant degree ($P = 0.01$). A statistically significant main effect of severe hypoglycemic episodes on cognitive function score was observed ($P = 0.002$). Participants who had never experienced severe episodes of hypoglycemia scored higher on cognitive function than those who reported more than one severe episode ($P = 0.03$) with a high effect rate ($d = 0.82$). Multiple regression analysis showed that the occurrence of a severe hypoglycemic episode 2 to 12 times ($b = -0.15$, $P < 0.05$) and age ($b = -0.31$, $P < 0.001$) were negative predictors of the score of the cognitive assessment.
Conclusions
Severe episodes of hypoglycemia were associated with cognitive decline in people with DM. Age was also a predictor of cognitive deficit. Further research studies are needed to clarify the relationship between hypoglycemia and cognitive function in order to improve the quality of life of people with DM.
Key words
Diabetes Mellitus, hypoglycemia, cognitive function
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EP322

JOINT1325

The evaluation of arterial stiffness indices in children and adolescents with type 1 diabetes mellitus or excess weight

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Purpose
The relationship between pediatric obesity or Type 1 Diabetes Mellitus and cardiovascular disease in adulthood is well established, with the pathophysiological mechanisms being already present in childhood. Arterial stiffness is a strong, independent predictor of cardiovascular disease in adulthood and the most widely accepted method for its evaluation is Pulse Wave Velocity (PWV). We evaluated PWV in children and adolescents with T1DM or excess weight, in order to detect subclinical vascular alterations at a very early stage.
Methods
A total of 199 children and adolescents aged 2-18 years participated in the study, including 96 with T1DM, 49 with overweight or obesity, and 54 healthy controls. PWV was measured using the automated oscillometric device Mobil-O-Graph.
Results
Systolic BP (SBP) and central SBP (cSBP) were significantly increased in both patients with overweight/obesity and those with T1DM compared to controls. Furthermore, overweight/obesity patients had higher SBP, cSBP and cDBP compared to T1DM patients, whereas DBP was significantly increased only in overweight/-obesity patients compared to controls. Pulse wave velocity values were also significantly increased in both overweight/obesity patients and those with T1DM compared to controls, while overweight/obesity patients had higher PWV when compared to patients with T1DM.
Conclusion
Impaired arterial elasticity, expressed as increased pBP, cBP, and PWV, was found in children and adolescents with T1DM and overweight/obesity, particularly in the latter. PWV could potentially serve as a screening and diagnostic tool for impaired vascular health and, perhaps, as a prognostic tool for future cardiovascular disease in children and adolescents with T1DM or overweight/obesity.
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EP323

JOINT472

Profile of chronic diabetes complications in hospitalized patients: A multicenter tunisian study

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Introduction
Diabetes, a chronic disease with a steadily increasing prevalence, is a significant public health issue in Tunisia and globally. Its chronic complications, both microvascular and macrovascular, are the leading causes of morbidity and mortality. While acute complications are well documented in hospital settings, data on chronic complications remain limited. This study aims to describe the profile of chronic diabetes complications in hospitalized patients.
Patients and methods
A descriptive cross-sectional study was conducted between February and March 2024 in three Tunisian university hospital centers: CHU Hedi Chaker in Sfax, CHU Habib Bourguiba in Sfax, and CHU Taher Sfar in Mahdia. The study included hospitalized diabetic patients from cardiology, pulmonology, urology, general surgery, and orthopedic departments. Data collected included diabetic retinopathy, chronic renal failure (defined by a glomerular filtration rate below 60 ml/min), stroke, coronary insufficiency, heart failure, and peripheral artery disease.
Results
A total of 315 patients were included with a male-to-female ratio of 2. The median age was 65 years, and the median duration of diabetes was 8 years. 87% ($n = 272$) had type 2 diabetes, 6% ($n = 19$) had type 1 diabetes, and 5.4% ($n = 17$) were newly diagnosed during hospitalization. 60.6% of patients ($n = 191$) had associated hypertension. Diabetic retinopathy was present in 26.5% of patients, and chronic renal failure was observed in 20.6% ($n = 65$), with 2.6% ($n = 8$) in the terminal stage. Twenty-four patients (7.6%) had a history of stroke before admission. Coronary artery disease was diagnosed before hospitalization in 65 patients, and peripheral artery disease was diagnosed in 29 patients (9%). Additionally, 24 patients (7.6%) were being followed for heart failure at the time of their inclusion.
Conclusion
This study highlights the high prevalence of chronic complications among hospitalized diabetic patients. These findings underscore the importance of systematic screening and early management of chronic diabetes complications in hospital settings, regardless of the admission reason, to reduce the morbidity associated with this condition.

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EP324

JOINT723

Impact of surgical interventions on glycemic control in hospitalized diabetic patients

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Introduction
Surgical interventions are high-risk situations for diabetic patients due to the metabolic disturbances induced by surgical stress and the resulting hormonal changes. These disturbances and sometimes inadequate therapeutic adjustments can impair glycemic control and increase the risk of acute complications. Despite its clinical significance, few studies have explored the impact of surgical interventions on the glycemic control of hospitalized diabetic patients. This study aims to assess the repercussions of surgical interventions on glycemic control.
Patients and methods
This multicenter cross-sectional study was conducted between February and March 2024 in three Tunisian university hospital centers: Hedi Chaker and Habib Bourguiba University Hospitals in Sfax, and Taher Sfar University Hospital in Mahdia. The study included diabetic patients hospitalized in medical and surgical departments. The collected data included the reason for admission, whether a surgical intervention was performed during hospitalization, the occurrence of acute hyperglycemic decompensation or hypoglycemia, and the assessment of glycemic control. Glycemic control was considered insufficient if less than 50% of measured capillary blood glucose levels (CBG) were below the intra-hospital target range (defined by the ADA between 1 and 1.8 g/l), moderate if 50 to 70% of CBG values were within the target range, and satisfactory if more than 70% of CBG values achieved this target.
Results
Among the 315 patients included, 102 (32%) underwent surgical intervention during their hospitalization. Diabetes was newly diagnosed in one patient following surgery. Acute hyperglycemic decompensation occurred in 21 patients (20.6%), while hypoglycemia was observed in 23 patients (22.5%). Poor glycemic control was noted in 41 patients (40.2%), and glycemic monitoring was not performed in 17 patients (16.7%). Insulin therapy was discontinued in 21 of the 49 insulin-treated patients who underwent surgery. Surgical interventions were not significantly associated with acute hyperglycemic decompensation ($P = 0.519$) or hypoglycemia ($P = 0.434$). Similarly, surgical interventions were not significantly associated with poor glycemic control ($P = 0.585$).
Conclusion
Contrary to expectations, surgical interventions were not systematically associated with acute decompensations or poor glycemic control in hospitalized diabetic patients. However, this study highlights the importance of optimized perioperative management to maintain adequate glycemic control and prevent associated complications.

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EP325

JOINT1910

The transition from pediatric to adult care in type 1 diabetes: A real challenge

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Introduction
The transition of type 1 diabetic patients from pediatric to adult care represents a real challenge in diabetes consultations, highlighting the importance of effectively 'bridging the gap. The aim of our work was to evaluate the impact of this transition on glycemic control.
Methods
A retrospective observational study including type 1 diabetic patients who were followed in the department C of the children's hospital and then referred to the transition consultations organized within department B of the National Institute of Nutrition between 2018 and 2023. Each transition consultation involved an endocrinologist, a nutritionist, and a nurse.
Results
The study included 28 type 1 diabetic patients. Fifty-three percent of the patients were male. The average age at the time of transition was 16 years $\pm$ 2 [11-21 years]. The average duration of diabetes was 10 years $\pm$ 4 [1-15 years]. Half of the diabetic patients were not on a complete basal-bolus regimen. Sixty-one percent of the patients were overdosed on basal insulin (with an average dose of 0.59 IU/kg), and 23% experienced frequent hypoglycemia. The average HbA1c at the time of transition was 10.2% $\pm$ 1.5 [8.2; 13.5]. Eighty-eight percent of patients consulted regularly after the transition. Half of the patients experienced a significant improvement in HbA1c after 6 months, with an average decrease of 1.7%. Additionally, 27% of patients continued to improve after 12 months, with an average HbA1c improvement of 2% compared to the baseline.
Conclusion
The care transition for diabetic patients faces the complexity of managing the disease during a phase characterized by multiple physical, psychological, and social changes. A structured approach, including therapeutic education and psychological support, must be implemented to prevent interruptions in care (care gap), ensure continuity, and successfully manage this transition.

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EP326

JOINT2479

Association of AGES and obstructive sleep apnea in patients with diabetes

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Background.
Obstructive sleep apnea (OSA) is a chronic sleep disorder characterized by repeated episodes of the upper airway obstruction during sleep, resulting in hypoxemia, hypercapnia, sleep fragmentation. Individuals with sleep apnea are often unaware of their breathing difficulties during sleep, leading to frequent underdiagnosis of the condition. If left untreated, OSA can lead to hypertension, cardiovascular diseases, neurocognitive impairments, and metabolic dysfunction.

OSA is frequently associated with type 2 diabetes (T2D), with prevalence reaching up to 86%, particularly among obese diabetic patients. OSA increases cardiovascular risk and is associated with high oxidative stress levels and inflammation. Under conditions of increased oxidative stress, the accumulation of advanced glycation end-products (AGEs) is accelerated. Higher AGEs levels are associated with metabolic syndrome, cardiovascular disease, and diabetes-related complications. This study aimed to analyze the relationship between AGEs levels and the presence of OSA in patients with diabetes.
Materials and methods
AGEs concentration in the skin was non-invasively measured using AGE Reader in 117 patients with type 1 diabetes (T1D, $n = 61$) and T2D ($n = 56$), with low ($n = 39$), intermediate ($n = 42$) and high ($n = 36$) risk of OSA. The STOP-BANG questionnaire, validated and adapted for Lithuanian patients, was used. High risk for OSA was defined by as any of the following: a total score of 5-8 points; positive responses to ≥ 2 of 4 questions plus male gender or plus BMI > 35 kg/m^2 or plus neck circumference ≥ 40 cm. Intermediate risk was defined by 3-4, low risk by 0-2 positive answers. Data on patients' clinical characteristics were collected from medical records.
Results
The median diabetes duration was 16 years (range1-60), age – 56 years (range 20-81). The study cohort consisted of 67 (57.3%) women and 50 (42.7%) men. The risk of developing OSA significantly depended on gender ($P < 0.001$) and type of diabetes ($P < 0.001$). Men and patients with T2D have higher risk of developing OSA compared with woman and patients with T1D. There were no significant associations between OSA and HbA1c or the duration of diabetes ($P = 0.602$ and $P = 0.267$, respectively). However, we revealed a progressive increase in AGE median values as OSA risk increases ($P < 0.05$).
Conclusions
Patients with T2D, particularly males, demonstrate a higher risk of developing OSA. Our findings suggest that non-invasive measurement of skin AGEs could be useful additional tool for OSA risk evaluation as the association between higher AGEs levels and OSA risk shows the potential role of oxidative stress in the pathophysiology of both conditions.

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EP327

JOINT11

Uncovering underlying causes: a crucial step in managing diabetic ketoacidosis

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Introduction
Diabetic ketoacidosis (DKA) is a serious complication of diabetes that can occur in type 2 diabetes mellitus, particularly with poor glycemic control and concurrent illnesses. This report details the presentation, management, and clinical outcomes of a patient admitted with DKA.
Case Presentation
A 62-year-old female with a history of type 2 diabetes managed with metformin, complicated by poor adherence, presented with gastrointestinal symptoms of nausea and vomiting. Her condition worsened, prompting an emergency visit where severe hyperglycemia (capillary blood glucose of 5 g/l), significant ketonuria (2+ acetone), and a raised anion gap (RA at 15) were identified, confirming DKA. On admission, she exhibited general weakness, abdominal tenderness, and an altered general condition. Laboratory findings included a white blood cell count of 10,600, elevated C-reactive protein (CRP) initially at 214 mg/l (decreasing to 66 mg/l), and negative infectious screenings (thoracic radiography and renal ultrasound). A thoraco-abdominopelvic CT scan revealed a perforated mucocele complicated by pseudomyxoma peritonei.
Discussion
Patients with mucinous neoplasms of the appendix present a clinically challenging spectrum of pathologic processes. Incidental discovery of an appendiceal mucocele is common. Pseudomyxoma peritonei (PMP), although more severe, frequently has a slow-growing course with non-specific symptoms, requiring high suspicion, especially with probable previous appendiceal pathology. Mucinous neoplasms of the appendix range from benign mucoceles to malignant cystadenocarcinomas. Accurate diagnosis and management are crucial, particularly in specialist centers focusing on preventing locoregional recurrence.
Conclusions
This case underscores the importance of recognizing and promptly treating DKA in type 2 diabetic patients, especially with poor glycemic control and additional conditions. Comprehensive management addressing underlying causes and complications is essential for optimal outcomes. Regular follow-up with thorough assessments is crucial for preventing recurrence and managing long-term complications.

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EP328

JOINT325

Relationship between polymorphic markers rs7903146 variant of TCF7L2 gene, rs10830963 variant of mtnr1b gene and rs1801282 variant of pparg (pro12ala) gene and various subtypes of gestational diabetes mellitus

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Introduction
Nowadays various pathogenetic subtypes of gestational diabetes mellitus (GDM) are distinguished: with predominant β-cell dysfunction and with prevailing insulin resistance (IR). Currently, many works are devoted to the study of polymorphisms of various genes that can influence the development of GDM. However, no attempt has yet been made to study the genetic markers of various subtypes of GDM, which could make a significant contribution to both the diagnosis and probable prevention of carbohydrate metabolism disorders during pregnancy.
Objective
To study the association of polymorphic markers rs7903146 of the TCF7L2 gene, rs10830963 of the MTNR1B gene and rs1801282 of the PPARG Pro12Ala gene with the presence of various subtypes of GDM in pregnant patients.
Materials and methods
130 pregnant women were divided according to the results of the Matsuda index: group I-45 pregnant women with GDM and β-cell dysfunction, group II-43 pregnant women with GDM and IR, group III-42 pregnant women without GDM (control). Single nucleotide polymorphisms rs7903146, rs10830963, rs1801282 were determined by allele-specific PCR. The differences were recognized as statistically significant at the level of $P < 0.05$. Calculations were performed in R (version 3.2, R Foundation for Statistical Computing, Vienna, Austria).
Results and discussion
In the course of this study, it was found that some polymorphic markers were associated with a reduced risk of having different subtypes of GDM. Thus, the genotype of T/T polymorphic markers rs7903146 of the TCF7L2 gene is associated with low risk and GDM with predominant IR (OR = 0.06, 95% CI: 0.004–1.18, $P = 0.045$), and with β-cell dysfunction (OR = 0.06, 95% CI: 0.003–1.13, $P = 0.04$). At the same time, the genotype of C/C polymorphic markers rs10830963 of the MTNR1B gene was associated with a reduced risk of only the GDM subtype with β-cell dysfunction (OR = 0.41, 95% CI: 0.174–0.98, $P = 0.049$). On the other hand, we found polymorphic markers that, on the contrary, were associated with an increased risk of having GDM with predominant IR. It turned out to be the genotype of T/C polymorphic markers rs7903146 of the TCF7L2 gene (OR = 2.53, 95% CI: 01.048–6.09, $P = 0.049$).
Conclusion
The results obtained indicate the potential role of the T/C genotype of polymorphic markers rs7903146 of the TCF7L2 gene in the development of the GDM subtype with predominant IR. The presented data certainly require further study to determine, first, the criteria for the diagnosis of various subtypes of GDM, depending on the mechanisms underlying the pathogenesis of carbohydrate metabolism disorders.

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EP329

JOINT2581

Effect of vitamin D supplementation on metabolic and psychopathological disorders in patients with type 2 diabetes mellitus in chronic stress conditions

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According to the IDF Diabetes Atlas 2021, there were 2,325,000 adult patients with diabetes aged 20-79 years in Ukraine, as well as 920,100 undiagnosed cases. The prevalence of depression in Ukraine civilians reached 30% in 2020 and has been growing since then. Patients with type 2 diabetes mellitus (T2DM) are more sensitive to the stress factor of war, which is added to traditionally common psychopathological disorders. They have a 20% higher prevalence of anxiety compared to those without diabetes. A mutual negative effect between the state of depression and the course of T2DM is well known. According to the results of assessing the vitamin D status of Ukrainian population, an unsatisfactory level was found in 47% of people. The aim of the study was to assess the effect of vitamin D supplementation on metabolic and psychopathological manifestations in patients with T2DM. 164 patients with T2DM aged 19-75 years, in D-deficit status, glycated hemoglobin of 7-8.5%, BMI 30-39 kg/m2 were included in the study. Exclusion criteria: CKD, pregnancy, BMI $\geq$ 40 kg/m2, vit D intake 3 months before, insulin therapy, antidepressants, tranquilizers, sedatives usage. Patients were randomized into 2 groups of 82 people in each, comparable by age and gender. Patients received oral antidiabetic agents. Additionally, vitamin D supplementation was used in the main group: 3 months 10,000 IU daily, then 3 months 4000 IU daily; in the control group: 3 months no vitamin D treatment, then 3 months 4000 IU daily. Depression, anxiety and stress grades were evaluated using DASS21 scale.

Results

Patients in the main group showed a statistically significant decrease of salivary cortisol levels, glycated hemoglobin A1c, HOMA index, BMI and levels of depression, anxiety and stress after 3 months of taking vitamin D. The effect was prolonged to 6 months. Among patients in the control group, the levels of glycated hemoglobin A1c and BMI did not significantly improve, psychopathological disorders have been worsened.

Conclusion

Vitamin D supplementation is recommended for patients with type 2 diabetes in chronic stress condition. Vitamin D supplementation for 3 months at a dose of 10,000 IU daily in T2DM patients in D-deficit status improved carbohydrate metabolism, contributed to the normalization of saliva cortisol levels, reduced the levels of depression, anxiety and stress.

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EP330

JOINT2129

Prevalence of sarcopenia and dinapenia in young population with type 1 diabetes mellitus

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Background

Sarcopenia is proposed as a complication of type 1 diabetes (T1D1). However, there are few studies on its prevalence and related clinical outcomes in TD1. Our aim was to analyze whether sarcopenia and dynapenia are more common in people with TD1, as well as to determine if there are associations with disease-related factors.

Methods

A cross-sectional study of young subjects with DT1 and healthy controls matched for age, sex and body mass index (BMI). The following variables were collected: DT1-related clinical and metabolic data, muscle strength measured with the Jamar dynamometer and quadriceps rectus femoris muscle mass (Y-axis, X-axis, area and circumference) measured with ultrasound. The appendicular skeletal mass index (ASMI) was assessed by calf circumference to define myopenia. Regarding dynapenia, a cut-off point at p10 was used according to the Spanish population percentile table. Statistical analysis was performed with IBM SPSS v.25.

Results

34 patients with DT1 (40 $\pm$ 14 years; 54.4 % female and BMI 24.4 $\pm$ 4.09 kg/m^2) were analyzed. In the case group, the mean HbA1c was 6.85 $\pm$ 1.84%, the frequency of microvascular complications was 32.4% (8.8% presented nephropathy, 23.5% retinopathy, 17.6% polyneuropathy). There were no patients with macrovascular complications. Regarding the strength measured by dynamometry was 31.2 $\pm$ 10.9 kg in cases vs. 34.2 $\pm$ 12.9 kg in controls (P= 0.313). Calf circumference values were significantly lower in the DT1 group (35.2 $\pm$ 2.7 cm vs. 37.8 $\pm$ 2.9 cm; P = 0.00). The ASMI value was 6.57 $\pm$ 1.21 kg/m2 in cases and 7.25 $\pm$ 1.31 kg/m2 in controls (P = 0.31). Patients with myopenia accounted for 29.4% of cases and 12.1% of controls (P = 0.082). The prevalence of dinapenia did not show statistically significant differences between groups (26.5% in cases vs. 18.8% in controls; P = 0.454). Finally, sarcopenia was observed in 2 cases and 1 control (5.9% vs. 2.9% respectively; P = 0.55).

Conclusions

Deterioration of muscle strength in DT1 and muscle mass was observed. However, the prevalence of dynapenia and sarcopenia was not significantly higher in DT1, at least, in this young population. Further studies are needed in this and other groups with larger sample to confirm these results.

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EP331

JOINT2617

Relationship between severe hypoglycemia and time in range in type 1 and type 2 diabetes patients

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Introduction

Time in Range (TIR) has emerged as a key therapeutic target in the management of diabetes, reflecting the proportion of time a patient's glucose levels remain within the recommended range (70–180 mg/dL). Maintaining an adequate TIR is associated with better glycemic control and a lower risk of diabetes-related complications. However, the relationship between TIR and the incidence of severe hypoglycemia remains unclear. Severe hypoglycemia, defined as an event requiring external assistance for recovery, represents a major concern in diabetes management due to its potential to cause cognitive impairment, cardiovascular complications, and increased morbidity. This study examines whether a lower TIR is associated with an increased likelihood of experiencing severe hypoglycemic episodes in patients with type 1 and type 2 diabetes.

Objective

To assess the impact of TIR on the probability of experiencing severe hypoglycemia and to evaluate its potential as a predictor of metabolic safety in diabetes patients.

Methods

A retrospective analysis was conducted using continuous glucose monitoring (CGM) data from a cohort of 70 patients with type 1 and type 2 diabetes treated at a hospital in southern Spain. TIR values, time spent in hypoglycemia ($<$70 mg/dL and $<$54 mg/dL), and the occurrence of severe hypoglycemia were compared between patients using non-parametric statistical tests. The primary outcome was the incidence of severe hypoglycemia in relation to different TIR thresholds.

Results

Patients who experienced severe hypoglycemia did not exhibit significantly lower TIR values compared to those without severe episodes. However, a subgroup analysis revealed that individuals with TIR below 60% tended to have a higher incidence of severe hypoglycemia. Although this difference did not reach statistical significance (P = 0.16), a clinically relevant trend was observed. Additionally, a greater percentage of time spent in hypoglycemia was noted in patients with severe episodes, reinforcing the importance of minimizing glucose variability.

Conclusions

While reduced TIR has been linked to poorer overall glycemic control and increased glucose variability, its specific role in predicting severe hypoglycemia remains uncertain. The findings suggest that TIR may be a useful indicator of metabolic instability, but its predictive capacity for severe hypoglycemia requires further validation. Larger prospective studies are needed to establish TIR as a reliable risk stratification tool and to optimize diabetes management strategies aimed at minimizing hypoglycemic events while maintaining optimal glycemic control.

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EP332

JOINT671

Impact of corticosteroid therapy on glycemic control in hospitalized diabetic patients

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Introduction

Corticosteroid therapy, widely used in hospital settings for its anti-inflammatory and immunosuppressive effects, is known for its hyperglycemic effects. Despite its frequent use, its impact on glycemic control in hospitalized diabetic patients remains underexplored. This study aims to evaluate the influence of corticosteroid therapy on glycemic control in hospitalized diabetic patients.

Patients and methods

We conducted a multicenter, cross-sectional study over three months in three Tunisian university hospitals: Hedi Chaker University Hospital in Sfax, Habib Bourguiba University Hospital in Sfax, and Taher Sfar University Hospital in Mahdia. The study included diabetic patients hospitalized in medical and surgical departments. Data collected included corticosteroid prescription during hospitalization, the dose of corticosteroid prescribed in prednisone-equivalent milligrams, the occurrence of acute hyperglycemic complication or hypoglycemia, and glycemic control evaluation. Glycemic control was classified as insufficient if less than 50% of capillary blood glucose (CBG) readings were below the in-hospital glycemic target (defined by the ADA as 1–1.8 g/l), moderate if 50–70% of CBG readings were within the target, and satisfactory if more than 70% of CBG readings met the target.

Results

The total number of patients included was 315, of whom 65% were men. Twenty-seven patients (8.5%) received corticosteroid therapy during their hospitalization. The median corticosteroid dose administered was 53 mg [50–75] of prednisone equivalent per day. Diabetes was newly diagnosed in three patients during corticosteroid therapy. Among patients treated with corticosteroids, glycemic monitoring was not performed in three cases, while four patients experienced acute hyperglycemic decompensation, one patient developed hypoglycemia, and 14 patients (51.9%) had poor glycemic control during hospitalization. Insulin therapy was used to manage hyperglycemia in 80% of corticosteroid-treated patients ($n = 21$), with sliding scale insulin being the most commonly prescribed regimen (16 patients, 59.3%). Corticosteroid therapy was not significantly associated with acute hyperglycemic decompensation ($P = 0.416$) or poor glycemic control ($P = 0.435$). However, corticosteroid therapy was associated with a significantly lower risk of hypoglycemia ($P = 0.027$).

Conclusion

This study demonstrates that corticosteroid therapy in hospitalized settings did not significantly influence the risk of acute hyperglycemic decompensation or overall glycemic control in diabetic patients. However, its use was associated with a significantly reduced risk of hypoglycemia.

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EP333

JOINT2028

What fears do women with gestational diabetes face?

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Introduction

Gestational diabetes (GD) is a condition that can make pregnancy emotionally challenging and filled with concerns, requiring significant lifestyle adjustments to manage stress. The objective of our study was to identify the different fears experienced by pregnant women in order to find solutions for managing them.

Methods

This descriptive study was conducted on 53 women diagnosed with GD, followed up in our GD unit at Service C of the Tunis Institute of Nutrition. Data were collected through direct interviews.

Results

The average age of the patients was 33.79 $\pm$ 4.8 years. Regarding medical history, 7.5% had hypertension, 3.8% had dyslipidemia, and 7.5% had hypothyroidism. The prevalence of anemia during pregnancy was 24.5%. Most patients had normal blood pressure (BP), with an average systolic BP of 11.43 $\pm$ 1.08 cmHg and an average diastolic BP of 6.7 $\pm$ 0.91 cmHg. Similarly, their diabetes was generally well-controlled, with an average HbA1c of 5.55 $\pm$ 0.67%, although 24.5% required insulin therapy. Regarding pregnancy progression, 28.3% of women were in the first trimester (T1), 47.2% in the second (T2), and 24.5% in the third (T3). Insulin therapy raised several concerns: 54.7% of patients feared injections, 50.9% had unfounded concerns about insulin's effects on the fetus, and 35.8% worried about hypoglycemia. Additionally, 58.5% of women found blood glucose monitoring through GAD to be restrictive. Fears related to GD complications were widespread: 77.4% of patients unjustifiably feared fetal malformations, 75.5% were concerned about the risk of diabetes in the newborn, and 71.7% worried about congenital infections. Furthermore, 30.2% were apprehensive about cesarean delivery, and 77.4% feared the persistence of diabetes in the postpartum period. However, no statistically significant association was found between pregnancy term and the various fears expressed by the patients (P = NS).

Conclusion

Our study highlights the importance of a comprehensive approach to GD management, addressing not only the medical aspect but also providing psychological and educational support to patients. Identifying and addressing their fears, while correcting misconceptions, could enhance treatment adherence and promote an optimal pregnancy outcome. A more personalized and empathetic approach could help build patient confidence and contribute to better maternal-fetal care.

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EP335

JOINT2767

Spontaneous pneumomediastinum: a rare complication of diabetic ketoacidosis

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Introduction

Pneumomediastinum is an entity defined with presence of free air in the mediastinum cavity. It is usually due to a trauma but it can occur spontaneously. Association with diabetic ketoacidosis (DKA) has been reported in few cases. Herein, we present the case of a patient who was diagnosed with DKA accompanied with spontaneous pneumomediastinum.

Case presentation

A 17-year-old male patient, with no medical history was admitted in our hospital in January 2025 for acute vomiting and general fatigue. He didn't report any history of trauma. Respiratory rate was 33 breaths/minute, heart rate was 121 beats/minute, blood pressure was 116/81mmHg. The patient was apyretic. Subcutaneous crepitus on chest and neck was found. Blood glucose was 5.3 g/l. Arterial gas showed pH of 6.85, HCO3- of 2.6, pCO2 of 15.1, pO2 of 128.8. The chest abdomen and pelvis scan demonstrated pneumomediastinum, subcutaneous emphysema and pneumoperitoneum. Severe DKA was confirmed. The patient received hydration with normal saline and intravenous rapid insulin infusion with relay to subcutaneous insulin. The pneumomediastinum was treated conservatively. The evolution was favorable. There was no dyspnea neither chest pain. Respiratoy rate was normal. A good glycemic control was obtained with basal-bolus insulin. A chest X-ray of control 13 days after the DKA was normal.

Comments and Conclusions

Spontaneous pneumomediastinum is a rare condition, first reported by Hamman in 1939. Pathophysiology was decribed by Maklin as an increase in intralveolar pressure, followed by alveolar rupture. This barotrauma can be the result of severe vomiting and Kussmaul breathing in DKA. Air dissects through the bronchovascular sheath into the mediastinum. It can also dissect through other serous structures, subcutaneous tissue and peritoneal cavity. It is generally a benign entity with a good prognosis. Spontaneous resolution of the pneumomediastinum was found in most reported cases. Careful attention to this particular condition is needed espacially by emergency physicians to avoid under-diagnosis.

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EP336

JOINT1592

A case of HAIRAN syndrome in a teenage girl with hirsutism and secondary amenorrhea

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Introduction
HAIRAN syndrome (Hyperandrogenism, Insulin resistance, Acanthosis nigricans) is a rare and severe subphenotype of polycystic ovary syndrome (PCOS), marked by hyperandrogenism, insulin resistance, and dermatologic manifestations, including acanthosis nigricans. This syndrome primarily affects young females and presents with symptoms like hirsutism, menstrual irregularities, and obesity. HAIRAN syndrome is distinct from typical PCOS due to the significant severity of insulin resistance and the associated metabolic disturbances. The clinical management of HAIRAN syndrome requires a comprehensive approach involving hormonal regulation, insulin-sensitizing agents, and supportive interventions to address both physical and psychological aspects of the condition.
Case Description
We present a 16-year-old female patient diagnosed with HAIRAN syndrome. The patient has a long history of obesity since childhood and presented with complaints of weight gain, excessive facial and body hair, and menstrual irregularities. She had menarche at age 12, but over the past 9 months, she experienced secondary amenorrhea with no menstruation. Her family history is significant for obesity and type 2 diabetes in her mother, and a sibling diagnosed with PCOS. On physical examination, the patient was found to be hypertensive and had severe acanthosis nigricans on the neck, axillae, and cubital fossae. Anthropometric measurements revealed a BMI of 43.7 kg/m^2, categorizing her as severely obese, with significant signs of insulin resistance. Laboratory investigations revealed elevated androgen levels, including total testosterone of 55 ng/dl (normal range $<$48 ng/dl), free testosterone of 85 pmol/l (normal range 10-45 pmol/l), and androstenedione levels of 8 nmol/l (normal range 0.8–6.1 nmol/l). Additionally, a low SHBG level of 13 nmol/l (normal range 40–90 nmol/l) was noted, further confirming the presence of hyperandrogenism and contributing to the diagnosis of HAIRAN syndrome.
Conclusion
This case highlights the clinical complexity of HAIRAN syndrome, emphasizing the importance of early diagnosis and comprehensive management. The patient's treatment regimen included insulin-sensitizing agents (metformin), anti-androgen therapy (spironolactone), and oral contraceptives (ethinylestradiol and cyproterone) for menstrual regulation and reduction of hirsutism. Amlodipine was prescribed to manage hypertension, and the patient was referred for psychological support to address self-esteem and quality of life concerns. Given the rare and multifactorial nature of HAIRAN syndrome, a multidisciplinary approach involving endocrinologists, gynecologists, dermatologists, and psychologists is essential for optimal patient care. Ongoing follow-up is necessary to monitor the patient's response to treatment and ensure the proper development of menstrual cycles and overall health.

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EP337

JOINT3986

PAX4 mody - a novel variant

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Introduction
The Paired Box Gene 4 (PAX4) encodes a transcription factor crucial for pancreatic beta-cell development and maintenance in a differentiated state. PAX4 mutations have been identified as a cause of maturity-onset diabetes of the young (MODY), and also in ketosis prone diabetes. MODY diagnosis requires a high clinical suspicion, encompassing a group of rare monogenic forms of diabetes. We report a novel variant of PAX4 in a 29-year-old female which appears to be pathogenic.
Case report
A 29-year-old female was referred to Endocrinology for diabetes. At diagnosis, four years ago, our patient had a BMI 31.1kg/m2 and was asymptomatic. Several random glucose tests were above 200mg/dL, and her HbA1c was 7.1%. Metformin 2000mg/day was started. She had no other significant medical history or medications. Her family history was notable for diabetes (DM), including both her parents, who were treated with oral antidiabetics, one of her sisters diagnosed at 30 years, and the other sister diagnosed at 18 years during pregnancy, who was treated with insulin due to chronic kidney disease. Additionally, all of her grandparents had DM, as did seven out of nine of her father 's siblings, and two out of five of her mother's siblings. On presentation to our clinic, she had no symptoms, no physical examination alterations, including acanthosis nigricans or other skin abnormalities, and no DM-related complications. Following lifestyle modification, her BMI reduced to 23.3kg/m2 and her A1c improved to 5.3%. Further testing revealed a normal C-peptide (2.69ng/mL, reference 1.10-4.40) paired with a normal glucose of 76mg/dL, negative auto-antibodies (anti-insulin, anti-ICA, anti-IA2 and anti-GAD). Exeter Diabetes Calculator ® revealed a 75.5% chance of having MODY. Next-generation sequencing for MODY identified a heterozygous mutation (NM_001366110.1(PAX4):c.1022G$>$A, p.(Trp341*)) in the PAX4 gene, resulting in a stop codon in the 341st position, classified as a variant of uncertain significance. Metformin was suspended and her A1c remained at 5.3%. Her family members were referred for genetic testing.
Conclusions
PAX4 variants are rare, and individuals affected have had clinical presentations and diagnoses ranging from ketosis-prone DM, to T1DM, T2DM and PAX4-MODY. Given our patient's family history and early onset of diabetes, PAX4-MODY is highly suspected. Genetic testing is increasingly available and should be done to allow for a better understanding of atypical types of DM and to improve patient management.

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EP338

JOINT3560

Sodium-glucose cotransporter 2 inhibitors in type 1 diabetes mellitus: prohibited?

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Introduction and objectives
Sodium-glucose cotransporter 2 (iSGLT2) inhibitors in type 2 diabetes (DM2) have demonstrated clear metabolic and cardio-renal benefits. Cardio-renal complications are also very common in patients with type 1 diabetes (DM1). However, the risk of developing diabetic ketoacidosis (DKA) has limited the use of these agents in DM1 and especially in certain DM1 subgroups where they would be beneficial. The aim of this study was to evaluate the renal and metabolic evolution of patients with DM1 and high cardiovascular risk at 6 and 12 months after the use of iSGLT2.
Material and methods
Prospective descriptive observational study analysing 22 patients with DM1 who were indicated to start treatment with iSGLT-2 in the Endocrinology outpatient clinic of the San Cecilio Hospital in Granada, Spain. Clinical and analytical variables were measured. The analysis was performed with SPSS 25.0.
Results
Twenty-two patients with DM1 aged between 18 and 65 years old (mean 49.4$\pm$11,5 years) were included, half of whom were male. The mean time of evolution of DM1 was 28.9$\pm$13.7 years. Thirteen were iSCI users and nine were MDI users. After initiation of iSGLT2 a mean weight loss of 1.8 and 2.8 kg was observed at 6 months and 12 months respectively. HbA1c decreased from a baseline mean of 7.8% to 7.5 and 7.3% at 6 and 12 months respectively. Renal profile: 45.45% of patients had diabetic nephropathy (3 macroalbuminuria and 5 microalbuminuria). From a mean baseline albuminuria of 232.4 mg/g, a decrease of 53 and 87.5mg/g was observed at 6 and 12 months respectively. No episodes of diabetic ketoacidosis (DKA) were observed during follow-up.
Conclusions
The use of iSGLT2 in a DM1 population at high cardiovascular risk resulted in improvement in terms of weight and metabolic control and, above all, a marked decrease in albuminuria without worsening of renal function and without significant DKA or other complications. Therefore, patients with DM1 at high cardiovascular risk and especially with established nephropathy may benefit from the use of iSGLT2.

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EP339

JOINT3921

Efficacy on functionality and perceived quality of life of a nutritional support programme with specific supplementation for people with type 2 diabetes at risk of malnutrition

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Introduction and Objectives
Diabetes mellitus is a highly prevalent disease that can affect nutritional status, as well as quality of life and functioning. The present study aims to evaluate the differences in nutritional status, by analysing functionality parameters and quality of life scales, in patients with diabetes and disease-related malnutrition (DRE) or high nutritional risk, at baseline and 3 months after starting specific nutritional supplementation.
Material and Methods
We selected 15 patients assessed in nutritional prehabilitation consultations, with a diagnosis of type 2 diabetes mellitus and digestive cancer, with DRE or high nutritional risk according to GLIM criteria, in active oncological treatment (chemotherapy, surgery). A nutritional support programme was initiated with dietary recommendations, exercise and specific supplementation for people with type 2 diabetes. Anthropometric assessments, functional tests (number of squats performed in 10 seconds, up and go test) and scales (diabetes stress scale, EQ-5D-5L) were performed at the first consultation and at a 3-month review. Differences were analysed using SSPS v.24 statistical software. A value of $P<0.05$ was considered statistically significant and trend to statistical significance $P<0.1$.
Results
Mean age 71.3 years (SDS 8.2). Antidiabetic treatment received by patients: 69% metformin, 31% iDPP4, 23% iSGLT2, 15% slow insulin, 8% rapid insulin, 8% sulphonylureas. Subjective global assessment at baseline was 61.5% moderate and 15.4% severe malnutrition. At 3 months, 46.2% were moderately malnourished and 53.8% were normonnourished. At 3 months after the start of nutritional supplementation, calf diameter had increased from baseline by a statistically significant 34.4cm vs 35.2cm ($P<0.05$). Diabetes stress scale scores 7.6 vs 4.2 points (NS) and EQ-5D-5L 7 vs 7.6 (NS) also improved. Functional tests of squats and TUG improved modestly 8.8 vs 10.1 squats (NS) and 10.9 vs 10 seconds ($P<0.05$). There was no change in dynamometry results 29.5 vs 29.1 kg (NS).
Conclusions
The implementation of a nutritional support programme in routine medical practice, based on dietary recommendations, exercise and specific supplementation for people with type 2 diabetes with malnutrition or high nutritional risk, improved functional outcomes and subjective assessment in our cohort of oncology patients.

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EP340

JOINT897

Vitamin D and glycemic control in type 1 diabetes

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Background
Type 1 diabetes (T1D) is a chronic autoimmune disorder that requires ongoing management of blood glucose levels to prevent long-term complications. Recent studies have suggested a potential link between vitamin D status and glycemic control in individuals with diabetes.
Purpuse
The aim was to study the relationship between 25-hydroxy vitamin D (25(OH)D) levels and glycemic control in patients with type 1 diabetes.
Methods
We conducted a cross-sectional study, including 50 type 1 diabetic patients. All participants underwent a thorough assessment, including the measurement of 25-hydroxyvitamin D, as well as the assessment of fasting blood glucose and hemoglobin A1c levels.
Results
The median age of the participants was 26 years [21.00 - 31.75], with a sex ratio (F/M) of 1.4. The median duration of diabetes was 13.00 years [9.25 - 17.75]. The average level of 25(OH)D was 11.14 $\pm$ 6.49 and 56% of patients had a severe deficiency ($\leq$10 ng/ml). The assessment of glycemic control showed that 78% of patients had a fasting blood glucose level above the therapeutic target (7.2 mmol/l), and 66% had an HbA1c $\geq$ 9%. The analysis of the association between glycemic control and 25(OH)D levels revealed that patients with elevated fasting blood glucose levels had a lower median 25(OH)D level compared to those with fasting blood glucose within therapeutic targets but without a statistically significant difference (8.93 ng/ml [7.57 – 13.89] versus 11.42 ng/ml [6.88 – 15.42]; $P = 0.61$). Furthermore, patients with an HbA1c $\geq$ 9% had a lower median 25(OH)D level compared to those with an HbA1c $<$ 9% (11.39 ng/ml [8.44 – 14.44] versus 8.74 ng/ml [7.08 – 13.25]; $P = 0.14$).
Conclusion
Although patients with elevated blood glucose levels tended to have lower median 25(OH)D levels compared to those with glycemic control within target ranges, these differences were not statistically significant. Further research with larger sample sizes may be needed to better understand the relationship between vitamin D levels and glycemic control in type 1 diabetic patients.

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EP341

JOINT2301

Fighting with a double-edged sword: a case of pancreatic transplant failure with resurgence of autoimmune diabetes in a patient with metastatic colon cancer treated with pembrolizumab

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Background
Pembrolizumab is a monoclonal antibody that inhibits PD-1 activity, enhancing cell-mediated cancer cell killing. However, it inadvertently increases the risk of autoimmunity and, in transplant patients, the incidence of graft failure.
Case presentation
A 50-year-old male presented to the hospital due to worsening hyperglycemia over 4 months. He had a past medical history of Type 1 Diabetes Mellitus, End Stage Renal Disease status post Kidney and Pancreatic transplant in 2007, reportedly compliant with Tacrolimus and Prednisone, recently diagnosed with Colon Cancer with metastasis to the transplanted kidney resulting in resection and reinitiation of hemodialysis, he is currently on Pembrolizumab which was started 4 months ago. He denied any fever, rash, polyuria, or diarrhea but reported abdominal pain. He has been off insulin since his transplant but was restarted on a basal-bolus insulin regimen 4 months ago for progressively elevated glucose levels uncontrolled by an insulin sliding scale. Vital signs were normal. Physical examination was unremarkable. Diagnostic tests showed Glucose 400 mg/dL, Beta-Hydroxybutyrate 1.8 mmol/l (ref $<$0.5 mmol/l), blood gas pH 7.43, HCO3 23, CO2 36, HbA1C 7%, C-peptide $<$0.10 ng/mL (ref 0.5-2 ng/mL), Lipase 20 IU/l, TSH and cortisol were normal. Abdominal ultrasound showed normal size and vasculature of the transplanted pancreas. The patient opted for an outpatient pancreatic biopsy. Endocrinology, Oncology, and Transplant teams were consulted, Pembrolizumab was discontinued, his basal-bolus insulin regimen was adjusted, and immunosuppressants were continued. His glucose control improved, and he was discharged with a close outpatient follow-up for further work-up.
Discussion
Our patient's worsening hyperglycemia is likely secondary to pancreatic transplant failure with concerns for the recurrence of autoimmune diabetes from Pembrolizumab. Pembrolizumab works by enhancing the cell-mediated killing of malignant cells. However, it can inadvertently attack donor alloantigens in the transplanted kidneys causing graft failure. Although, the recurrence of autoimmune diabetes in a transplanted pancreas is rare since immunosuppressants effectively control autoimmunity, the concomitant use of Pembrolizumab can inhibit immunosuppression and cause a resurgence of autoimmunity.
Conclusion
Pembrolizumab remains central in the management of multiple malignancies. However, its use is associated with risks for autoimmune endocrinopathies and organ transplant rejection. Therefore, all physicians should properly educate patients regarding the risks and benefits of treatment and ensure close multidisciplinary follow-up.
Reference
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EP342

JOINT941

When karyotype is necessary in hyperinsulinemic hypoglycemia:a case report in mosaic turner syndrome

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Background
Hyperinsulinemic hypoglycemia is a common cause of hypoglycemia in neonates and infants, with several etiologies including syndromic disorders such as Turner syndrome. Turner syndrome linked to glycaemic dysregulation, including diabetes mellitus and, less typically, neonatal hyperinsulinemic hypoglycemia. Turner syndrome and hyperinsulinism are linked by an unknown aetiology.
Case Presentation
We report the case of a 4.5-year-old girl who developed a seizure at the age of 3 months as a result of hypoglecemia. She was born at term, weighing 3,120 g, with AGA. At a blood glucose level of 34 mg/dL, the critical blood sample revealed insulin 3.0 uIU/mL, serum ketones $<$ 0.3 mmol/l, growth hormone (GH) 9.81 ng/mL, and cortisol 16.6 ng/dL. As a result, hyperinsulinemic hypoglycemia is diagnosed, and she has now begun therapy with Diazoxide at a dose of 10 mg/kg/day. The Diazoxide dose has been titrated based on blood sugar, and the most current dose is 3.5 mg/kg/day, which is well managed. A whole genome sequencing investigation for common hyperinsulinism target genes yielded no results. Height velocity has diverged from the 3rd percentile from the age of two, with an average annual height gain of 3.3 cm. At the age of 4.5 years, her height was 91 cm (-3.4 SDS), her BW was 13.5 kg (-1.7 SDS). The paternal and maternal height are 178 and 160 cm, respectively and mid-parental height is 162.5 cm. The normal workup for short stature was completed, including a karyotype analysis. Mild dysmorphic characteristics, such as a bilateral epicanthal fold, clinodactyly in both hands, and hyperconvex nails, were discovered, but otherwise are unremarkable. A film X-ray of the hand reveals slight shortening of the 4th metacarpal bone. A karyotype examination of 50 metaphases found mosaic Turner syndrome with a marker chromosome (46,X,dup(X)(q22q28)/45,X(1)/46,X,+mar(1)).
Discussion
Unlike usual cases of congenital hyperinsulinism, which are linked with increased height and weight, this individual had short stature and borderline low weight, indicating Turner syndrome. Reports from case series and case reports in the literature suggest a link between Turner syndrome and hyperinsulinism, albeit the mechanism is unknown. Some instances have been associated with islet cell nucleomegaly and *KDM6A* haploinsufficiency.
Conclusion
This report emphasizes the significance of examining Turner syndrome in females who appear with unexplained hyperinsulinemic hypoglycemia, especially when coupled with growth failure. More study is needed to understand the processes driving hyperinsulinism in Turner syndrome.

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EP343

JOINT1394

Incidence and survival implications of diabetic nephropathy in post-heart transplant patients

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Background
Evidence of diabetic nephropathy (DN) following heart transplantation (HTx) in Asian populations remains scarce. This study aimed to assess the incidence, risk factors of post-HTx DN and evaluate its impact on patient survival.
Methods
A retrospective cohort study was conducted on consecutive adult patients who underwent their first HTx at a single center between 2019 and 2023 and survived to hospital discharge. These patients were prospectively followed until December 31, 2024. Post-HTx DN was defined as the concurrent presence of new-onset diabetes mellitus (demonstrated by $\geq$2 consecutive HbA1c $\geq$6.5% or fasting plasma glucose $\geq$126 mg/dL) and albuminuria (urine albumin-to-creatinine ratio $\geq$30 mg/g) in patients without pre-existing diabetes, assessed from three months after heart transplantation onward. Patient survival was assessed using the Kaplan-Meier method, with group comparisons performed using the log-rank test. Cox proportional hazards models were employed for multivariate analysis. Statistical analyses were conducted using STATA version 16 (StataCorp, Texas, USA).
Results
Among 52 patients (85% male, mean age 47.2$\pm$11.8 years, mean BMI 21.7$\pm$3.3 kg/m^2), 10 (19%) had pre-existing diabetes mellitus (DM) before HTx. During a median follow-up of 36 months, 11 patients (21%) developed post-HTx DM, with 2 (4%) progressing to DN. Among patients without pre-existing DM before HTX, new-onset post-HTx DN showed no significant associations with patient characteristics, choice of immunosuppressant regimens, or the occurrence of at least one episode of grade $\geq$2R allograft rejection requiring steroid pulse therapy. Post-HTx DN was independently associated with a sustained decline in kidney function (hazard ratio [HR] 17.4, $P = 0.001$), defined by the persistence of one of the following criteria for at least 4 weeks: $\geq$ 40% decline in eGFR, eGFR $<$ 15 ml/min/1.73 m^2, doubling of serum creatinine, or initiation of dialysis. During the follow-up period, four deaths were recorded, with causes including hemorrhagic stroke, cardiac arrest, sepsis with multiple organ failure, and an unknown cause. Both post-HTx DN (HR, 47.3; $P = 0.007$) and post-HTx dialysis (HR, 45.4; $P = 0.002$) were identified as significant independent risk predictors of all-cause mortality.
Conclusions
Approximately 4% of HTx patients developed post-HTx DN, which may serve as one of the prognostic indicators for their survival outcomes. Further studies on a larger sample size are needed to identify risk predictor of post-HTx DN, enabling the implementation of effective preventive measures.

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EP344

JOINT2529

Prediabetes and systemic inflammation

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Introduction
Systemic inflammation may play a central role in the pathogenesis of diabetes and atherosclerosis. C-reactive protein (CRP), a marker of systemic inflammation, is an independent risk factor for cardiovascular disease. Elevated CRP levels are also present in patients with glucose intolerance (IGT). and diabetes. Several prospective studies have shown that an elevated CRP level is an independent risk factor for the development of diabetes. Although these findings indicate that peripheral blood CRP levels are closely related to glucose levels, it remains unclear whether this relationship exists at glycemic levels in the prediabetic range.
Methods
The study included 106 patients with angiographically diagnosed coronary artery disease, who, based on the oral glucose tolerance test (OGTT), were classified into a group with type 2 diabetes (T2D, $n = 34$), a group with impaired glycemia and glucose intolerance (IFG /IGT, $n = 38$) and a group with normal glucose tolerance (NGT, $n = 34$). The control group consisted of subjects with normal glucose tolerance and no coronary disease ($n = 100$), individually matched by age and body mass index (BMI) with coronary patients included in the study. The circulating level of lipids, insulin, hsCRP, the albumin level in the morning urine sample, and the insulin resistance index HOMA were determined in all of them.
Results
The level of hsCRP was elevated in the group of coronary patients with diabetes ($P<0.05$), as well as in the group of patients with prediabetes

($P<0.05$), compared to the control group. hsCRP values were not significantly different in coronary patients, regardless of glycemic status ($P>0.05$). There is a higher BMI in the group of coronary patients with diabetes and prediabetes ($P<0.05$). A significant correlation of hsCRP with glycemia in 120 min OGTT test was found. ($P<0.05$), independent of existing obesity.

Conclusion

Patients with coronary disease and prediabetes and new onset T2D did not differ significantly in the level of systemic inflammation. Chronic subclinical inflammation, detected by an elevated level of C-reactive protein, is more strongly associated with post load glycemia than with fasting glycemia.

Key words

C-reactive protein, prediabetes, coronary disease

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EP345

JOINT702

Hypogonadism - is it more frequent in males with type 1 diabetes mellitus?

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Introduction

Diabetes mellitus is a chronic metabolic disease, well known for its systemic effects. Type 1 diabetes mellitus (T1DM) is an autoimmune disease with leading insulinopenia and hyperglycaemia but also been linked to the influence of the hypothalamic-pituitary-gonadal axis (HPG) and fertility issues in both men and women, including development of hypogonadism. The aim of the study was to investigate the serum androgen levels in men with T1DM and age- and BMI- matched clinically healthy men of active reproductive age to determine the presence of hypogonadism.

Materials and methods

The study included 71 individuals – 30 men with T1DM and 41 clinically healthy men serving as a control group. A detailed medical history related to disease duration, type of insulin administered, total daily insulin dose (TDI), insulin dose per kilogram (dose/kg) was taken. Anthropometric measurements of weight (kg), height (cm), were performed on all participants, body mass index (kg/m2) (BMI) was calculated. Basal levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), testosterone (T), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), thyroid stimulating hormone (TSH), serum prolactin (Prl), were studied. Free androgen index (FAI), calculated free testosterone (cFT) and bioavailable testosterone (BioT) were calculated. Biochemical studies included levels of total protein (TPROT), albumin (ALB) and creatinine (CREA), fasting blood glucose (FBG), glycated hemoglobin (HbA1C) and microalbuminuria (U-ALB)

Results

The mean age of the studied men was 31.72 ± 6.05 years and the mean BMI was 24.87 ± 6.03 kg/m2 and no statistically significant difference was found between the groups ($P = 0.944$, $P = 0.537$ respectively). All participants had normal levels of total protein and albumin in the absence of statistically significant differences between the examined men ($P = 0.188$, $P = 0.600$, respectively). As expected, HbA1C and fasting blood glucose levels were higher in men with T1DM compared to healthy controls ($P = 0{,}000$, respectively). Men with T1DM had statistically significantly higher SHBG levels ($P = 0.000$) and lower FAI levels compared to controls ($P = 0.004$). Lower levels of BioT compared to the control group were detected in the DM1 group, but without reaching a statistically significant difference ($P = 0.071$). There were no significant differences in the levels of LH, FSH, LH / FSH, E2, T and cFT in the two groups of men ($P = 0.126$, $P = 0.553$, $P = 0.284$, $P = 0.900$, $P = 0.101$, $P = 0.465$, respectively). All participants had euthyroid function and normoprolactinaemia.

Conclusions

Men with T1DM of active reproductive age had comparable with healthy controls levels of androgens and no presence of hypogondism.

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EP346

JOINT3827

Fear of hypoglycemia: a significant challenge for pregnant women with type 1 diabetes

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Introduction

Pregnant women with type 1 diabetes face an increased risk of maternal and neonatal complications. While tight glycemic control is beneficial in reducing these risks, it can also increase the risk of hypoglycemia, leading to recurrent episodes and potentially severe hypoglycemia, which may culminate in an excessive and pathological fear of hypoglycemia

Objective

This study aims to assess the link between severe hypoglycemia and pathological fear of hypoglycemia in pregnant women with type 1 diabetes, considering factors like diabetes characteristics and mental health.

Methods

A prospective study enrolled 70 pregnant women with type 1 diabetes between March 2022 and December 2024. Fear of hypoglycemia was assessed using the HFS-II scale. Severe hypoglycemia was defined as an event requiring assistance due to altered mental or physical status, regardless of blood glucose level. Data analysis was performed using Tibco Spotfire, with Chi-square tests for categorical variables and Kruskal-Wallis tests for numerical and categorical comparisons.

Results

The frequency of severe hypoglycemia was 47 %, and the mean HFS II score was 31 in this group (G1). In the second group (G2), 53 % of patients had no episodes of severe hypoglycemia, and the mean HFS II score was 7. Group 1 demonstrated poorer glycemic control, evidenced by a higher frequency of severe hypoglycemia, lower hypoglycemia awareness, and higher HbA1c levels. This group also exhibited a higher prevalence of diabetes-related complications, including retinopathy and nephropathy. Furthermore, Group 1 demonstrated less SMBG and fewer adjustments to their diabetes management regimen. In contrast, Group 2 exhibited better glycemic control, lower complication rates, and improved self-care practices. Potential contributing factors are the longer duration of diabetes and the presence of autoimmune diseases in Group 1. The factors that were found to be significantly correlated with a high HFSII score were anxiety ($P = 0.0007$), depression ($P = 0.0009$), the perception of receiving inadequate care and emotional support ($P = 0.0065$), and the presence of diabetic retinopathy ($P = 0.005$). Severe hypoglycemia was associated with anxiety ($P = 0.0009$), depression ($P = 0.0006$), perceived inadequate care and support ($P = 0.0011$), recurrent hypoglycemia ($P = 0.0001$), hypoglycemia unawareness ($P = 0.0001$), poor glycemic control ($P = 0.0008$), and diabetic retinopathy ($P = 0.034$). Lipodystrophy areas demonstrated a strong association, although it did not reach statistical significance ($P = 0.0672$).

Conclusion

Severe hypoglycemia affected 47 % of pregnant women with type 1 diabetes, raising concerns due to its association with fear of hypoglycemia and its link to factors like anxiety and inadequate care.

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EP347

JOINT684

Dysglycemias in HNF1-b-associated disease: phenotype-genotype correlations

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Introduction

Hepatocyte nuclear factor 1-b (*HNF1-β*)-associated disease is a multisystem entity.

Objective
To describe the degree of dysglycemia in patients with *HNF1-β* variants diagnosed at *INGEMM* between 2009 and 2024.
Methods
Multicenter retrospective observational study including 67 patients (33 pediatric and 34 adult, 29 cases were family cases) with *HNF1-β* variants identified by MLPA and a custom NGS panel (including 473 genes associated with dysglycemia). Variant filtering, classification and prioritization was performed with VarSeqV2.6.2 and Alamut Visual Plus V1.12, using confidence and quality criteria, (depth >100x; % bp 20x >95%) allele frequency <1% (gnomAD V2.1.1 controls) and *in silico* prediction of pathogenicity (CADD V1.6 score > 20).
Results
45/67 patients (67.2%) presented heterozygous SNV in *HNF1-β* (88.9% missense, 6.7% frameshift, 4.4% nonsense), 46.6% classified as VUS and 26.7% as probably pathogenic or pathogenic. 22/67 patients (32.8%) presented a heterozygous deletion in 17q12 including all *HNF1-β* exons. 13 variants were *de novo*, of which, 69.2% were 17q12 deletions. In the group with *HNF1-β* SNVs, diabetes mellitus (DM) was predominant (62.2%, 28/45 patients), with mean diabetic debut at 32.8 years (11-59 yrs), mean current HbA1c 7.2±0.9%; 20/28 (74%) had microvascular (17/20 nephropathy, 5/20 retinopathy, 3/20 neuropathy) , and 4/28 (14.8%) macrovascular (3/4 ischemic heart disease, 1/4 peripheral arterial disease) complications. 18/28 (66.6%) are on insulin therapy (50% in combination with other hypoglycemic agents- OHAs). Normoglycemia and prediabetes were present in 22.2% and 15.6%, respectively. In 17q12 recurrent deletion syndrome (17q12RDS) cases, normoglycemia predominated (45.4%, 10/22), followed by prediabetes (36.4%, 8/22) and DM (18.2%, 4/22), with mean diabetic debut at 32.9 years (12-33 yrs), mean current HbA1c 6.9±0.7%, 1 patient presented microvascular complications (retinopathy and nephropathy), everyone under insulin therapy (75% in combination with OHAs). Among the prediabetes cases, there was 1 case with transient neonatal DM. In both groups, the most frequent comorbidities were urinary abnormalities (73.2% vs 100% mostly with neonatal diagnosis) and liver disease (56.1% vs. 59.1%). In the group with SNV, hyperuricemia/gout (32.5%), hypomagnesemia (30.8%) and pancreatic atrophy/agenesis (29.3%) stood out. In the group with 17q12RDS, hypomagnesemia (70%), neuropsychiatric disorders (36.4%), and genital abnormalities (22.7%) were the most frequent findings.
Conclusions
The clinical expression of *HNF1-β*-associated disease is highly variable, even within families, requiring a specialized multidisciplinary approach. Sporadic cases are frequent, especially in 17q12RDS, in which neonatally diagnosed genitourinary abnormalities, hepatopathy, hypomagnesemia and neuropsychiatric alterations predominate. Most cases with SNVs develop mainly insulin-dependent DM due to advanced nephropathy and pancreatic dysgenesis.

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EP348

JOINT3907
Study of the clinical profile of diabetics followed up in front-line structures

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Introduction
Diabetes is a major public health problem, responsible for life-threatening complications. Maintaining therapeutic control in diabetics is a challenge for all primary care physicians. We aimed to study the clinico-biological profile of diabetics followed up in primary care centers, to identify factors predictive of metabolic control and to evaluate the quality of management of these patients in these centers.
Methods
It was observational, descriptive, cross-sectional and retrospective study, conducted in three primary care facilities: Mhamdia, Megrine and Megrine Chaker. Recruitment took place from February 1 to July 31, 2023. We collected the clinical and biological data of the included patients from the medical files and by interrogation carried out by the investigator.
Results
We collected 221 type 2 diabetics with a mean age of 64.67 ± 11.04 years, predominantly female (sex ratio = 0.38). The mean duration of diabetes was 11.8 ± 8.79 years. Glycemic, blood pressure and lipid control were attained in respectively 38.7%, 27.2% and 12.4% of patients. The multivariate study showed poor glycemic control in diabetics who were elderly ($P = 0.05$); on insulin therapy ($P = 0.001$); had a frequent consumption of sweets ($P = 0.009$) and consumed bread excessively ($P = 0.010$). Better blood pressure control was found among those on antihypertensive treatment ($P < 0.0001$) and non-smokers ($P = 0.037$). Better lipid balance was noted in patients at low to moderate cardiovascular risk ($P < 0.0001$). Hypoglycemia was observed in 37.1% of patients. Risk factors independently associated with the occurrence of hypoglycemia were overweight ($P = 0.004$), insulin therapy ($P = 0.006$) and the presence of macroangiopathy ($P = 0.038$). At least one microangiopathic and macroangiopathic complication was noted in 37.1% and 19% of diabetics respectively. Protective factors against the onset of microangiopathy were dietary reminders at each consultation ($P = 0.006$), metformin intake ($P = 0.027$) and target blood pressure ($P = 0.037$). The development of macroangiopathy was significantly associated with insulin therapy ($P = 0.008$). Glycated hemoglobin was tested as recommended in 63.8% of patients.
Conclusion
The present study showed a discrepancy between the recommendations and our results. The management of diabetics needs to be improved in primary-care center.

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EP349

JOINT2831
Retrospective evaluation of clinical and metabolic differences in the course of diabetic ketoacidos in patients with diabetes mellitus using SGLT-2 inhibitors: a single center study

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Objective
There is increasing data that sodium glucose cotransporter 2 inhibitors (SGLT-2i) may increase the risk of euglycemic diabetic ketoacidosis (DKA). This study aims to retrospectively evaluate clinical and metabolic differences observed during the course of DKA among type 2 diabetic patients (T2DM) using or not using SGLT-2i and type 1 diabetic patients (T1DM). The differences in treatment modalities and intensive care processes among the groups were also assesed.
Materials and Methods
Demographic data, treatment modalities, laboratory results (plasma glucose, HbA1c, C-peptide, blood gas analysis, electrolytes, inflammation markers), clinical parameters [Glasgow Coma Scale (GCS), vital signs], micro- and macrovascular complications and DKA management parameters (ICU admissions, time to resolution of ketosis, the duration of insulin infusion, the amount of HCO3 and saline requirement) were obtained by reviewing electronic medical records and patient files.
Results
Among included 124 patients (61F, 63M), 30,6% were diagnosed with T1DM (n:38), while 69.4% had T2DM (n:86). Among patients with T2DM, 37.2% (n:32) of them were receiving SGLT-2i. The average diabetes duration was similiar among the groups (13.5 years in SGLT-2i users vs. 13.6 years in non-SGLT-2i users vs.12.2 years in T1DM; $P > 0.05$). Infection was the main precipitating factor for DKA in (13 out of 32) SGLT-2i users. There was no statistically significant difference among the groups regarding GCS, other vital signs, or ICU admission rates. Initial glucose levels, HbA1c, C-peptide, lipid profile, blood gas ph, lactate, electrolyte levels were similiar among the groups. But, all patients with euglycemic DKA with plasma glucose < 300 mg/dL ($n = 9$, 7.2%) were found in the SGLT-2i users group. On the otherhand, SGLT-2i users had higher degree of ketosis compared to patients non-SGLT-2i users (keton 3 positivity, 65.6% vs. 35.2%, $P < 0.05$). Moreover, ketonemia resolution time and insulin infusion duration were significantly higher in patients using SGLT-2i compared to other groups ($P < 0.05$ for all). In addition, more amount of HCO3 (6.59±8.68 mmol/l in SGLT-2i users vs. 2.41±4.67 mmol/l in non-SGLT-2i users vs. 3.11±5.71 mmol/l in T1DM; $P < 0.05$) and saline infusion (6078.1±1739.9 mL in SGLT-2i users vs. 3894.4±965.3 mL in non-SGLT-2i users vs. 4894.7±1732.3 mL in T1DM; $P < 0.05$) was required in SGLT-2i users compared to other groups during the treatment.
Conclusion
Considering the association of SGLT-2i use with prolonged ketone negativity and insulin infusion time and increased HCO3 and fluid requirements, intensive care

treatment protocols should be personalized and more stringent control and follow-up protocols should be developed for these patients.

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EP350

JOINT3940

Trends in diabetic foot infections in albania: a decade of insights into etiology and risk factors

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Diabetic foot infections (DFIs) are a leading cause of morbidity and amputation in patients with diabetes, yet, the etiology and risk factors are not fully understood. This study analyzes temporal trends in DFI causes, microbiological profiles, and clinical outcomes over a 10-year period, using data from three different cohorts (2013, 2019, and 2024) of 400 patients treated at Reha Diabetic foot clinic. Our results show that there is an important change in the microbiological profile of DFIs with increasing incidence of multidrug-resistent organisms (MDRO), especially MRSA. Between 2013 and 2024, the proportion of MDRO-related infections rose significantly and correlated with previous antibiotic treatment and longer hospitalization. In 2013, Pseudomonas aeruginosa was the most common microorganism, whereas in 2024, Staphylococcus aureus became the dominant species. Additionally, we identified key risk factors for severe DFIs, including peripheral arterial disease (PAD), poor glycemic control (HbA1c $>$ 9%), and late admission to specialized care. Patients with PAD had an increased risk for the development of osteomyelitis ($P<$ 0.01), while those with HbA1c $>$ 9% had a 40% higher risk of amputation ($P<$ 0.05). Our study highlights the changing nature of DFIs and the importance of early treatment to improve patient outcomes. Using broad-spectrum antibiotics alongside a multidisciplinary approach can help manage infections more effectively. By identifying and addressing the factors that contribute to these infections and staying aware of evolving microbial patterns, we can take important steps toward reducing the risk of severe complications, including disability and death from diabetic foot disease.

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EP351

JOINT2586

The importance of interleukin 6 in the detection of silent myocardial ischemia in patients with tipe 2 diabetes

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Introduction and aim
A special feature of Coronary Heart Disease (CHD) in patients with type 2 diabetes (T2D) is that it is often asymptomatic and occurs as a consecuence of cardiovascular auotonomic neuropathy. Predicting the risk of cardiovascular events occurrence and progression of atherosclerosis and correlation of inflammatory agents in its progression has increasingly been the focus of research. Increased levels of interleukin 6 (IL-6) accelerates atherosclerosis and occurrence of cardiovascular complications in patients with T2D. Therefore, the determination of IL 6 in these patients would be significant in stratifying the risk of CHD. The aim of the study was to evaluate the importance of determining inflammatory cardiovascular risk markers IL-6 in screening for the presence of CHD in asymptomatic patients with T2D.
Methods
The cross-sectional study included 159 patients with T2D, without any symptoms and signs of CHD and no previous history CHD. Ergometric testing proved or ruled out the presence of silent CHD. The levels of IL-6 were determined by ELISA.
Results
IL6 values were significantly higher in patients with positive ergometric test (5.83 ± 1.99 pg/mL) compared to patients with negative ergometric test (2.04 ± 1.39 pg/mL) ($P<0.001$). The patients with higher IL-6 values were 1.457 more likely to have positive ergometric tests than those with lower IL-6 ($P<0.05$). The combination of IL-6, glycoregulation parameters (HbA1c) and duration of diabetes are significant predictors of silent ischemia. With their increase, the probability of a positive ergometric test also increases ($P<0.01$).
Conclusion
It was proven that there was a greater possibility of the presence of silent CHD in asymptomatic patients with T2D with higher values IL-6 and their determination could be recommended in improving cardiovascular risk stratification in asymptomatic patients with T2D.

Key words
diabetes mellitus, coronary heart disease, interleukin 6.

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EP352

JOINT2891

Multifocal sporadic insulinoma with both intra- and peri-pancreatic lesions: a rare case report

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Background
Insulinomas are functioning neuroendocrine neoplasms (NENs) characterized by autonomous secretion of insulin. The incidence of insulinomas is 1-4 people per million per year which peaks in the fifth decade of life with a female preponderance. The vast majority (90%) of insulinomas are solitary, benign, pancreatic lesions with a diameter of <2 cm. Ectopic insulinomas are extremely rare ($<2\%$), most frequently arising in peri-pancreatic or peri-duodenal regions. Extra-pancreatic NENs secreting insulin have also been described in the liver, the cervix, the kidney and the pelvis.
Case presentation
A 29-year-old woman was referred to Endocrinology Department with features of Whipple's triad during recurrent episodes of hypoglycemia. Symptomatic hypoglycemia (glu 39mg/dl), developed twelve hours after the initiation of a 72-hour fast, with increased insulin and c-peptide levels (insulin$=$ 60.4μIU/ml, c-peptide$=$4.3ng/ml). Insulin antibodies were undetectable and insulin-like growth factor 2-mediated hypoglycemia was excluded. An abdominal MRI was performed which showed a 3 cm mass at the anatomic site between the spleen, the left kidney and behind the pancreatic tail, but failed to reveal any pancreatic lesions. Further imaging with ^{68}Ga-DOTATATE PET/CT was in accordance with the MRI findings and showed increased radiotracer uptake (SUVmax 29.6) by the aforementioned tumor. However, on endoscopic ultrasound, a small lesion (<1 cm) in the tail of pancreas was localized in addition to the primary lesion. Ultrasound-guided fine needle aspiration was performed on both lesions and the presence of neuroendocrine neoplasmatic cells was confirmed in both the pancreatic tumor and the peri-pancreatic one. Distal pancreatectomy, splenectomy and resection of the extra-pancreatic lesion were performed. Histopathology revealed two well-differentiated, neuroendocrine neoplasms grade 2 (NEN-G2) of intermediate malignancy with a Ki-67 of 3%. Immunostaining was positive for insulin, glucagon, NSE, CD-56, synaptophysin and chromogranin. The pancreatic insulinoma measured 0.6 cm and the peri-pancreatic one 4 cm. Given that multiple insulinomas are characteristic of MEN-1 syndrome, genetic testing for *menin* variants was performed which was negative. Post-operative period was uneventful and during a 6-month follow-up period the patient has remained asymptomatic and euglycemic.
Conclusions
To our knowledge, this is the first report of sporadic multifocal insulinoma with both intra-pancreatic and peri-pancreatic lesions. In addition, our case emphasizes the importance of successful pre-operative insulinoma localization in order to ensure definite curative treatment.

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EP353

JOINT360

Increased utilization of diabetes technology and improved glycaemic control among children with type 1 diabetes in Hong Kong over the past 8 years

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Background
New technological devices are increasingly used in the management of children with type 1 diabetes (T1D) worldwide and has been shown to improve glycaemic control and reduce risk of hypoglycaemia. In the past, there was considerable barrier in accessing these technologies locally. Territory-wide funding programme for CGMS and limited sponsorship for insulin pump have rolled out in the past few years. However, there is limited data on whether this has impacted glycaemic outcomes.
Method
This retrospective study assessed the use of CGMS and insulin pump in Hong Kong from 2017 to 2023. Data were retrieved from the Hong Kong Childhood Diabetes Registry. HbA1c over time, rates of DKA and severe hypogylcaemia (requiring glucagon injection/hospitalization) were evaluated. Additionally, HbA1c was compared between users versus non-users of CGMS and insulin pump in 2023.
Results
Table 1 showed an expansion of both regular CGMS and insulin pump use from 0% to 41.7% and 3.1% to 9.6% respectively from 2017 to 2023. There was significant improvement in HbA1c levels ($P < 0.05$) over the same period. No change in rates of DKA or severe hypogylcaemia was found. In 2023, regular CGM users demonstrated lower HbA1c levels compared to non-users (7.6 ± 1.2 vs 8.4 ± 1.8, $P < 0.05$). HbA1c was also lower among insulin pump users (7.5 ± 1.4 vs 8.0 ± 1.4, $P < 0.05$), with more achieving the target HbA1c $< 7\%$ (44.7% vs 19.8%, $P < 0.05$).
Conclusion
While coverage of diabetes technologies remained much lower than that of many developed countries, utilization has expanded in the past 8 years in Hong Kong. Those who used these technologies had better glycaemic control. With this, policy change to allow broader coverage in children with T1D should be enforced.

Table 1.

Year	No of children with T1D	Regular CGM use (>80% time) (%)	Insulin pump (%)	Average HbA1c (%)	DKA	Severe hypoglycaemia
2017	325	0	3.1%	8.2 ± 1.7	8.3%	1.2%
2018	365	10.4%	5.5%	8.3 ± 1.8	2.5%	0.8%
2019	389	9.5%	6.4%	8.2 ± 1.8	3.1%	2.3%
2020	375	12.8%	7.2%	8.0 ± 1.6	2.4%	2.9%
2021	367	27.7%	6.8%	7.9 ± 1.5	3.0%	0.8%
2022	382	34.6%	7.9%	8.0 ± 1.6	2.9%	1.3%
2023	396	41.7%	9.6%	8.0 ± 1.5	2.8%	2.3%

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EP354

JOINT1876

Early diagnosis of acromegaly in patient with with type 1 diabetes based on glycemic data measured using an advanced hybrid closed loop system

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Introduction
A spectrum of metabolic alterations in acromegaly predisposes patients to diabetes mellitus, with chronic overproduction of growth hormone (GH) induced insulin resistance representing the most significant underlying mechanism.
Aim
We present a comprehensive case report detailing the clinical findings and advanced hybrid closed-loop (AHCL) system data of a female patient with Type 1 diabetes mellitus diagnosed with GH-secreting pituitary adenoma.
Case description
41-year-old female patient with Type 1 diabetes mellitus diagnosed at the age of 13, treated previously with intensified conventional therapy (ICT), was initiated continuous glucose monitor at the age 39 due to poor glycemic control (HbA1C 9.1%), despite adequate dietary compliance and close to normal weight (BMI 25.7 kg/m2). Initially, small improvement in her glycemic control was achieved (insulin need decreased from 0.93 to 0.73 U/kg/day). Throughout one-year glycemic control worsened (insulin need increased to 0.9 U/kg/day, time in range (TIR) decreased from 59 to 40%), and the patient was diagnosed with hypertension. The decision to transition to AHCL system was made, which despite improving glycemic control (TIR:68%), could not decrease insulin need (0.81 U/kg/day). The suspicion of GH-induced insulin resistance, raised based on slight clinical features, was confirmed by elevated level of IGF-1 (784.00 mg/l). Hormonal panel showed intact adrenal, thyroid and gonadal axes and normal prolactin level. GH suppression test using glucose was omitted, instead, GH profiling in an euglycemic state was performed with 2-hour interval measurements for 8 hours that revealed an elevated average GH level of 56,6 mg/l. A pituitary MRI showed a macroadenoma (16x15x14 mm), with a slight protrusion in the left sinus cavernosus (Knosp grade 2). Echocardiography, abdominal ultrasound and colonoscopy revealed no abnormalities. The patient was started on somatostatin analogue therapy and successful pituitary surgery was performed. Pathological examination showed mammosomatotroph pituitary neuroendocrine adenoma with elevated proliferation rate (Ki-67 index 5%). Postoperative GH and IGF-1 levels decreased and glycemic control improved (insulin need decreased: 0,55 U/kg/day, TIR: 73% and HbA1C: 7,5%).
Conclusion
The diagnosis of acromegaly in patients with Type 1 diabetes can often be challenging, early recognition of decreased insulin sensitivity in a previously well-controlled patient and characteristic clinical features are essential for accurate and timely diagnosis.

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EP355

JOINT3480

A 3-year follow-up of a diabetes-nephrology outpatient service for managing patients with type 2 diabetes and chronic kidney disease

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Background and Aims
Diabetic Kidney Disease (DKD) is one of the most common complications of diabetes mellitus (DM) and the leading cause of dialysis worldwide. Previous multidisciplinary approaches have been attempted with varying success. This study aims to assess the results of a three-year diabetes-nephrology outpatient program established at an Italian Research Hospital.
Materials and Methods
A single-centre, retrospective, observational study involving 306 patients with type 2 DM and CKD, who received at least two evaluations in the multidisciplinary service, consisting in simultaneous joint medical visits conducted by a diabetologist and a nephrologist. Anthropometric and biochemical parameters, as well as therapies, were compared between first evaluation (V0) and latest

follow-up visit (V1). Estimated glomerular filtration rate (eGFR) slope was calculated as *(eGFR V1- eGFR V0)/(time of follow-up).*

Results

Of the 306 patients evaluated, 60,5 % had stage G3a-G3b CKD and 58,7% had stage A3 albuminuria according to KDIGO classification. Mean time of follow-up was 27 ± 12 months. Significant improvements between V0 and V1 were seen in BMI (mean BMI at V0 30,5 ± 7,4 vs 29,4 ± 5,4 kg/m^2 at V1, $P<0{,}001$), waist circumference, systolic and diastolic blood pressure, total and LDL-cholesterol (LDL-c V0 93,8 ± 41,2 vs LDL-c V1 70,2 ±34,2 mg/dl, $P<0{,}001$), triglycerides (170,5 ± 124,1 vs 143,1 ± 65,9 mg/dl, $P<0{,}001$), uric acid and HbA1c (mean HbA1c 55,8 ± 12,8 at V0 vs 52,2 ± 11,5 mmol/mol at V1, $P<0{,}001$). In the multivariate regression analysis, greater reduction in HbA1c was associated with higher baseline HbA1c and treatment with glucagon-like peptide-1 receptor agonists (GLP-1 RA). The eGFR showed a significant decline between V0 and V1 (52,3 ± 22,6 at V0 vs 48,6 ± 22,9 ml/min at V1, $P<0{,}001$), with a mean eGFR slope of -2,1 ±7,0 mL/min/1,73m^2/year. Moreover, a significant reduction in urine albumin-creatinine ratio (uACR) was observed from V0 to V1 (median uACR at V0 138,5 [23-554] mg/g vs. 83,5 [20 - 501] mg/g at V1, $P = 0{,}002$). In a multivariate regression analysis, a slower eGFR decline was linked to treatment with sodium glucose co-transporter 2 inhibitors (SGLT2i), while a higher baseline eGFR, greater baseline 24-hour proteinuria and older age were associated with faster eGFR decline.

Conclusions

This study suggests an effective and simply viable model of care for the integrated management of co-morbid type 2 DM and CKD and confirms the central role of SGLT2i and GLP-1 RA in this context.

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EP356

JOINT298

Evaluation of clinical, laboratory and immunological characteristics in the early onset (diagnosed age

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Aims

The classification of early onset (< 30 years old) patients with diabetes mellitus (DM) as either type 1 diabetes (T1D) or type 2 diabetes (T2D) can be a challenge due to their similar overlapping phenotypes. In our present study, we attempted to utilize various clinical and laboratory characteristics in combination with immunological factors in the blood to determine whether it would be possible to distinguish and more accurately characterize our patients as T2D.

Methods

Electronic medical records were evaluated to obtain information categorized as either early onset patients with DM ($n = 102$) and patients with T1D ($n = 89$). Using the stored serum from these patients, autoantibodies of anti-IA2, anti-ZnT8 and anti-GAD were measured

Results

In the clinical characteristics, early onset patients with DM ($n = 102$) were younger (31.7 ± 7.0 years old, $P< 0.01$), more overweight (28.1 ± 5.5 kg/m^2, $P< 0.05$), shorter duration of diabetes (10.4 ± 7.3 years, $P< 0.01$) and a more prevalent family history of diabetes (81%, $P< 0.0$) than patients with T1D. The laboratory values from early onset patients with DM exhibited lower HbA1c (8.0 ± 2.1%, $P< 0.01$) and glucose levels (165 ± 73 mg/dL, $P< 0.01$) with conversely higher C-peptide levels (2.2 ± 1.2 ng/ml, $P< 0.01$). Measurements of immunological factors, demonstrated that the prevalence of anti-ZnT8 (2%) and anti-GAD antibody (2%) in early onset patients with DM was significantly lower ($P<0.01$) compared to patients with T1D (13% for anti-ZnT8 and 38% for anti-GAD). The prevalence of anti-IA2 was not significantly different between early onset patients with DM (13%) versus patients with T1D (11%). In the multivariate logistic regression analysis, C-peptide level (B 4.453, S.E 0.844, Wald 27.808, $P< 0.001$) was the strongest independent factor to distinguish early onset patients with DM as T2D. After adjusting C-peptide level, family history of diabetes (B 0.830, S.E 0.420, Wald 3.909, $P = 0.048$), BMI (B 0.111, S.E 0.039, Wald 8.167, $P = 0.004$) and the relative negative status of anti-GAD (B -2.041, S.E 0.597, Wald 11.670, $P< 0.001$) were determining factors in our analyses.

Conclusions

In this study, our findings suggested that early onset patients with DM may be more accurately diagnosed as T2D if they have a compilation of elevated C-peptide levels, higher BMI, more prevalent history of familial diabetes and the absence of detecting anti-GAD antibodies.

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EP358

JOINT3549

New technologies counteracting genetic errors: a case report

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Introduction

Among the diagnostic criteria for Diabetes Mellitus (DM) is the determination of glycated hemoglobin levels. In addition, it plays a crucial role in the long-term monitoring of diabetic patients, as it has been identified as a significant predictor of chronic complications of the disease. Hemoglobin is a hemoprotein found in red blood cells. Several pathologies can affect this protein, including hemolytic anemias (which may be intrinsic, such as hemoglobinopathies, enzyme defects, membrane disorders, or extrinsic, such as immune/non-immune causes). Thus, the glycated hemoglobin values used for DM monitoring may be altered in the presence of any of these hematological diseases.

Clinical Case

A 46-year-old male was referred from the Primary Care consultation after being diagnosed with type 2 DM. The diagnosis was made incidentally due to elevated fasting blood glucose levels during pre-anesthetic laboratory studies. The reason for referral was the presence of abnormally low glycated hemoglobin levels in relation to the blood glucose levels usually presented by the patient. The patient's personal medical history includes grade 2 obesity, cholelithiasis, hepatic steatosis, and monoclonal gammopathy of uncertain significance. Upon the first evaluation, it was found that the patient's son is being studied for chronic hemolytic anemia and type 1 DM. Given the characteristics of the patient and his offspring, it was decided to rule out any erythrocyte abnormalities in both individuals and to conduct a genetic panel study.

Results

The following analytical results were obtained during the next evaluation:

- Fasting blood glucose of 140 mg/dL, glycated hemoglobin of 4.20%.
- Hemoglobinopathies and enzyme defects were ruled out. A heterozygous mutation in the PIEZO1 gene, c.7367G > A (p. Arg245His), was detected in both the father and the son. This mutation is responsible for the membrane disorder known as hereditary dehydrated stomatocytosis or hereditary xerocytosis. Hereditary xerocytosis arises due to alterations in erythrocyte permeability. It is characterized by chronic hemolytic anemia, primarily due to a slight increase in erythrocyte potassium permeability, leading to dehydration, rigidity, and hemolysis of red blood cells.

Conclusion

In some cases, such as hereditary xerocytosis and other hemolytic anemias, glycated hemoglobin is not useful for routine chronic monitoring of diabetic patients, as its values may be altered. In these cases, as demonstrated in this patient, glucose monitoring systems play a crucial role and serve as an excellent tool for improving the control of diabetic patients.

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EP359

JOINT2106

Blood sugar peaks and valleys: visualizing glucose patterns through world's highest mountains

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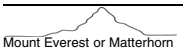
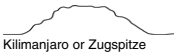
Background and aims
Continuous Glucose monitoring (CGM) has become a standard practice in diabetes diagnostic. The resulting daily blood glucose profiles often resemble mountain landscapes, leading to the use of metaphors such as a "mountain and valley" to describe sharp rises and falls in blood sugar levels. These fluctuations are primarily influenced by dietary choices, activity levels, insulin balance and individual insulin sensitivity or treatment. In our clinical practice, we have observed that visual analogies, such as mountain comparisons, facilitate patients' comprehension of CGM patterns. Notably, terms like "Matterhorn" and "Kilimanjaro" were recalled and referenced by patients in following consultations.
Materials and methods
We analyzed CGM curves, including basic glucose metrics (e.g., glucose variability), daily and meal-related patterns (e.g., fasting, postprandial, and nighttime trends), insulin effects, the influence of physical activity, and the occurrence of hypoglycemia, to identify patterns.
Results
Inspired by the Swiss mountains, our article visualizes the most common blood glucose profile patterns by comparisons with the world's highest and most iconic peaks, which can empower patients to make informed lifestyle and treatment decisions.
Conclusion
This approach underscores the role of CGM as a pivotal tool, transforming abstract data into actionable insights for personalized care. Visual representations can help simplify the complexity of blood glucose patterns, making them more accessible and easier for patients to understand.

Mountain	Description of glucose	Possible causes
 Mount Everest or Matterhorn	Rising throughout the day, especially evening-time and declining at night	Carbohydrate/fast acting insulin imbalance
 Kilimanjaro or Zugspitze	Elevated blood glucose levels persisting throughout the day (plateau-shape)	Carbohydrate-rich diet with insulin imbalance or non-adherence to insulin treatment (e.g. fear of hypoglycemia)
 Mount Watzmann	Elevated blood glucose levels after the evening meal, persisting throughout the night (U-shape)	Carbohydrate/insulin imbalance during the night, e.g. fear of nocturnal hypoglycemia or Intense physical activity during the day
 Three Peaks (of Lavaredo)	Alternating increase and decrease (peak-valley pattern)	Carbohydrate-rich meals, often followed by a rapid decline in blood glucose level
 Mount Fitz Roy or Mount Whitney	No clear pattern or consistency in blood glucose levels	Inconsistent diet or incorrect carbohydrate estimation
 a small hill nearby, e.g. Uetliberg for people from Zurich	stable blood glucose levels	Good diabetes management

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EP360

JOINT919

18p deletion syndrome associated with type 1 diabetes and hashimoto's thyroiditis: a case report on autoimmune disorders and genetic factors

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Introduction
18p deletion, first described by Jean de Grouchy in 1963, is a rare chromosomal anomaly caused by the partial or complete loss of genetic material on the short arm of chromosome 18. This syndrome occurs in approximately 1 in 50,000 live births and exhibits various phenotypic features, including mild to moderate intellectual disability, short stature, speech delay, and facial dysmorphisms. Additionally, this syndrome has been associated with autoimmune diseases such as autoimmune thyroid disorders, rheumatoid arthritis, celiac disease, lupus, and alopecia. However, the molecular mechanisms explaining the connection between 18p deletion syndrome and autoimmunity remain unclear.
Case Report
A 3-year-8-month-old girl presented with complaints of polydipsia and polyuria. Physical examination revealed dysmorphic features, including a round face, broad nasal bridge, long philtrum, hypertelorism, and a short neck. Cardiovascular evaluation detected a 3/6 systolic murmur. Laboratory investigations showed glucose 339 mg/dL, insulin 11.43 mU/l, C-peptide 1.26 ng/mL, HbA1c 9.4%, and positive Anti-GAD and Anti-insulin antibodies. The patient was diagnosed with Type 1 Diabetes Mellitus (T1DM) and insulin therapy was initiated. Further evaluations revealed bilateral sensorineural hearing loss, myopia, IgA deficiency, and subaortic stenosis. At the age of five, epilepsy developed, and antiepileptic therapy was started. Array CGH analysis revealed a 13.7 Mb deletion in the 18p11.32-p11.21 region (arr[hg19] 18p11.32p11.21(148963-13875138)x1). During follow-up, elevated Anti-TPO and Anti-TG antibodies led to the diagnosis of Hashimoto's thyroiditis, and levothyroxine therapy was initiated.
Discussion
18p deletion syndrome is a rare genetic condition with a broad spectrum of clinical features. Common findings include short stature, facial dysmorphisms, intellectual disability, skeletal deformities, and ophthalmologic problems. 18p deletion syndrome is associated with early-onset autoimmune thyroid diseases, T1DM, and other immune system disorders. Genetic analysis highlighted the loss of *PTPN2, PTPRM, ADCYAP1, USP14,* and *LPIN2* genes. *PTPN2* plays a critical role in regulating immune responses, increasing the risk of T1DM and autoimmune diseases. *PTPRM* negatively regulates STAT3 phosphorylation; its loss may lead to increased Th17 cell fractions and accelerated autoimmune processes. *ADCYAP1* protects beta cells from cytokine-induced apoptosis, while *USP14* maintains cellular homeostasis by preventing beta-cell apoptosis. *LPIN2* regulates lipid metabolism and inflammatory responses; its deficiency may cause immune system hyperactivity, triggering T1DM. The loss of these genes has been highlighted as potential mechanisms underlying autoimmunity and diabetes pathogenesis.

Key words
18p deletion syndrome, Type 1 Diabetes Mellitus, Hashimoto's thyroiditis, Autoimmune diseases

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EP361

JOINT3446

Two rare monogenic diabetes cases due to CEL mutations: one with MODY 8 phenotype, one presenting as type 1 diabetes

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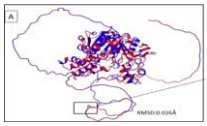
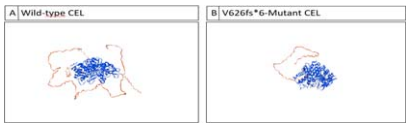
Introduction
Monogenic diabetes accounts for approximately 1-5% of all diabetes cases. Carboxyl-Ester Lipase(CEL) gene mutation-associated diabetes is extremely rare, accounting for less than 1% of all monogenetic diabetes. It is usually associated with MODY-8 but can cause different clinical presentations. CEL mutations can lead to islet cell loss due to defective protein accumulation in the pancreas. While insulin deficiency is expected, the coexistence of T1DM with autoimmune markers is notable. **Case 1:**A 52-year-old male with a 15-year history of diabetes mellitus(DM) and 13 years on insulin therapy presented for blood glucose regulation. His BMI was 23 kg/m^2, and his physical examination was unremarkable. He was on insulin glargine (28 U, OD), insulin aspart (14 U, TID), vildagliptin/metformin (BID), and dapagliflozin(OD). HbA1c was 8.7%, C-peptide 0.77 ng/mL, and Anti-GAD was negative. Other laboratory tests, including hemogram, renal function, and liver function tests, were within normal limits, with no albuminuria. Non-proliferative diabetic retinopathy was detected. His father and six siblings had been diagnosed with DM at a young age. Genetic

analysis revealed a heterozygous CEL(c.1966G>C, p.A656P) mutation(Table 1).
Case 2:A 28-year-old female with T1DM since age two presented for follow-up. Her BMI was 22 kg/m^2, and her physical examination was normal. She was on insulin aspart/degludec(30 U, BID) and insulin aspart(8 U, OD). HbA1c was 9.4%, C-peptide<0.1 ng/mL, and Anti-GAD was elevated(47.5 U/mL), while other diabetes-related autoantibodies were negative. Renal and liver function tests were normal, and the albumin-to-creatinine ratio was 76 mg/day, leading to ramipril(2.5 mg, OD) initiation. No diabetic retinopathy was found. She had no family history of DM. Genetic analysis identified a homozygous frameshift mutation in CEL (c.1876_2039del, p.V626fs*6). The 3D structures of wild-type and mutant proteins were predicted using SWISS-MODEL(Table 2).
Conclusion
Cases of diabetes associated with CEL gene mutations are extremely rare and typically present as a form of diabetes requiring insulin therapy. While these mutations can lead to monogenic diabetes cases associated with MODY-8, their potential association with T1DM, as observed in our second case, suggests a broader clinical spectrum. Increased reporting of monogenic diabetes forms will enhance the recognition of diabetes-associated genes and contribute to a better understanding of its etiopathogenesis.

Table 1: In silico analysis results of CEL c.1966G>C;p.A656P variant

Varyant	Mutation-Tester	SIFT	SIFT Score	PANTHER	AlphaMis-sense	FATHMM
CEL, c. 1966G>C; p.A656P (NM_ 001807.6)	Benign	Uncertain	0.01	Probably Benign Pdel:0.19	likely_ benign Pathogenic score: 0.069	Benign Score: 0.02312

Table 2 3D structures of CEL created using Swiss-Model and visualized with Chimera

	3D structures of CEL
Case 1 CEL c.1966G>C;p.A656P (NM_001807.6)	
Case 2 CEL (c.1876_2039del, p.V626fs*6).	

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EP362

JOINT3793

Frequency of cardiovascular autonomic neuropathy and its association with microvascular complications in states of glucose tolerance abnormalities

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Introduction
Cardiovascular autonomic neuropathy (CAN) is significant cause of mortality and morbidity in diabetic individuals. Postprandial hypotension (PPH) is one of the clinical manifestation of CAN. The aim of study was to explore the frequency of CAN and spesifically PPH in different glucose tolerance abnormality states meeting prediabetes criteria, besides the relationship between CAN, PPH, and diabetic microvascular complications.
Methods
A total of 82 patients who met the criteria for prediabetes according to fasting, random blood glucose or HbA1c levels included in the study. During OGTT, blood pressure and heart rate were evaluated in 0, 10, 20, 30, 45, 60, 75, 90, 105 ve 120. minutes. Resting heart rate and heart rate after inspiration, orthostatic hypotension assessment, ECG recording following Valsalva maneuver, handgrip test were performed for evaluating CAN. One test positivity was accepted possible CAN, while 2 or more test positivity were considered confirmed CAN according to Toronto Consensus Criteria. Microvascular complications were evaluated in all patients.
Results
At least one positive test result was found in all 70 patients performed CAN tests. Of these patients, 8 (11.4%) were diagnosed with possible CAN, while 62 (88.6%) were detected confirmed CAN. Confirmed CAN were detected in 14 (87%) patients with IFG, 25 (96%) patients with IGT, 29 (91 %) patients had both IFG and IGT. Possibly CAN were detected in 2 (13 %) patients with IFG, 1 (4%) patients with IGT, 1 (9 %) patients had both IFG and IGT. The remaining patients were diagnosed with prediabetes based on HbA1c levels. PPH was detected in 27 patients (33.3%) during one or more measurement points of OGTT. This rate was 30%(n =21) among patients who underwent CAN testing. Of patients with PPH, 19 (27%) had confirmed CAN, and 2 (0.2%) had possible CAN. No cases of orthostatic hypotension were observed. Rates of microalbuminuria and peripheral neuropathy were 7.5% and 68.1% in prediabetic patients. The rates were 12.5% and 57% in possible CAN patients, while they were 6.7% and 71% in patients with confirmed CAN. No cases of diabetic retinopathy were observed.
Conclusions
Microvascular complications can develop in prediabetic state. CAN and PPH can be frequently observed in different glucose tolerance abnormalities. As part of routine evaluation in prediabetic patients, screening for CAN, PPH, and microvascular complications should be implemented.

	Possibly CAN n =8		Confirmed CAN n =62	
	n	%	n	%
IFG (n =16)	2	13%	14	87 %
IGT (n =26)	1	4 %	25	96 %
IFG & IGT (n =11)	1	9 %	10	91 %

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EP363

JOINT1613

Type 2 diabetes was linked to asthma: a meta-analysis

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Background and Objectives
Asthma and diabetes pose major global health concerns. While the link between asthma and type 1 diabetes is well-documented, the connection between asthma and type 2 diabetes (T2DM) remains less explored. Recent findings suggest that this relationship is more intricate than previously believed, extending beyond the conventional T-helper 1/2 paradigm. This systematic review and meta-analysis aimed to examine the association between asthma and T2DM, as well as to explore potential contributing factors and mechanisms.
Methods
A comprehensive literature search was performed across four databases up to October 31, 2013, to identify studies investigating the relationship between asthma and T2DM. Studies that did not specify the type of diabetes were excluded. Data on disease risk, including event counts and odds ratios (ORs), were extracted and analyzed using meta-analysis techniques. Pre-specified analyses included subgroup analysis, meta-regression, sensitivity analysis, and dose-response analysis.
Results
Fourteen studies, encompassing a total of 17 million participants, were included in the analysis. A bidirectional association between asthma and T2DM was observed ($P<$ 0.01), suggesting potential shared pathological mechanisms. The presence of hypertension and dyslipidemia may partially mediate this relationship. Additionally, asthma severity, rather than disease duration, was linked to an increased risk of T2DM (P = 0.01) in a dose-dependent manner. Sensitivity analyses confirmed the robustness of these findings.
Conclusions
This study identifies a reciprocal association between asthma and T2DM, emphasizing the need for early screening and preventive interventions for one condition when the other is diagnosed.

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EP364

JOINT41

Treatment of hyperuricemia as an option for slowing the progression of diabetic nephropathy

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Introduction
Diabetic nephropathy is the main cause leading to end-stage renal disease. Uric acid may play a role as the underlying cause of diabetic nephropathy. The serum level of uric acid is also a risk factor for cardiovascular disease and atherosclerosis. It's a complex interplay among hyperuricemia, diabetes melitus and the progression of diabetic nephropathy. Our aim is to evaluate allopurinol effects on proteinuria in diabetic patients with nephropathy.
Material and methods.
80 patients with type 2 diabetes mellitus and incipient diabetic nephropathy were included. 40 patients were randomized to receive allopurinol (100 mg/d) and 40 were randomized to receive placebo. Administration of antihypertensive and renoprotective drugs (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) continued for both groups, without changes in dosage. Proteinuria was compared at baseline, 2 and 4 months among the two groups.
Results
Each group consisted of 19 men and 21 women. After four months of treatment, serum levels of uric acid ($P = .02$) and 24-hour urine protein ($P = .049$) were significantly lower in the patients on allopurinol treatment, compared with the control group.
Conclusions
Treatment with hyperuricemia can reduce severity of proteinuria. So, it's important to use them as an adjuvants cost-effective therapy for patients with diabetic nephropathy.

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EP365

JOINT743

Main epidemiological indicators of diabetes mellitus among the urban population on the example of Minsk (2014–2024)

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Aim
To assess the dynamics of the prevalence of DM among the Belarusian urban population in the period 2014-2024.
Materials and methods
Data from the official statistics of the Ministry of Health of Belarus and demographic indicators were the subject of the study.
Results
The prevalence of diabetes increased from 2296.4 cases in 2014 to 4588.6 cases per 100,000 population in 2024. The average annual increase in DM prevalence was 7.6% (type 1 DM - 4.1%, type 2 DM - 7.9%). The primary incidence of diabetes was 202.7 - 416.0 cases per 100,000 population, of which T1DM: 9.0 - 11.0, T2DM: 196.4 - 405.0 cases per 100,000 population. The average annual increase in the primary incidence of diabetes was 8.3% (T1DM - 2.9%, T2DM - 8.4%). The increase is the result of active measures to diagnose T2DM in at-risk groups. Gender characteristics: T2DM is 1.9 times more common in women than in men, in people with T1DM was the same for both sexes, other types of diabetes are 2.7 times more common in men. Diabetes affects 5.6% of the adult population of Minsk, a figure in line with WHO projections. The proportion of working-age people was on average 87% among those with T1DM, 21% among those with T2DM, and 75% among those with other types of diabetes. On average, 3.7% of people with DM die each year, and 92.3% of these deaths occur in people over working age. The leading cause of death was cardiovascular disease: DM1 - 49.0% of deaths, DM2 - 67.9%. Malignant neoplasms came second: 5.5% of deaths in T1DM and 14.9% in T2DM. The proportion of deaths due to complications of DM, including emergencies, was less than 0.1%.
Conclusions
The above data indicate that the quality of medical care, availability of antihyperglycaemic drugs, including insulin, and means of self-control ensure a low mortality rate from diabetes mellitus, but at the same time emphasise the need for management decisions on the prevention of cardiovascular pathology and early detection of malignant neoplasms.

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EP366

JOINT3822

The transition phase and glycemic control: insights from 100 patients study

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Introduction
The transition period from pediatric to adult diabetology is particularly critical. Transferring care to adult services is often associated with a deterioration in glycemic control. We aimed to assess glycemic control among type 1 diabetics during this transition phase.
Patients and Methods
This was a retrospective descriptive study involving 100 type 1 diabetic patients initially followed in pediatrics before transitioning to the endocrinology-diabetology department at CHU Ibn Rochd. Data were collected on glycemic balance, follow-up regularity, and treatment adherence at the time of transition and afterward, from January 2021 to September 2024. Statistical analysis was performed using IBM SPSS software.
Results
The average age of our patients was 16 years (range: 14 to 18), with a female predominance (56%). The duration of diabetes was approximately 5 years, and the transition occurred at an average age of 14 years. Transition announcements were made by pediatricians for all our patients. The interval between referral and the first consultation was less than three weeks. Patients attended an average of 3.3 consultations per year at the start of the transition, and 2.1 consultations per year afterward. All patients were on a basal-bolus insulin regimen, with 14% using human insulin and 86% using insulin analogs, and performed approximately four capillary blood glucose tests per day. the average Hba1c was 10.1% before the transition and 9.23% afterward ($P < 0.001$). Nine patients were hospitalized for diabetic ketoacidosis due to treatment discontinuation after the transition. Regarding degenerative complications, 11 patients exhibited diabetic retinopathy at the time of transition.
Conclusion
The transition from pediatric to adult diabetology is a critical phase for type 1 diabetic patients. Our study highlights a decline in medical follow-up. However, the observed reduction in HbA1C levels demonstrates the potential for modest improvement. These findings underline the need to strengthen support and coordination between pediatric and adult services to improve clinical outcomes and the quality of life of young patients.

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EP367

JOINT3740 Glycemic control in type 1 diabetes patients transitioning from pediatric to adult care

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Introduction and Objective
The transition of adolescents with Type 1 Diabetes Mellitus (T1DM) to adult Endocrinology services coincides with significant personal changes. Interstitial glucose monitoring is a key tool for diabetes management. This study aims to evaluate metabolic control in adolescents after transitioning to adult endocrinology follow-up.
Materials and Methods
A descriptive observational study was conducted on patients aged 14–18 years who had at least one data download in 2024 while under follow-up at the General Endocrinology outpatient clinic of Hospital Universitario Clínico San Cecilio (Granada). Anthropometric variables, treatment characteristics, and disease control parameters (glucometry and HbA1c) were analyzed. Statistical analysis was performed using SPSS v.15.

Results
A total of 35 patients with T1DM were included, 54.3% male, with a mean age of 16.2 ± 1.4 years. All were on basal-bolus insulin therapy (1 ± 0.4 U/kg), with a mean disease duration of 7 ± 4.2 years. The mean follow-up period was 9.7 ± 8.2 months. Mean BMI was 22 ± 3.4 kg/m^2, and mean HbA1c was 7.9 ± 1.6%. The average insulin sensitivity factor was 33 ± 20.6. The mean time in range (TIR) was 51%, time above range (TAR) 44%, and time below range (TBR) 5%. The mean coefficient of variation was 40.2 ± 7.5%, with a Glucose Management Indicator (GMI) of 7.5 ± 1%. The mean number of daily sensor readings was 10 ± 2, with an average sensor activity rate of 76 ± 20%. Three patients experienced one or more episodes of severe diabetic ketoacidosis requiring hospitalization and intensive care unit (ICU) admission since starting follow-up.
Conclusions
This study highlights suboptimal metabolic control in T1DM patients transitioning from pediatric to adult care. The creation of specialized transition units could improve metabolic outcomes and prevent complications in this population.

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EP368

JOINT507

Early-onset diabetic neuropathy in a teenager with brittle type 1 diabetes: a case report

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Introduction
Diabetic neuropathy (DN) is one of the most common complications of diabetes, affecting approximately 50% of patients, typically after 5 years of type 1 diabetes (T1DM). DN is associated with increased risks of falls, fractures, amputations, high economic costs, and a significant reduction in quality of life.
Case Presentation
We report the case of a 17-year-old male diagnosed with brittle T1DM 4 years ago. His diabetes has been poorly controlled, with frequent hospitalizations due to diabetic ketoacidosis and recurrent severe hypoglycemic episodes. Contributing factors include recurrent infections, lipodystrophy at insulin injection sites, and psychological factors such as denial of the disease and treatment non-adherence. His HbA1c was 17%. The patient presented with paresthesia in all four limbs, scoring 4/10 on the Douleur Neuropathique 4 (DN4) questionnaire. Neurological examination revealed errors on the monofilament test, indicating neuropathy, though there were no significant sensory or motor deficits. Electromyography (EMG) confirmed early-stage sensory-motor axonal neuropathy with conduction blocks and bilateral carpal tunnel syndrome. No other diabetes-related complications, such as retinopathy, were detected. Other causes of neuropathy, including vitamin B12 deficiency, thyroid dysfunction, and renal failure with electrolyte imbalance, were excluded. Symptoms significantly improved with optimized glycemic control and the initiation of amitriptyline (10 mg/day).
Discussion
According to Yoon Hi Cho *et al*., approximately 16% of patients with newly diagnosed T1DM within 2 to 5 years develop diabetic neuropathy. Hyperglycemia is the primary risk factor for DN, and both the duration of diabetes and poor glycemic control contribute significantly to nerve damage. Additionally, the neurotrophic action of insulin is deficient even in the early stages of T1DM, contributing to the development of neuropathy. Maintaining rigorous glycemic control from the onset of diabetes is essential to prevent or delay the development of neuropathic complications.
Conclusion
Early screening for diabetic neuropathy should be considered even in patients with recent-onset T1DM, as early intervention with glycemic optimization and symptomatic treatment can improve outcomes and prevent further complications.

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EP369

JOINT211

Ultrasound monitoring for chemotherapy complications in diabetic patients

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Background and Aims
Chemotherapy often induces complications in multiple organs, necessitating early detection to optimize therapy and improve patient outcomes. However, assessing the structural and functional conditions of organs like the pancreas, kidneys, thyroid, nerves, and colon remains challenging. Multiparameter ultrasound (US) shows promise in providing precise information during cancer diagnosis and treatment. This study aimed to assess US utility in detecting complications early among diabetic patients undergoing chemotherapy.
Methods
We included 12 diabetic and 10 non-diabetic patients undergoing chemotherapy. Routine clinical and laboratory tests, along with multiparameter abdominal US, were performed weekly. Assessments included colonic wall thickness, peristaltic waves, Doppler spectral analysis of mesenteric blood flow, bile duct measurements, and evaluations of the liver, kidneys, pancreas, thyroid, and nerves.
Results
Key observations included:

1. **Pancreas**: Six patients showed increased pancreas size and two developed hypoechoic lesions within the first week. Pancreatic size decreased later (after 3 weeks), with one patient diagnosed with pancreatitis.
2. **Kidneys**: Early signs included elevated resistive index (RI) and increased parenchymal thickness, though velocities remained normal.
3. **Thyroid**: Three patients exhibited hypoechoic heterogeneous textures, while two showed reduced thyroid size by weeks 2-3.
4. **Colon**: Diabetic patients showed less colonic wall thickening (3-6 mm) versus controls (7-8 mm) and reduced peristalsis. Mesenteric Doppler revealed higher peak systolic velocities (up to 200 cm/sec) in diabetics compared to controls (140-170 cm/sec).
5. **Neuropathy**: Three patients presented with numbness in limbs. US revealed increased fascicle diameters (1.5-2.5 mm).

Conclusions
Multiparameter US markers provide critical insights into early chemotherapy-related complications across various organs, enabling timely therapy adjustments and improved prognosis. Monitoring with US is particularly effective for diabetic patients, revealing distinct changes and enhancing clinical care.
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EP370

JOINT300

A rare case of MODY12 (ABCC8 Mutation) presenting with both congenital hyperinsulinism and maturity onset diabetes of the young

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Background and Aim
MODY 12 (Maturity-Onset Diabetes of the Young, type 12) is a rare form of monogenic diabetes caused by mutations in the ABCC8 gene. The current report describes the case of a young patient diagnosed with Type 1 Diabetes, who experienced prolonged intervals of hyperglycemia alternating with episodes of hypoglycemia and vice versa. Further investigation through genetic testing identified a heterozygous (HG38, chr11:17394379C>T, c.4432G>A) mutation in exon 37 of the ABCC8 gene, leading to the p.(Gly1478Arg) variant. The aim of the report is to show the difficulties and uncertainty of the management and treatment of patients with such clinical presentations.
Case Presentation
A 13-year-old Caucasian male, presented to the Emergency Department, with complaints of polyuria, polydipsia, and nocturia last 30 days. He also reported a weight loss of about 10 kg, current weight was 57kg (SDS = +0,96). HbA1c was 8.2%, fasting glucose was 19mmol/l, C-peptide was 1.48ng/ml (normal = 1.1-4.4), antidiabetic antibodies were negative. The patient was initially diagnosed with type 1 diabetes with ketosis and subcutaneous insulin-therapy started with total of 0.105 units/kg of rapid-acting insulin. During next several years he stopped insulin-therapy and initiated again 2-3 times per year due to ketosis. After approximately four years the patient began experiencing frequent episodes of

hypoglycemia, with blood glucose levels dropping as low as 2.0mmol/l without insulin injections, alternating with periods of hyperglycemia. Continuous alternation between hyperglycemia and hypoglycemia, prompted a genetic test. Since opportunities for genetic testing are limited in our country, the patient underwent testing abroad, in Moscow. In the ABCC8 gene (NM_000352.6), a heterozygous variant HG38, chr11:17394379C>T, c.4432G>AHG38, chr11:17394379C>T, c.4432G>AHG38, chr11:17394379C>T, c.4432G>A was identified in exon 37, resulting in the amino acid substitution p.(Gly1478Arg) p.(Gly1478Arg)p.(Gly1478Arg), with a sequencing depth of 225x (rs72559715rs72559715rs72559715). This variant has been previously reported as pathogenic in patients with autosomal dominant congenital hyperinsulinism and autosoma ldominant ABCC8-associated diabetes (MODY 12) (PMID: 19475716, 30098243, 30977832, 32928245). Now, the patient is 21 years old and experiences hypoglycemic episodes approximately 7–8 times per year without receiving any specific treatment.

Discussion

Current case highlights the diagnostic and clinical challenges associated with rare conditions, particularly in countries like Armenia, where access to genetic testing is limited. On the other hand, due to the lack of precise guidelines for the treatment and management of such patients, they could be misdiagnosed with other types of diabetes and receive inappropriate management.

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EP371

JOINT3808

From group to individual: how paediatric diabetes education is changing in the era of technology

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Objective

Has the focus on technology in diabetes care influenced the type and frequency of diabetes education programs for children and adolescents with type 1 diabetes (T1D) in Germany and do we see general differences in age and sex regarding the participation of educational programs over the last years?

Methods

This analysis is based on data from the German DPV registry (status of 03/2024), including 42,975 paediatric patients with T1D aged 0–18 years from 364 centres in Germany. Patients with a diabetes duration of <6 months and those from centres without documented education were excluded (<1%). The frequency and type of education for multiple age groups and sexes were analysed for 2010–2023 using multivariable regression models to assess temporal trends (SAS 9.4, SAS Institute Inc., USA).

Results

International guidelines recommend regular education every 2 years. However, only 54.7% of patients attended structured diabetes re-education programs within five years after diagnosis. Those with belated re-education showed higher HbA1c levels across all groups. While the frequency of individual education remained relatively stable over time, with a temporary decrease during the pandemic, the group education programs significantly declined from 46.4% (2015) to 28.9% (2020) and could only slightly recovery to 31.3% in 2023 ($P<$ 0.0001 respectively). Adolescents >12 years (46.3%) were less likely to receive education than families of younger children <6 years (56%, $P<0.0001$). Girls (56.8%) participated in educational programs more frequently than boys (52.8%, $P<0.0001$). Their attendance in group education was also significantly higher ($P<0.0001$). The share of patients receiving individual insulin pump training increased from 36.6% (2015) to 51.0% (2023), reflecting the growing role of technology in diabetes management and need for resources in clinics and doctors' offices.

Conclusion

Diabetes education for children and adolescents with T1D has undergone visible changes in recent years. There is a shift towards more individual and technology-focused education, requiring more personnel and neglecting the essential understanding of basics and personal development with T1D. Later re-education showed associations with higher HbA1c. Where younger children and girls received more structured diabetes education, adolescents and boys participated less frequently. Additionally, with the substantial decline in group education children lose secondary benefits like peer contact. These disparities highlight the need for targeted strategies to ensure adequate education for all. Innovative approaches, such as the "GaDiaKi" program for group education and telemedicine-based interventions, may help address these gaps and improve long-term diabetes care.

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EP372

JOINT812

Donohue syndrome: three case studies illustrating clinical heterogeneity and management challenges

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Three cases of Donohue syndrome, a rare disorder of severe congenital insulin resistance due to INSR gene mutations, are presented. All patients exhibited severe intrauterine growth restriction (IUGR), failure to thrive (FTT), dysmorphic features, extremely high insulin and C-peptide levels at birth.

Case 1

A 7-month-old male infant had metformin initiated at 50 mg/kg/day at three weeks. He developed severe hypertrophic cardiomyopathy, requiring beta-blocker therapy, and was treated with ursodiol for cholestatic liver disease. Frequent enteral feedings enriched with polycose via gastrostomy were provided to prevent hypoglycemia. Continuous glucose monitoring (CGM) indicated 80% time in range (55-180 mg/dL), 18% above range (>180 mg/dL), and 2% below 55 mg/dL. Last measured length and weight SDS were -5.0 and -4.0, respectively. Despite treatment, he died at seven months, with a hypoglycemia episode near the time of death.

Case 2

A 13-month-old female infant had metformin initiated at 50 mg/kg/day at one month, along with continuous PZ feedings and MCT oil due to recurrent hypoglycemia. The CGM was unreliable, and metformin did not improve HbA1c or C-peptide levels, leading to its discontinuation. Liver dysfunction with cholestasis and synthetic impairment was treated with ursodiol, vitamin K, and ADEK. She experienced ovarian torsion at six months, hyperandrogenism, respiratory distress managed with Vapotherm, nephrocalcinosis, and difficulty to mange central hypothyroidism. Current length SDS is -5.0, weight SDS is -4.5.

Case 3

A 21-month-old female infant had metformin started at 40 mg/kg/day at one month, with recombinant IGF-1 (0.2 mg/kg/day) added at 11 months. Glycemic control improved: 84% time in range 55-180 mg/dL, yet growth parameters remained poor (weight -9.8 SDS, length -5.5 SDS). Current IGF-1 levels are measurable, and C-peptide levels have decreased, but insulin levels remain extremely high. She presented with enlarged ovaries, hyperandrogenism, cardiomyopathy (beta-blocker treated), restrictive lung disease requiring ventilation, and well-managed central hypothyroidism.

Differences

While all patients exhibited significant challenges, the specific manifestations and responses to treatment varied. Case 1 presented cardiac complications earlier and had a fatal outcome. Case 2 involved significant liver dysfunction. Case 3 demonstrated some improvement in glucose control using multiple treatments, but persistent growth failure, and respiratory difficulty.

Conclusion

Donohue syndrome presents significant diagnostic and therapeutic challenges. The variability in presentation and treatment response underscores the need for individualized management, close monitoring, and multidisciplinary care. Further research into this rare syndrome is crucial for improving outcomes and understanding its pathophysiology.

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EP373

JOINT1661

Impact of smoking and physical activity on cardiovascular outcomes in type 2 diabetes with metabolic dysfunction-associated steatotic liver disease: a nationwide study

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Background
This study investigated the effects of smoking and regular physical activity (PA) on the risk of composite cardiovascular disease (CVD) outcomes in type 2 diabetes mellitus (T2DM) patients across different steatotic liver disease (SLD) categories.
Methods
We used a health examination database from 2015 to 2016, with follow-up data for 1,921,310 patients aged 20 years and older with T2DM. Participants were categorized based on SLD status where hepatic steatosis was defined as a fatty liver index (FLI) $\geq$ 30. Cox analyses were used to analyze the association between smoking, regular PA and the risk of composite CVD event, myocardial infarction (MI), ischemic stroke, and cardiovascular mortality.
Results
Among current smokers in each SLD group, the adjusted hazard ratios (HR) for composite CVD events significantly increased from no steatosis to metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-related steatotic liver disease (MetALD), and alcohol-related liver disease (ALD), with the highest HR observed in ALD (aHR, 2.14; 95% CI, 2.04–2.24). The ALD group without regular PA had the highest risk of composite CVD event (aHR, 1.33; 95% CI, 1.28–1.38). The highest risk of composite CVD event was found among current smokers without regular PA, with the aHR increasing in a stepwise manner from no steatosis to MASLD, MetALD, and ALD, the latter showing the highest (aHR, 2.67; 95% CI, 2.53–2.82).
Conclusion
Smoking and physical inactivity significantly increase CVD risk in T2DM patients, with the highest risk observed in the ALD group, underscoring the need for targeted lifestyle modifications, including smoking cessation, regular PA, and alcohol abstinence, to reduce CVD risk in this high-risk population.

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EP374

JOINT319

Yellowish appearance - an unusual presentation of type 1 diabetes mellitus in children

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Type 1 diabetes mellitus (T1DM) in children is commonly associated with other autoimmune diseases, especially coeliac disease and autoimmune thyroiditis. Autoimmune hepatitis (AIH) is rare among patients with type 1 diabetes with a reported prevalence of 3.8%. However, none has been reported to present with acute liver failure with hyperglycaemia prior to diagnosis. We describe a case of 9-year-old girl developed icterus with acute liver failure and incidental finding of asymptomatic hyperglycaemia (lab glucose 20 mmol/l and ketone of 0.1 mmol/l) at presentation. Her initial laboratory investigations revealed hyperbilirubinaemia (179μmol/l) which consisted mainly of conjugated bilirubin (156μmol/l) with raised liver enzymes (aspartate aminotransferase (212IU/l), alanine aminotransaminase (248IU/l) and gamma-glutamyl transferase (132IU/l)). Furthermore, coagulation profile was found to be deranged with a prothrombin time of 34.2s and INR of 2.71, fulfilling the Paediatric Acute Liver Failure (PALF) study group definition of acute liver failure. Concurrently, her HbA1C was raised at 6.8% with positive T1DM autoantibodies for Anti Glutamic Acid Decarboxylase (> 280,000IU/ml), Anti Islet Cell (75.31 IU/ml) and Anti Insulinoma Associated Antigen 2 (5.801IU/ml) confirming a diagnosis of T1DM. Interestingly, she has a normal random C-peptide (703pmol/l) and insulin (301pmol/l) at presentation prior to the initiation of insulin therapy. However, a repeated c-peptide showing a rapid drop to a low level after 6 weeks. Her subsequent investigations fulfilling the scoring list for autoimmune hepatitis issued by the International Autoimmune Hepatitis Group (IAIHG), leading to a definite diagnosis of AIH. She responded well to prednisolone (2mg/kg/day) and azathioprine, leading to a normalisation of her co-agulation profile. However, she required a daily insulin dose up to 2.8unit/kg/day to achieve a good glycemic control during her treatment period. This leads to an improvement of her HbA1C down to 5.8% after 6 weeks. Screening of other associated autoimmune diseases were negative (Normal thyroid function tests with negative thyroid peroxidase antibodies, anti-endomysium and anti-tissue transglutaminase antibodies) In summary, we have presented the case of a 9-year-old girl developed T1DM and AIH at the same time. Although patients with T1DM commonly present with polyosmolar symptoms or diabetic ketoacidosis at diagnosis, our case illustrate that severe AIH can occurs at presentation of T1DM in children. Therefore, there should be a high index of suspicion for other rare forms of autoimmunity in children with T1DM.

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EP375

JOINT1602

Neonatal diabetes mellitus in a boy with wolfram-like syndrome

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Introduction
Wolfram syndrome is a rare progressive neurodegenerative disorder caused by a recessive mutation in the WFS1 or WFS2 gene, typically characterized by diabetes mellitus and optic atrophy. Other symptoms include AVP deficiency and hearing loss. Wolfram-like syndrome is caused by an autosomal dominant mutation in the WFS1 gene and characterized by congenital hearing loss, optic atrophy and diabetes mellitus. We describe a case of a boy with Wolfram-like syndrome.
Case report
The boy was born after 38 weeks and 5 days gestation, weighing 2270grams (< -2SD) with multiple dysmorphic features. He had hearing loss and vision impairment. Genetic testing (5GPM) revealed a heterozygous pathological variant c.2425G>A/p.Glu809Lys located in exon 8 of the WFS1 gene. This mutation has been previously reported in 5 different children who developed diabetes mellitus at a very young age; ranging from the age of 3 months to 3 years. At the age of 4 months, after correction of clubfeet, a high glucose of 23mmol/l was measured without ketoacidosis or other symptoms of hyperglycemia. He started on a low dose of insulin detemir with a glucose sensor and after a few days the treatment was changed to subcutaneous insulin via a pump at a dose of 0.4U/kg/day, allowing for his discharge. After 14 days the glucose suddenly increased and remained high continuously. Despite receiving extra insulin glucose levels could not be controlled. He was restless and readmitted again. A few days later he experienced a general convulsion. Despite the administration of anti-epileptic drugs he continued to show epileptic activity on EEG. He was switched to intravenous insulin and the dose had to be increased to about 2U/kg/day to control his glucose levels. Unfortunately, at the age of 5 months the boy died due to severe epileptic encephalopathy following therapy resistant epileptic activity.
Conclusion
Patients with Wolfram-like syndrome can develop diabetes mellitus before the age of 6 months. Glucose levels should be evaluated regularly.

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EP376

JOINT2563

Type 1 diabetes, SARS-CoV-2 and vitamin D3

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The aim of the study was to assess the relationship between vitamin D3 concentration and the titer of anti-SARS-CoV-2 IgG antibodies in type 1 diabetes children (T1D).
Methods
Between June 1, 2021 and June 1, 2024, a cross-sectional study was conducted among T1D children. The control group consisted of children without carbohydrate metabolism disorders and autoimmune diseases. The titer of anti-SARS-CoV-2 IgG antibodies, the concentration of 25(OH) vitamin D3 and

HbA1c were determined. Vitamin D3 deficiency was diagnosed if <30 ng/ml, and anti-SARS-CoV-2 IgG seropositivity if ≥ 7.1 BAU/ml.
Results
The study group included 232 children (122 boys), 196 people with diabetes, aged 12.5 $\pm$ 4.0 years, in whom a total of 289 tests were performed (in 51 T1D children test was performed $\geq$twice). The median 25(OH)D3 concentration was 26.6 [IQR = 15.6] ng/ml and did not differ depending on gender, diagnosis of T1D or co-occurrence of other diseases ($P > 0.05$). Vitamin D3 deficiency was diagnosed in 178 children (61.6%). The concentration of 25(OH)D3 was lower in the group of children with new T1D (Me = 21.8 [IQR = 9.5] ng/ml), compared to long-lasting T1D (Me = 27.75 [IQR = 17, 2] ng/ml) and in the controls (Me = 28.3 [IQR = 18.6] ng/ml), $P = 0.0093$. Anti-SARS-CoV-2 IgG Ab seropositivity reached 95.5%, median titer was 307.2 [IQR = 624.8] BAU/ml, did not differ depending on gender, vitamin D3 supplementation and vaccination ($P > 0.05$), as well on the co-occurrence of other diseases ($P > 0.05$). In T1D, the anti-SARS-CoV-2 IgG Ab titer was higher than in the controls (Me = 328.7 [IQR = 677.4] BAU/ml vs. Me = 169.4 [IQR = 402.6] BAU/ml), $P = 0.0130$. The Ab titer in new T1D (Me = 122.0 [IQR = 559.4] BAU/ml) was lower compared to the long-lasting T1D (Me = 359.7 [IQR = 678.6] BAU /ml) and controls, $P < 0.0001$. There was a correlation between anti-SARS-CoV-2 IgG Ab and age (R = 0.3359, $P < 0.0001$) and HbA1c and 25(OH)D3 (R = -0.3267, $P < 0$, 0001). Children seronegative for SARS-CoV-2 ($n = 13$, 5.6%) were younger (7.4 $\pm$ 5.4 years vs. 12.6 $\pm$ 3.9 years), $P = 0.0241$, 25 (OH)D3 (Me = 25.9 [IQR = 114.7] ng/ml vs. Me = 26.6 [IQR = 16.2] ng/ml) and HbA1c (Me = 8.0 [IQR = 6).6] % vs. Me = 7.3 [IQR = 2.5] %) were comparable to AntiSARS-Cov2(+).
Conclusions
In children with type 1 diabetes, the titer of anti-SARS-CoV-2 IgG antibodies did not depend on the concentration of vitamin D3, however, in the group of children with the lowest 25(OH)D3 concentration, the titer of IgG anti-SARS-CoV-2 antibodies was also lowest. Lower titers of these antibodies in younger children indicate a weaker immune response in this group. Vitamin D3 deficiency occurring in the majority of respondents indicates the need for its systematic supplementation.

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EP377

JOINT1171

Technological implementation and evolution of metabolic control in pediatric T1D patients: "real life experience"

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The technological advances in the treatment of pediatric patients with Type 1 Diabetes (T1D) facilitate metabolic control. The ISPAD in 2018 and the ADA in 2020, proposed reaching an HbA1c $<7\%$ as a goal. Basque Country (November 2017), the first autonomous community at Spain to approve continuous glucose monitoring (CGM) systems for pediatric T1D patients.
Objective
To know the evolution of metabolic control in T1D patients in a tertiary hospital and its possible relationship with the implementation of technologies. To compare two samples exploiting data exported in 2019 and 2023 from the SWEET registry(*) and the mean Hba1c with that published in our department prior to technological implementation (AvDiabetol.2014;30:82).
Patients and methodology
$n = 170$ patients in 2023. Variables: age, sex, age at T1D onset, time of evolution, insulin therapy regimen, use of CGM systems, DKA at onset, HbA1c, time in range(TR) and associated comorbidity. Results were compared with another cohort controlled in 2019 ($n = 141$) and the mean HbA1c with that previously published in 2000 ($n = 82$), 2008 ($n = 76$) and 2013 ($n = 106$).
Results
2023 cohort $n = 170$, data in Table 1. Subgroup with AID system ($n = 49$) are younger, younger age at onset and better HbA1c (7.04% $\pm$ 0.6 vs 7.4% $\pm$ 0.9). The subgroup with DKA at onset ($n = 87$) has a longer time of evolution and worse metabolic control (7.47% $\pm$ 0.98 vs 7.12% $\pm$ 0.76). **Comparison cohort 2023 and 2019**: The proportion of CGM and AID systems use is higher in 2023, no change in the rest of the variables (Table 1).
HbA1c evolution Mean HbA1c at years 2019 and 2023 is lower than reported in the 3 cohorts studied (8.2% vs 7.9% vs 7.8%; years 2000, 2008 and 2013).
Conclusions
The use of AID system is associated with improved metabolic control, being the DKA at onset a risk factor for not achieving it. Technological implementation is associated with an improvement in HbA1c. Metabolic control is acceptable at present, can still be optimized.

Table 1. Student's t-test for quantitative variables, chi-square for qualitative variables. Statistical significance level $P < 0.05$.

Descriptive	2019($n = 141$)	2023($n = 170$)	p
Age at onset(years)	6.9 $\pm$ 3.9	6.5 $\pm$ 3.7	ns
Age at the consultation(years)	12.8 $\pm$ 4.5	12.1 $\pm$ 4.2	ns
Evolution time(years)	5.8 $\pm$ 4.3	5.5 $\pm$ 3.9	ns
HbA1c(%)	7.4 $\pm$ 1.03	7.3 $\pm$ 0.8	ns
Insulin dosage(UI/kg/día)	0.83 $\pm$ 0.3	0.75 $\pm$ 0.26	$P = 0.006$
Sex(% female)	44.7	45.3	ns
DKA at onset (severe) (%)	49(7.8)	51(7.6)	ns
Proportion using AID systems(%)	14	29	$P = 0.002$
Proportion using CGM systems(%)	77	91	$P < 0.001$

*SWEET registry (*Better control in Pediatric and adolescent diabeteS: Working to crEate cEnTers of reference*)

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EP378

JOINT194

Lada diabetes in older patients: clinical diagnostic implications of imaging and laboratory biomarkers

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Introduction
Latent autoimmune diabetes in adults (LADA) is a hybrid form of diabetes often misdiagnosed as type 2 diabetes mellitus (T2DM) in older adults. Early and accurate diagnosis of LADA is critical for effective management and prevention of complications. Ultrasound (US) has emerged as a valuable tool for stratifying patients with LADA by assessing metabolic and structural changes in associated organs [1-4].
Materials and Methods
We evaluated 10 cases of LADA treated at an endocrinology clinic (age 56–70 years, 6 females). Clinical and laboratory assessments included:
- Measurement of glutamic acid decarboxylase antibodies (GAD-Ab) and islet cell antibodies (ICA-Ab).
- Abdominal ultrasound (2–10 MHz convex probe) to assess multiparameter features of the kidneys, pancreas, and liver.
- Doppler ultrasound, shear wave elastography (SWE), and quantification of visceral fat (VF) and subcutaneous fat (SF) thickness and areas.

Results
- All patients had increased antibody levels, with positive GAD-Ab and ICA-Ab confirming LADA.
- Treatment with anti-inflammatory agents led to improved glycemic control and normalization of laboratory parameters.
- US findings included:
  - Pancreatic hypoechoic loci in all patients.
  - Signs of autoimmune thyroiditis in 6 patients, with corresponding US changes.
  - Altered liver parenchyma attenuation and abnormal renal Doppler flow in a subset of patients.
- Body composition analysis revealed overweight in most cases, one patient was underweight, and visceral fat accumulation was prominent.

Conclusion
A comprehensive diagnostic approach integrating imaging and laboratory biomarkers is essential for stratifying LADA in older patients. Ultrasound techniques such as SWE and Doppler imaging provide valuable insights into metabolic and structural organ changes, supporting tailored therapeutic strategies to optimize glycemic control and manage comorbidities.
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EP379

JOINT259

Evaluating the reach of hellotype1: a digital innovative educational platform in regional languages for diabetes education in southeast asia

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Background
Amidst the pandemic in 2021, HelloType1.com was developed by Action4Diabetes (A4D), a non-governmental organization collaborating with local healthcare professionals in Southeast Asia, as an innovative digital educational platform for Type 1 diabetes (T1D) in regional local languages. HelloType1 was launched in Cambodia, Vietnam, Thailand, and Malaysia from 2021 to 2023, with Memorandums of Understandings (MOUs) signed between A4D and each country. HelloType1 Facebook page was also created for each country in their local languages for sign-posting to the HelloType1 website.
Aims
This study aims to investigate the usability and internet data analytics of HelloType1 within each participating country from 2021-2023
Methods
Data analytics utilised Google Analytics (GA4) with tracking data from the website *hellotype1.com,* and Facebook analytics were analysed from the Facebook online metrics
Results
The total number of users of the HelloType1.com digital platform grew by 382% between 2021 and 2022 with the launch of the programme in Vietnam (March 2022) and in Thailand (November 2022) and by 47% between 2022 and 2023 with the launch of the programme in Malaysia (May 2023). In 2023, 20% of the total users of the programme are Facebook followers and 80% are website users. The average pages per sessions increased from 2 pages to more than 3 pages in 2023 showing the interest of the user to browse for more content. More than half of the traffic of HelloType1.com originated from search engines (56% in 2023). On the Facebook sites, the organic page reach has increased by 120% between 2022 and 2023 with an increased engagement rate from 8% to 14% in 2023 which demonstrate the high interest from the followers and their willingness to interact and share the HelloType1 Facebook content with their community.
Conclusions
These internet analytics offer valuable insights into the delivery of an innovative diabetes educational resource in local languages, particularly in low-middle income countries with limited resources. Future plans are underway to use the platform to create a local community support and a peer-to-peer networks with online workshops for patients and caregivers, where the community can ask their questions via cha forums on the Facebook site that can be moderated by patients and caregivers. In addition, we hope that the programmes will be supported by local governments for example in Malaysia, the Hellotype1 in the local language is endorsed by the Ministry of Health.

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EP380

JOINT793

Association of metformin use and vitamin b intake with dementia risk in non-diabetic people: insights from the UK biobank

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Background
The relationship between metformin and dementia remains complex and controversial. Previous epidemiological studies have presented conflicting evidence regarding potential neuroprotective effects or cognitive risks associated with metformin use. This study aimed to comprehensively examine the association between metformin use, vitamin B12 intake, and dementia risk, considering both diabetic and non-diabetic populations.
Methods
A retrospective cohort study was conducted using data from 499,804 participants in the UK Biobank, selected from an initial cohort of 502,422 after excluding incomplete data. The research employed multivariate logistic regression models stratified by type 2 diabetes status and categorized vitamin B12 intake across quartiles to assess dementia risk factors and potential interactions.
Results
Of the 499,804 participants, 6,893 were diagnosed with dementia. The analysis revealed significant findings across different population subgroups. Non-diabetic males showed a marked association between metformin use and increased dementia risk (Odds Ratio 3.83, 95% Confidence Interval 1.15–12.75). Among non-diabetic females, metformin use combined with vitamin B12 deficiency was linked to elevated dementia odds (OR 1.63, 95% CI 1.04–2.55). Notably, no statistically significant associations emerged for participants with type 2 diabetes.
Conclusion
The study demonstrates that metformin use in non-diabetic individuals, particularly with vitamin B12 deficiency, may increase dementia risk. These findings warrant further investigation into the mechanisms linking metformin, vitamin B12, and cognitive health, and emphasize the importance of monitoring vitamin B12 levels in non-diabetic metformin users.

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EP381

JOINT52

In the heat of the moment: burns uncover the silent diabetes

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Introduction
Diabetic patients with peripheral neuropathy are particularly vulnerable to foot burns, which are often complicated by infections, delayed wound healing, and severe outcomes such as amputations. Although rare, these cases highlight the importance of early and adequate care.
Case Presentation
We present the case of a 41-year-old male admitted for a severe inaugural decompensation of diabetes associated with bilateral thermal foot burns. The burns, neglected for 10 days, were severely infected. Despite hospitalization involving daily wound care, strict glycemic control, and antibiotic therapy, healing was suboptimal. The progression to deep infections and osteomyelitis resulted in bilateral amputations to control septic complications.
Discussion
This case highlights the critical nature of foot burns in diabetic patients, exacerbated by peripheral neuropathy and delayed medical attention. Consistent with findings, these injuries are associated with high infection rates, severe complications, and frequent surgical interventions, including amputations. Preventive education and prompt care are vital in mitigating these adverse outcomes.
Conclusion
Diabetic foot burns constitute a medical emergency with potentially devastating consequences. This case underscores the necessity of early, intensive, and multidisciplinary management. Enhanced strategies for prevention and care are essential to reduce morbidity and improve outcomes.

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EP382

JOINT3904

Prevalence and clinical impact of obesity in patients living with type 1 diabetes

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Introduction
Although traditionally linked to type 2 diabetes, obesity is becoming increasingly prevalent among patients living with type 1 diabetes.
Objective
To assess the prevalence of obesity in T1D patients and identify associated factors, guiding prevention and management strategies.
Materials and Methods
A retrospective descriptive study was conducted on 755 T1D patients followed in the our department. Obesity was defined as a body mass index (BMI) greater than 30 kg/m^2. The data are analyzed using the IBM SPSS Statistics 27.0 software
Results
The study included 755 patients with a mean age of 25.7 $\pm$ 9.5 years and an average HbA1c of 12.48 $\pm$ 2.6%. The prevalence of overweight and obesity was 20.2% and 8.1%, respectively. Women accounted for 67% of obese patients, with a male-to-female ratio of 0.3 among obese individuals ($P = 0.02$). Hypertension (HTN) prevalence was significantly higher in obese patients (44.5%) compared to normal-weight individuals (18.9%, $P < 0.01$). Dyslipidemia was more frequent in obese patients (32.7%) than in non-obese patients (12.3%, $P = 0.02$). Retinopathy was observed in 26% of obese patients compared to 17.3% in normal-weight patients. Furthermore, 66% of obese patients were using human insulin.
Conclusion
Our study highlights specific and modifiable risk factors in obese T1D patients, including associations with cardiovascular and microvascular comorbidities. A proactive approach, incorporating lifestyle interventions and personalized management, is essential for optimal care.

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EP383

JOINT1471

Effect of subcutaneous semaglutide in patients with type 2 diabetes mellitus on the degree of systemic inflammation

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Introduction
Type 2 diabetes mellitus (T2DM) is a chronic disease that combines insulin resistance and metabolic alterations, being one of the leading causes of global morbidity and mortality. Its management includes improving glycemic control, reducing body weight, and optimizing the lipid profile. Additionally, controlling systemic inflammation is key to reducing cardiovascular and hepatic complications. New therapies, such as GLP-1 receptor agonists, have been shown to be effective in the comprehensive treatment of this condition.
Objective
To evaluate the effect of semaglutide on anthropometric, metabolic parameters and the systemic inflammation index (SII) after six months of treatment in patients with T2DM.
Materials and Methods
A retrospective study was conducted on 250 patients with T2DM treated at the Endocrinology and Nutrition Department of the Virgen de las Nieves Hospital in Granada, who started subcutaneous semaglutide treatment. Follow-up was carried out over approximately six months. Anthropometric (weight) and analytical data were collected, including glucose, cholesterol, neutrophils, lymphocytes, and SII. The following SII grades were defined: normal range (<381), low-grade inflammation (381 - 525), and severe inflammation (>525). Data obtained at baseline and after six months were analyzed using the statistical software Jamovi, applying the paired sample T-test with a per-protocol approach.
Results
From the total number of patients, comparable SII values before and after the intervention were obtained for 171 individuals. Of these, 48% were women, with a mean population age of 58 years at the beginning of semaglutide treatment. A significant reduction in weight ($P < 0.001$), glucose ($P < 0.001$), and total cholesterol ($P = 0.004$) was observed, indicating improvements in weight, metabolic, and lipid control (Table 1). No significant changes were recorded in neutrophils ($P = 0.485$), lymphocytes ($P = 0.582$), or the systemic inflammation index (SII; $P = 0.773$), which remained stable, suggesting the preservation of immune balance after the intervention.

Table 1 Baseline and post-intervention effects of semaglutide

Variable	Pre-treatment	Post-treatment	p-value
Weight (kg)	108.39 $\pm$ 26.62	102.45 $\pm$ 25.13	< 0,001
Glucose (mg/dL)	156.62 $\pm$ 65.11	127.60 $\pm$ 50.19	< 0,001
Total cholesterol (mg/dL)	174.55 $\pm$ 46.98	164.46 $\pm$ 46.82	0,004
Neutrophils (x10^3/µL)	4.99 $\pm$ 1.75	5.24 $\pm$ 1.75	0,485
Lymphocytes (x10^3/µL)	2.47 $\pm$ 0.95	2.49 $\pm$ 0.92	0,582
SII ratio	581.45 $\pm$ 355.26	593.23 $\pm$ 487.66	0,773

Conclusion
Treatment with semaglutide in patients with T2DM significantly improved weight, metabolic, and lipid control after six months, while the SII and immunological parameters remained stable, without significant changes.

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EP384

JOINT3440

Effect of subcutaneous semaglutide on liver fibrosis degree in patients with type 2 diabetes mellitus measured by the FIB-4 index

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Introduction
The incidence of non-alcoholic fatty liver disease (NAFLD) has reached approximately 20-30% in recent years, with obesity, insulin resistance, and lipid metabolism disorders being the main risk factors. NAFLD can present in various stages, ranging from simple steatosis to fibrosis. In most cases, assessing fibrosis requires a liver biopsy. The FIB-4 index is a recently developed non-invasive tool that helps identify patients with significant fibrosis using age, AST, ALT, and blood platelet count, improving accessibility for diagnosing liver fibrosis.
Objective
To determine the degree of liver fibrosis measured by the FIB-4 index in patients with Type 2 Diabetes Mellitus (T2DM) at the start of subcutaneous semaglutide treatment and compare it six months after initiation.
MaterialS and Methods
A retrospective study was conducted on 250 patients with T2DM treated at the Endocrinology and Nutrition Department of Virgen de las Nieves Hospital in Granada, who started subcutaneous semaglutide treatment. Follow-up was carried out for approximately six months. Anthropometric (BMI) and laboratory data were collected, including HbA1c (%), triglycerides (mg/dL), ALT (U/l), AST (U/l), and FIB-4 score. The FIB-4 score was classified into three risk categories: low (<1.36), intermediate or gray zone (1.36-2.67), and high (>2.67). Data obtained at baseline and six months later were analyzed using the Jamovi statistical software, applying the paired t-test with a per-protocol approach.
Results
Of the total patients, comparable FIB-4 values before and after the intervention were obtained in 64 patients, with a mean age of 58 years and a female representation of 43%. As shown in Table 1, a significant reduction was observed in BMI ($P = 0.03$), HbA1c ($P < 0.001$), triglycerides ($P = 0.001$), ALT ($P < 0.001$), and AST ($P = 0.003$). The FIB-4 score showed a trend towards reduction, but it did not reach statistical significance ($P = 0.155$) after six months of semaglutide treatment.
Conclusion
Subcutaneous semaglutide as a treatment for T2DM significantly reduced several metabolic and hepatic parameters after six months; however, the decrease in the FIB-4 index was not statistically significant.

Table 1. Baseline and post-intervention effects of semaglutid

Variable	Pre	Post	p-value
BMI (kg/m^2)	37.0 $\pm$ 8.2	35.6 $\pm$ 6.8	0.03
HbA1c (%)	8.3 $\pm$ 1.5	7.1 $\pm$ 1.2	0.001
Triglycerides (mg/dL)	239.9 $\pm$ 236.6	169.9 $\pm$ 93.9	0.001
ALT (U/l)	32.4 $\pm$ 23.8	25.4 $\pm$ 14.4	0.001
AST (U/l)	28.9 $\pm$ 18.3	23.6 $\pm$ 9.9	0.003
FIB-4 score	1.2 $\pm$ 0.6	1.1 $\pm$ 0.5	0.155

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EP385

JOINT3415

Biological changes in new-onset diabetic ketoacidosis (DKA) before and during covid-19

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Introduction
DKA is a serious life-threatening complication of diabetes mellitus, with its incidence increasing over the past decades. Recent evidence suggests that COVID-19 may play a role in the pathophysiology of new-onset diabetes mellitus

by triggering islet autoimmunity. The aim of this work is to compare the biological characteristics of new onset DKA before COVID-19 with those during the pandemic.
Patients & Methods
This is a cross-sectional analytical study carried out in the Diabetology & Endocrinology department of Farhat Hached University Hospital of Sousse. The study population included all the patients who had been hospitalized for new onset DKA between the year 2018 and 2022, divided in two groups: Group1(G1) :patients hospitalized before COVID-19 since the first of March of 2018 until first of March 2020 and Group2(G2):patients hospitalized during COVID-19 since second of March 2020 until 28thFebruary 2022. A metabolic, renal, hormonal, and immunological assessment has been requested.
Results
A total of 340 patients were evaluated:137 were registered in G1, while 203 were registered in G2. There was no significant difference in WBC count, hemoglobin or platelets between G1 and G2. Creatinine levels were significantly higher in G2 compared with G1 with a median of 52 [Q1–Q3]=[41.5–63] µmol/l and 56.6 [Q1–Q3]=[46–69] µmol/l respectively (***P* = 0.006**). Urea levels did not differ significantly between the two groups ($P = 0.262$). CRP was comparable between the two groups with a mean of 5 [Q1–Q3]=[2–14.5]mg/l in G1 and 6 [Q1–Q3]=[2–11.5] mg/l in G2 ($P = 0.791$). No significant difference was detected regarding Triglycerides, HDL-cholesterol, TC or LDL-cholesterol levels between G1 and G2. Hypertriglyceridemia was present in 32% patients in G1 vs 33% in G2 ($P = 0.470$). LDL-cholesterol was outside objective range according to cardiovascular risk in 56% of patients in G1 vs 65% patients in G2 ($P = 0.214$). Anti-GAD antibodies titers significantly increased during the pandemic period compared with the pre-pandemic period with a median value of 92.5 [Q1–Q3]=[22.5–1074] in G1 vs 330 [Q1–Q3]=[58.5–1795] in G2 (***P* = 0.021**). Anti-IA2 antibodies titers significantly increased as well during the pandemic period compared with the pre-pandemic period with a median value of 0 [Q1–Q3]=[0–104.75] in G1 vs 93 [Q1–Q3]=[0–3571] in G2(***P* = 0.009**). No significant difference was found regarding anti-ZNT8 titers between the two groups ($P = 0.475$)
Conclusions
Our study suggests a potential link between COVID-19 and increased islet autoimmunity, as evidenced by higher anti-GAD and anti-IA2 antibody titers in post-pandemic patients.

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EP386

JOINT1393

Study on insulin gene rs689 polymorphism in patients with diabetic neuropathy

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Diabetic neuropathy (DN) is one of the most common complications affecting more than 67% of patients with diabetes. In this regard, identifying genetic markers of the risk of developing DN is of great importance for the early diagnosis of this disease. The relationship between the rs689 polymorphism of the insulin gene and the development of diabetic neuropathy was studied.
Materials and Methods
The study included 2 groups: the main group was patients with DN and the control group - people without signs of DN. To study the rs689 polymorphism of the INS gene, we used a modified allele-specific PCR method. Genotyping was carried out using a programmable thermal cycler Applied Biosistems-2720 (USA).
Results and Discussion
Our findings demonstrated that the genotype distribution for rs 689 polymorphic locus of the INS gene in DN and control complied with Hardy -Weiberg equilibrim. The frequency of occurrence of the wild A allele of the INS gene in the main and control groups was 72.7% and 83.3%, respectively. The unfavorable T allele was less common in the population sample compared to the main group (16.7% and 27.3%, respectively). An analysis of the distribution of genotypes revealed that the most common genotype among the examined groups was the homozygous genotype AA (51.5% in the group with DN and 69.2% in the control group). The frequency of the heterozygous AT genotype in the sample of patients and in the control group was 42.4% and 28.2%, respectively. The distribution frequencies of the TT genotype in patients with DN are 6.1%, in the control group 2.6%, respectively. The ratio of allele frequencies and genotypes by polymorphic variant for patients with DN showed a statistically significant increase in the risk of developing this disease in carriers of the T allele (RR=1.64; 95% CI: 1.05–2.56, $\chi2=4.76$; $P = 0.029$), AT genotypes (RR= 1.56; 95% CI: 1.0–2.44, $\chi2=3.89$; $P = 0.049$), TT (RR= 2.95; 95% CI: 0.57–15.3, $\chi2=1.85$; $P = 0.18$). From the results obtained, it follows that carriers of the T allele and AT genotypes have an increased risk of developing DN, while carriers of the A allele and A/A genotype have a reduced risk of developing the disease. The findings may have important clinical implications for predicting the risk of developing diabetic neuropathy.

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EP387

JOINT150

Treatment of 1182 early type I DM with a combination of 3 immune modulatory drugs Eight years of experience

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Background and Aims
Immune modulation of type I diabetes has failed in the last 90 years ago. Increase of C-Peptide has never been seen. Based on experience with harmless immune modulatory drugs in other disease such as alopecia areata, multiple sclerosis, and …. we tried to treat type I DM in the last 7 years ago. The treatments were changed gradually and the most effective protocol is presented.
Materials and Methods
Eleven hundred eighty-two patients were treated with Azithromycin 250mg, Vit A 25000IU twice weekly, and Atorvastatin 10-40mg every night as the immune modulatory block. Dapagliflozin (or Empagliflozin), Glucophage and Pioglutazone were used to reduce the need for insulin. In refining and defining response rate, serum fasting and 2hpp Insulin and C-Peptide, HbA1C, anti-Gad and anti-Islet cell Ab were measured at beginning and every 3 months.
Results
Hundred percent of the patients responded to at least one of the seven parameters with a reduction of HbA1c at 1.4-9.4 percent. Patients could omit their short acting insulin at evening, morning and noon in 100, 87 and 69% respectively. Reduction of anti-GAD and Anti Islet cell AB were encountered in 96 and 92 percent from a high of up to 2000 and 150 down to below 5 and 1.2. Fasting and 2hpp Insulin, fasting and 2hpp C-Peptide were increased in 86%, 88%, 68% and 82% from a low of 0.2, 0.4, 0.001, 0.001 to a high of 4.2, 16.2, 0.3 and 7.6 respectively. Three hundred eighty-eight (32.8%) patients discontinued their insulin completely and 198 (16.7%) awaits this.
Discussion
The astonishing results of increased C-Peptide with declaration of 2hpp C-Peptide as a novel response marker denotes that either increased secretion of insulin or increased beta cell proliferation (like DYRK-1 pathway) is possible *in vivo*. More sophisticated techniques are needed.

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EP388

JOINT1448

Superimposition of increased beta oxidation due to insulin deficiency is the principal molecular mechanism of diabetic ketoacidosis: a proportional hazard model

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Relative insulin deficiency and high Glucagon level are the hallmark of DKA. What is the exact mechanism? When does exactly the cascade begin? How we can prevent it? Is there a cascade of events that begins days before overt clinical presentation and can we stop it?
Aim
Finding molecular pathogenesis of ketoacidosis
Methods
In a 6 years research we used immune modulatory drugs to stop type I DM. Cox multivariate analysis on 1700 patients was done. Many combinations were used and those without response were omitted. Earlier combinations included Nicotinic acid but our triumphant combination with significant c-Peptide increase did not.
Results
Although socioeconomic status, omission of Insulin and infection were the three strongest risk factors, patients (763) on Nicotinic acid showed almost no case of DKA in the first year and only 6 in the second year that was later found to be due to Nicotinic acid discontinuation. The protocol without Nicotinic acid showed 26 cases of DKA in almost 650 patients. A proportional hazard study showed very

indirectly that the DKA process begins at least 2 weeks before overt clinical presentation and can be prevented by pharmacological intervention. Some patients showed deterioration of well being with urinary ketone of 1+ that seemed not to need treatment.

Conclusion

Increased activity of ATGL, HSL augmented by loss of inhibition of Perilipin-1 causes high load of Acetyl-CoA within the mitochondria that overrides its clearing potential. Acids leak out of it and the cytoplasm has no enzymatic weapon to counteract it. Extrusion of acid into the circulation re-established cytoplasmic milieu at the expense of generalized acidity. This can be blocked by anti-lipolysis agents such as Nicotinic acid or Acipimox. Increased incidence of DKA coincident with DDP-4 or SGLT-2 inhibitors is not a per se phenomenon but due to less insulin use and lower energy expenditure. Many data shows that Insulin concentrations less than 72ng/dl in mice can cause ketoacidosis.

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EP389

JOINT1702

Association between body composition parameters, disease duration, and glycemic control in adult patients with type 1 diabetes: a cross-sectional study

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Introduction

Alterations in body composition, such as reduced lean mass and increased adiposity, may negatively influence insulin sensitivity, glycemic control, and contribute to cardio-metabolic risk in patients with type 1 diabetes (T1D). These changes may result from insulin therapy, inadequate eating patterns, physical inactivity, or inflammatory processes associated with the disease. Understanding the interplay between T1D, body composition and metabolic parameters may help optimizing patient care. This study aimed to investigate the relationships between body composition parameters, clinical characteristics and glycemic control in a cohort of Italian adult patients with T1D.

Methods

This cross-sectional study included 94 patients with T1D (mean age $\pm$ standard deviation 43 $\pm$ 15 years); 58.5/41.5% males/females) with mean disease duration of 16 years (range 10-27), mean body mass index 24.6 kg/m^2 (21.8-27.7). Body composition was assessed using bioelectrical impedance analysis, measuring fat mass (FM), fat-free mass (FFM), skeletal muscle mass (SMM), sarcopenic index (SI), and phase angle (PA). Glycemic control was evaluated using continuous or flash glucose monitoring systems-derived metrics. Clinical data included diabetes-related complications, and patients' comorbidities and concomitant medications. Daily insulin requirements were also calculated.

Results

Correlation analysis showed significant associations between disease duration and FFM (r = -0.21, P = 0.0382), SMM (r = -0.31, P = 0.0024), and SI (r = -0.28, P = 0.0064). Daily insulin requirements positively correlated with FM (r = 0.29, P = 0.0047). PA was inversely associated with glucose management indicator (GMI r = -0.22, P = 0.0482), while positively correlated with time in range (TIR r = 0.22, P = 0.0436). Gender analysis revealed that females had significantly higher FM, and lower of FFM, SMM, SI, and PA values compared with males.

Conclusions

These finding suggests that long-standing T1D negatively affects muscle-mass measures. Moreover, poor glycemic control can negatively influence PA, a marker of cellular health, which has been associated with adverse clinical outcomes in several pathological conditions, including cancer, infections, and metabolic diseases. Furthermore, the positive relationship between FM and daily insulin requirements emphasizes the role of body fat in insulin resistance. Therefore, our study suggests the importance of monitoring and optimizing body composition as part of the comprehensive management of T1D. Significant gender-specific differences in body composition also highlight the need for personalized therapeutic strategies. Further research is needed to clarify the mechanisms underlying these relationships and their implications for clinical care in T1D patients.

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EP390

JOINT3510

Demographic and clinical characteristics of patients with LADA diabetes at hospital universitario de canarias, spain

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Introduction

The diagnosis of diabetes between the ages of 25 and 45 can be complicated, as the less common subtypes of diabetes sometimes overlap with characteristics typical of type 1 and type 2 diabetes mellitus (DM). Latent Autoimmune Diabetes in Adults (LADA) shares an autoimmune component with DM1, and therefore, there is an early progression towards insulinopenia compared to DM2. However, in most cases, patients initially present good control using only non-insulin antidiabetic drugs, similar to DM2. For this reason, patients are often initially misdiagnosed with DM2. In patients with clinically compatible characteristics, it is essential to determine autoantibodies against pancreatic beta-cell structures to establish the correct diagnosis. The literature indicates that the most frequently present and sensitive antibodies are anti-glutamic acid decarboxylase antibodies (anti-GAD). However, other autoantibodies may also be present.

Material and Methods

A descriptive and cross-sectional study was conducted to assess the clinical and demographic characteristics of patients with LADA. A sample of 44 patients aged between 38 and 72 years (mean age of 50.9 years), 56.8% of whom were women, was evaluated between 2022 and 2023 in the Endocrinology Department of "Hospital Universitario de Canarias", Spain.

Results

A retrospective assessment was made regarding the following: diagnosis change, diagnostic delay, presence of autoantibodies (anti-GAD and anti-IA2), initial glycated hemoglobin, final glycated hemoglobin, C-peptide levels, time treated only with non-insulin antidiabetic drugs, time treated only with basal insulin, time to the initiation of basal-bolus regimen, and the use of continuous glucose monitoring (CGM) systems.

- Mean time of diagnostic delay (years): 6.5
- Mean initial HbA1c: 8.7%
- Mean final HbA1c: 7.4%
- Mean treatment time with non-insulin antidiabetic drugs (years): 2.65
- Mean time treated with only basal insulin (months): 9
- Mean time until the initiation of basal-bolus regimen (years): 3.7
- **Diagnosis change:**81.8% of patients
- **Use of CGM:**88.6% of patients
- **Autoantibodies:**Only anti-GAD positive: 48.7%; Only anti-IA2 positive: 15.38%; Both positive: 35.89%
- **C-peptide levels (ng/mL):** $<$0.5: 38.7%; 0.5-2: 54.83%; $>$2: 10.52%

Conclusion

Although LADA is a recognized form of diabetes, no specific guidelines have been established for its management, and it is often confirmed years after an initial diagnosis of DM. An individualized approach should be taken, considering the metabolic characteristics as well as the signs and symptoms of insulinopenia (emphasizing the importance of determining C-peptide levels in diagnosis and follow-up).

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EP391

JOINT3539

Characteristics of patients with diabetes mellitus evaluated by hospital interconsultations at the canarias university hospital (HUC)

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Introduction

A significant proportion of hospitalized patients have some form of diabetes mellitus (DM). Achieving optimal glycemic control in hospitalized patients requires consideration of multiple factors, including food intake, fasting for tests/procedures, clinical deterioration, and corticosteroid use. Blood glucose levels outside the safe range (140 mg/dL–180 mg/dL) increase the risk of complications during hospitalization.

Objectives
To describe the characteristics of diabetic patients evaluated in the Endocrinology and Nutrition consultations at the Hospital Universitario de Canarias (HUC).
Materials and Methods
A descriptive observational study was conducted on a sample of 118 diabetic patients monitored through Endocrinology and Nutrition consultations at HUC from October to December 2024. The variables analyzed included age, sex, type of diabetes, referring hospital department, blood glucose levels at initial and final evaluations, HbA1c, treatment, associated comorbidities, and follow-up plan.
Results
A total of 53 women and 65 men were studied, with most patients aged 70–80 years (31%) and an average age of 65 years. Among them, 90 patients (76%) had type 2 diabetes (T2DM), 25 (21%) had type 1 diabetes (T1DM), and 3 (3%) had latent autoimmune diabetes in adults (LADA). The hospital department requesting the most consultations was Vascular Surgery (14%), followed by Gastroenterology (13%) and Nephrology (11%). At the initial evaluation, 29% of patients had blood glucose levels between 250–300 mg/dL, while 16% had levels exceeding 400 mg/dL. Before the endocrinology assessment, 44% of patients were on a sliding-scale insulin regimen, but 74% required an immediate transition to a basal-bolus insulin regimen. When analyzing blood glucose levels, it was noted that 31% of patients were receiving corticosteroids. Regarding HbA1c levels, 27% of patients had values between 7% and 8% (mean: 8.28%), while 14% had HbA1c levels $>10\%$. Among the associated comorbidities, 37% had diabetic retinopathy, 43% had nephropathy, and 24% had polyneuropathy. For follow-up after discharge: 28% were referred to primary care physicians. 52% were scheduled for endocrinology outpatient follow-up. The remaining 20% included deceased patients, patients discharged without notification, voluntary discharges, and those followed up outside the island.
Conclusions
The limited effectiveness of sliding-scale insulin regimens in hospitalized patients is demonstrated. Maintaining blood glucose levels between 140 and 180 mg/dL is a safe target for hospitalized patients. Strengthening adherence to glycemic control protocols in hospitalized patients is essential. Additionally, hospitalization provides an opportunity to reinforce diabetes education, optimize home treatment, and assess follow-up needs upon discharge.

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EP392

JOINT2869

A diagnosis of MODY 2 following MIS-C

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Background
Maturity-Onset Diabetes of the Young (MODY) due to *GCK* mutations is a form of monogenic diabetes characterized by mild fasting hyperglycemia. Here, we present a pediatric case of GCK-MODY diagnosed after Multisystem Inflammatory Syndrome in Children (MIS-C).
Case
A 4-year-old girl, born at term with a birth weight of 3,200 g, was referred for persistent hyperglycemia. She had been hospitalized for three weeks due to MIS-C, before her visit. Family history revealed diabetes in her maternal grandfather, aunt and mother necessitating the use of antidiabetic medications, which raised concerns for MODY. Initial labs showed fasting glucose of 120 mg/dL and HbA1c of 5.4%. An OGTT revealed 0-minute glucose of 136 mg/dL and 120-minute glucose of 151 mg/dL, with an insulin response suggesting preserved beta-cell function. Genetic testing identified a heterozygous pathogenic variant in GCK (c.214G$>$A, p.Gly72Arg, rs193922289), confirming GCK-MODY. However during follow-up after MIS-C, postprandial hyperglycemia and an HbA1c of 8% raised concerns for insulinopenic diabetes. Further rise of blood glucose levels necessitated use of insulin. Autoimmune diabetes markers (IAA, ICA, GADA) were negative. The patient was also screened for other antibodies related to autoimmune thyroiditis and celiac disease, which were negative. After 6 months of treatment, insulin was discontinued.Duringthelast 2.5 years of follow-up,the patient remained stable, with anHbA1c of 5.9%at her last visit.
Discussion
Recent studies suggest COVID-19 may increase diabetes risk, but its exact role is unclear. The mechanisms likely involve systemic inflammation, glucocorticoid use, endothelial dysfunction, and persistent viral presence affecting pancreatic β-cell function and insulin sensitivity. Some propose classifying post-COVID diabetes as a distinct syndrome. In this case, initial postprandial hyperglycemia and an HbA1c of 8% raised concerns for insulinopenic diabetes, leading to autoantibody testing. However, negative autoantibodies, stable glucose after insulin withdrawal, and the presence of a GCK variant suggest transient hyperglycemia was MIS-C-induced. The exact mechanism remains unknown, highlighting the need for long-term follow-up. This case also underscores the importance of considering MODY in pediatric patients with persistent hyperglycemia with strong family history. Dynamic follow-up and a tailored approach are crucial to avoiding unnecessary treatments.

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EP393

JOINT1261

Melatonin levels across patients with type 2 diabetes mellitus with and without sleep disorders

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Melatonin is a hormone that significantly impacts our sleep and circadian rhythms. It also influences glucose metabolism, but how exactly it happens is still unclear. Due to the Timing Model, low melatonin levels during the night may limit β-cell recovery, while high levels with food intake may lead to an increased risk of diabetes. Nowadays, the number of sleep disorders has increased, and a lot of people, including patients with type 2 diabetes, choose to take melatonin pills as these are available over the counter without a prescription. The purpose of this study was to determine the relationship between levels of melatonin, diabetes mellitus, and sleep disorders.
Methods
This was a quantitative research study with 77 patients included. Participants' ages ranged from 32 to 69 years (M = 54,3, SD = 8,27), with 41 (53%) identified as female. Avarage HbA1c was $9,28 \pm 2,14$. As for years from the beginning of diabetes - 7[5; 10,25]. All patients have confirmed diabetes mellitus type 2 and were screened for sleep disorders with the Pittsburgh Sleep Quality Index (PSQI) questionnaire. Melatonin levels were indicated in the salvia, which was collected at night. We use the colorimetric method to test samples with the Melatonin Elisa kit (ab283258) supply. Statistical analysis was provided in Microsoft Office Excel.
Results
The study found that 45 patients (58%) had normal melatonin levels, 17 patients (22%) had elevated levels, and 15 patients (20%) had reduced levels. Among women, 12 patients (29%) had high levels, 7 patients (17%) had low levels, and 22 patients (54%) had normal levels. Among men, 5 patients (14%) had high levels, 8 patients (22%) had low levels, and 23 patients (64%) had normal levels. Furthermore, 25 participants (32.4%) scored above 5 on the PSQI, indicating poor sleep quality. Within this group, 3 patients (12%) had high melatonin levels, 7 patients (28%) had low levels, and 15 patients (60%) had normal levels. The correlation between melatonin levels and sleep disturbances was 0.11.
Conclusions
Melatonin levels have a weak correlation with sleep disorders, which means this hormone is not the leading cause of this problem. It is essential to check the level of melatonin before administering it to patients with diabetes to provide personalized treatment and avoid harming someone who has a normal or elevated level of melatonin.

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EP394

JOINT1190

Fibrocalculous pancreatic diabetes (SPINK 1 mutation) in klinefelter syndrome: first case report

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Background
Klinefelter Syndrome (KFS) is the most common sex chromosome disorder in males, typically characterized by a 47, XXY karyotype, hypergonadotropic hypogonadism, infertility, and metabolic complications such as insulin resistance and type 2 diabetes. Fibrocalculous Pancreatic Diabetes (FCPD), a unique form of diabetes prevalent in tropical regions, is associated with pancreatic calcification, exocrine insufficiency, and insulin dependence. The coexistence of KFS and FCPD is exceedingly rare, presenting significant challenges in diagnosis and management due to overlapping endocrine and metabolic dysfunctions.
Case Presentation
We report a case of a 48-year-old male with KFS and FCPD. The patient was diagnosed with diabetes mellitus four years prior to hospital admission and presented with progressive weight loss, steatorrhea, and intermittent abdominal pain. Despite intermittent insulin use, he experienced poor glycemic control with an HbA1c of

17.7% and random blood glucose of 500 mg/dL at admission. Clinical evaluation revealed primary infertility, decreased libido, and small, firm testes. Imaging confirmed pancreatic calcifications and ductal dilation, while genetic testing identified a pathogenic SPINK1 gene mutation (N34S 101 A>G). Karyotype analysis established a 47, XXY diagnosis, consistent with KFS. Further investigations revealed primary hypogonadism, osteoporosis, vitamin D deficiency, and low lipid levels. The patient was managed with a basal-bolus insulin regimen, pancreatic enzyme replacement, vitamin supplementation, zoledronic acid for osteoporosis, and testosterone replacement therapy.

Discussion

This case highlights the complex interplay of metabolic and endocrine dysfunction in the rare coexistence of KFS and FCPD. KFS contributes to insulin resistance via increased adiposity and reduced muscle mass, while FCPD adds challenges of pancreatic exocrine insufficiency and insulin dependence. Additionally, hypogonadism in KFS exacerbates metabolic derangements, with testosterone deficiency linked to increased insulin resistance and bone loss. Multidisciplinary management is essential, addressing glycemic control, pancreatic insufficiency, and hormonal replacement.

Conclusions

The coexistence of KFS and FCPD underscores the need for comprehensive evaluation and personalized management of patients with overlapping metabolic and endocrine disorders. This case emphasizes the importance of a multidisciplinary approach integrating insulin therapy, enzyme and vitamin replacement, and testosterone therapy to optimize metabolic outcomes and quality of life.

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EP395

JOINT970

Localized scleroderma in a type 1 diabetic patient : a case report

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Introduction

Morphea or localized scleroderma is a rare disease characterized by excessive collagen fiber production in the dermis, leading to the appearance of indurated subcutaneous areas. The association of systemic scleroderma and type 1 diabetes has been reported but not morphea. We report the case of a 16-year-old girl who consulted for diabetes type 1 with extensive lipodystrophic areas.

Observation

A 16-year-old girl presented to the Endocrinology Department for uncontrolled diabetes. Her medical history included an auto-immune hypothyroidism treated with 75 mg/day of levothyroxine. She has been diabetic since the age of 8, diagnosed following a biological screening due to a cardinal syndrome. Anti-GAD65, IAA, ICA and anti-ZNT8 antibodies were negative. She was treated with insulin analogs: insulin detemir and aspart. Initially, she developed large indurated subcutaneous areas and atrophic zones in insulin injection sites (abdomen, arms, and thighs), despite right injection techniques and rotation. Progressively, new indurated subcutaneous areas appeared outside of the injection sites. The diagnosis of morphea was suspected and confirmed by a skin biopsy showing a homogenized reticular dermis, with collagen bundles that were more or less thick and dense, and either horizontal or parallel to the surface. Dot sclerosis was negative. The patient was started on methotrexate at 12.5 mg/week, and an insulin pump was proposed to obtain a better control of diabetes with reduced the number of injections.

Conclusion

The identification of localized scleroderma in a patient initially thought to have lipodystrophy highlights the importance of considering rare and atypical diagnoses in patients with diabetes as they can have a significant impact on diabetic control.

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EP396

JOINT1248

Predictors of diabetes in tropical calcific pancreatitis - a cross sectional, observational study

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Introduction

Diabetes in tropical calcific pancreatitis is a common complication with prevalence ranging from 5-10% in western population and 15-20% in southeast Asian population. Compared to type 2 diabetes, these patients need insulin earlier, have higher risk of hypoglycemia. Knowledge about risk factors would help early intervention and delay development of diabetes. In this study we have assessed the risk factors for the development of diabetes among the TCP patients.

Aim

To identify the risk factor of development of diabetes in subjects with tropical calcific pancreatitis (TCP)

Methodology

The study is a cross-sectional study conducted in a tertiary care hospital. All the patients above 18 years of age attending the Endocrinology or Gastroenterology OPD with a diagnosis of idiopathic chronic pancreatitis were included in the study. Relevant clinical history, examination and were done. Imaging details of patients were taken. For patients without diabetes OGTT was done.

Results

Total 219 patients have been enrolled whom 143 (65%) are diabetic and 76 (35%) are non-diabetic. Diabetes has a mean age of 34.7 ± 12.7 years which is significantly higher than non- diabetics 28 ± 10.8 years ($P = 0.00$). A greater number of diabetes patients had a history of surgery (15% vs 5%) and exocrine insufficiency (80.4% vs 67%) compared to non- diabetes. There is no significant difference in BMI, history of acute pancreatitis, family history of diabetes or chronic calcific pancreatitis in the two groups. Biochemical parameters showed a significantly lower C-peptide, amylase and lipase levels in diabetics compared to non-diabetics. On pancreatic imaging it is found that significantly higher number of patients with diabetes have pancreatic atrophy (95% vs 86%), parenchymal calcifications (65% vs 51%) and a larger duct size of 7 (4.2-9) vs 5 (3.8-7) mm. Multivariate logistic regression showed pancreatic parenchymal atrophy OR- 14.3 (CI-1.1-179), exocrine insufficiency (steatorrhea) OR-5.1 (CI-1.3-20), older age OR-1.05 (CI-1.0-1.1) and lower C-peptide OR- 0.05 (CI- 0.005-0.6) as risk factors for diabetes in TCP patients.

Conclusion

Among patients with TCP, those with older age, history of surgery, exocrine insufficiency and lower C-peptide levels have higher risk of diabetes mellitus. In pancreatic imaging, parenchymal calcifications, atrophy and ductal dilatation were found to be risk factors for diabetes mellitus.

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EP397

JOINT1595

The importance of cardiovascular implementation tests in diagnostic of the diabetic cardiovascular autonomic neuropathy

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Introduction

The chronic vascular complications are the most common cause of death and invalidity of diabetic patients, and cardiovascular chronic complications are the most affected. The diabetic cardiovascular autonomic neuropathy (CAN) is chronic complication of diabetes mellitus, frequently without any symptoms, and with high mortality which demands early detection.

Aim

Aim of this work was to establish: possibility of CAN early detection with the implementation of cardiovascular dynamic tests and diagnostic value each of those cardiovascular tests.

Methods

During this research we have evaluated 90 examinees: 30 of them with diabetes type 1, 30 with diabetes type 2 and 30 healthy examinees – without primary cardiac disease and diabetes. The autonomic nervous system function was examined by 5 tests for cardiovascular reflexes, with those tests we have evaluated cardiac rate reaction on various stimuli (Valsalve maneuver, deep breathing test, stand-up after lying position test) or blood pressure (orthostatic hypotension test and Hand grip test). In performing of these tests, we have used: sphygmomanometer, ECG machine, aneroid manometer and manual manometer.

Results

Results have showed that the most common pathological test in diabetes type 1 (71,4%, $P < 0.001$) and type 2 (83,3%, $P > 0.001$) was stand-up from lying position test, and afterwards deep breathing test – in diabetes type 1 (66,7%, $P < 0.001$) and

type 2 (80,0%, $P < 0.001$). Valsalve maneuver, orthostatic hypotension test and Hand grip test were pathological in 33,3% of the patients with autonomic neuropathy in type 1 of diabetes, and in type 2 (46,7%, 13,3% and 20,0%).
Conclusions
The cardiovascular tests enable early detection of the presence of CAN and objective assessment of the cardiovascular function, and have great prognostic, diagnostic and therapeutic significance. Stand-up test from lying position and deep breathing test were the most often pathological in CAN patients, and therefore having the greatest diagnostic value. Cardiovascular tests should be accepted as golden standard in CAN diagnostic and put it in everyday clinical practice. Correct interpretations of these tests enable categorization of damage degree of autonomic nerve system, which has great importance in further treatment and management of these patients.

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EP398

JOINT2133

Prevalence of obesity and diabetes in reproductive age (20–44 years) in the bulgarian population

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Obesity and overweight (BMI >25 kg/m^2), affecting all age groups, are considered major risk factor for the onset of diabetes/prediabetes outside of pregnancy and for hyperglycemia during pregnancy.
Aim
To investigate the relationship between BMI >25 kg/m^2 in the young reproductive age group (20–44 years) and the development of diabetes/prediabetes.
Materials and Methods
A total of 931 individuals (20–79 years) were studied, divided into three age groups: 20–44 years (n-340, 36.5%), 45–59 years (n-300, 32.2%), and 60–79 years (n-291, 31.3%). The analysis focused on 340 individuals from the reproductive age group (20–44 years), consisting of 158 women (46.5%) and 182 men (53.5%). Height and weight were measured, and BMI was calculated.
Results
The current diabetes prevalence in Bulgaria is 16.55%, distributed across the age groups as follows: 4.1% (14/342) in 20–44 years, 18.3% (55/301) in 45–59 years, and 29.55% (86/291) in 60–79 years. In the young group, BMI >25 kg/m^2 was observed in 56.2% (191/340), distributed between women (30.4%, 58/191) and men (69.6%, 133/191), with a significant gender difference ($P<0.001$). Among this group, diabetes was present in 4.1% (14/340), prediabetes in 10.3% (35/340), and no carbohydrate metabolism disorders in the remaining 85.6% (291/340). In this young group obesity was identified in 57.1% (8/14)* of individuals with diabetes, 45.7% (16/35) of those with prediabetes, and 19.9% (58/291)* of individuals without carbohydrate metabolism disorders (*$P<0.05$). In our earlier study on pregnant Bulgarian women, hyperglycemia was identified in 14.4% (79/547), with 7.5% (29/386) occurring before 24 gestational weeks and 31% (50/161) after 24 gestational weeks ($P<0.01$)[1]. A significant relationship with pre-pregnancy weight was also observed: women with hyperglycemia (n-79) had an average BMI of 26.10 ± 6.65 kg/m^2 compared to 22.89 ± 4.57 kg/m^2 in those with normoglycemia ($P<0.001$).
Conclusion
Over 56% of individuals in the young reproductive age group (20-44 y) have a BMI >25 kg/m^2, a strong risk factor for the development of diabetes/prediabetes and a risk factor for hyperglycemia during pregnancy. Upon the onset of pregnancy, screening for glucose tolerance disorders is essential, particularly in women with obesity or overweight at the time of conception.

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EP399

JOINT2227

New-onset autoimmune diabetes mellitus concomitantly with myositis secondary to pembrolizumab treatment in a patient with squamous lung cancer: a case report

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Background
Immunotherapy displays a prominent role in the current treatment of many malignancies. However, several adverse events of immune checkpoint inhibitors (ICIs) have been described so far. We present a rare case report of pembrolizumab–induced autoimmune diabetes mellitus (DM) concomitantly with myositis.
Case presentation
A 65-year-old Caucasian male, with no personal or family history of DM, was treated with pembrolizumab for squamous lung cancer. Two months after the 1st dose of treatment, he presented to the emergency department due to muscle weakness, fatigue and high plasma glucose levels (>500mg/dl). The patient also reported polyuria, polydipsia, mouth dryness, weight loss and abdominal pain over the last three days. Physical examination revealed tachycardia, tachypnea, dehydration, numbness of the lower extremities and left eyelid ptosis. The patient did not experience any cardiac symptoms and the electrocardiogram was normal. Laboratory tests were indicative of diabetic ketoacidosis concomitantly with myositis. Further investigation, for DM, revealed low c-peptide (0,55 ng/dl), and insulin concentration ($<1,6$ μUI/ml). Immediate treatment was initiated, including hydration, intravenous insulin infusion and high-dose intravenous methylprednisolone of 1gr daily with significant clinical and biochemical improvement. He was subsequently switched to subcutaneous insulin therapy and to 1mg/kg methylprednisolone orally which was slowly tapered over the next two months. The patient tested positive for autoantibodies against glutamic acid decarboxylase (anti-GAD) and islet cell autoantibodies (ICA). These data established the diagnosis of new-onset autoimmune DM. The antibodies for myasthenia Gravis were negative. Six months later, the patient presented within glycemic targets along with a significant improvement of the left eyelid movement and fatigue.
Discussion
Pembrolizumab is an ICI, widely used in cancer treatment. Its main action is to inhibit lymphocytes' PD-1 receptors and elicit an immune response. This allows the immune system to target and destroy cancer cells, but also, leads to immune-related adverse events (irAEs) in various organ systems. Immune-mediated destruction of pancreatic β-cells and myositis by pembrolizumab are rare disorders. This is the first case report of pembrolizumab-induced autoimmune DM concomitantly with myositis, described so far. Monitoring of early signs of these adverse events and medical professional awareness are crucial, as some of these could be life-threatening. The exact mechanisms are yet to be elucidated.

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EP400

JOINT2217

Type 2 diabetes and quality of life in relation to perceived psychological stress

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Aim
To investigate quality of life (QoL) in patients with type 2 diabetes (T2DM) experiencing low perceived psychological stress level and high perceived psychological stress level.
Methods
Perceived psychological stress level and QoL were assessed in 146 patients with T2DM (57 men, 89 women, age 56.7 ± 12.6 years, T2DM duration 7.4 ± 6.9 years, body mass index (BMI) 33.6 ± 5.7 kg/m^2, HbA1c level 7.7 ± 1.6%), using Perceived Stress Scale (a higher score denotes a higher level of stress) and WHO Bref Quality of Life questionnaire (a higher score denotes better QoL).
Results.
Patients with high perceived stress level had lower scores in physical health (10.9 ± 1.6 vs. 13.9 ± 2.4, $P<0.001$), psychological health (11.4 ± 2.8 vs. 13.7 ± 2.1, $P=0.018$), and social relations domains (12.3 ± 1.9 vs. 13.6 ± 2.6, $P=0.038$) than those with low perceived stress level. No significant differences were found in QoL environmental domain as well as in age, T2DM duration, BMI, HbA1c level between patients experiencing low and high perceived stress. Perceived stress level in patients with T2DM correlated negatively with QoL physical health score ($r=-0.255$, $P=0.015$).
In conclusion.
Patients with type 2 diabetes experiencing high perceived psychological stress level have worse quality of life in terms of physical health, psychological health and social relations than those with low level of perceived psychological stress.Perceived stress level in patients with type 2 diabetes is related to physical health.

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EP401

JOINT452

Hypoglycemia in an insulin-treated diabetic: when causes pile up

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Introduction
Hypoglycemia is a frequent and potentially severe complication in insulin-treated diabetics, requiring meticulous management to prevent instability and adverse outcomes. While its primary etiology often stems from insulin mismanagement, hypoglycemia can also have multifactorial origins. Here, we present the case of an adult with recurrent hypoglycemia due to a combination of complex, overlapping factors.
Case Report
A 56-year-old male, diabetic for 36 years, presented with recurrent unrecognized hypoglycemic episodes, occasionally resulting in loss of consciousness. His medical history included combined spinal sclerosis and bipolar disorder, managed with sodium valproate and risperidone. The patient was on a basal-bolus regimen of human insulin (1.25 IU/kg), administered exclusively postprandially. Clinical examination revealed severe malnutrition (BMI: 13.8 kg/m^2), depressive syndrome, edentulism, and prominent lipodystrophies at the arms, the sole injection sites. An extensive evaluation for malnutrition, including biological tests, tumor markers, tuberculosis screening, and imaging, yielded negative results, and hormonal profiles revealed no deficiencies. Initial management involved correcting therapeutic errors, transitioning to insulin analogs with appropriate dose adjustments, and implementing gradual nutritional repletion. While these interventions led to partial improvement, recurrent hypoglycemia persisted. Hypoglycemic episodes confirmed exogenous hyperinsulinism. The persistence of hypoglycemia prompted suspicion of iatrogenic factors. Sodium valproate and risperidone were reviewed, and their potential contributions to hypoglycemia were explored. Discontinuation of risperidone and dose reduction of sodium valproate (guided by elevated serum levels) resulted in resolution of hypoglycemia and progressive weight gain.
Discussion and Conclusion
Severe hypoglycemia in insulin-treated diabetics often originates from improper insulin administration, as seen in our patient's use of restricted injection sites with associated lipodystrophy. Insulin overdose, although common, is frequently underestimated. The multifactorial malnutrition in this case required a multidisciplinary approach, particularly collaboration with the treating psychiatrist to optimize nutritional status. Sodium valproate-induced hypoglycemia, though rare, is attributed to impaired hepatic gluconeogenesis mediated by decreased L-carnitine levels. Similarly, risperidone has been implicated in hyperinsulinism through pancreatic alpha-2 receptor antagonism, although this mechanism remains debated. The absence of hypoglycemia awareness in this patient likely resulted from autonomic neuropathy compounded by recurrent episodes and vitamin B12 deficiency. This case underscores the importance of a comprehensive evaluation in patients with insulin-treated diabetes and recurrent hypoglycemia. Identifying and addressing multifactorial causes, including drug-induced hypoglycemia, is essential. Long-term follow-up is critical to ensure sustainable therapeutic success and to mitigate the risk of recurrence.

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EP402

JOINT2306

Evolution of glycemic profile of diabetic women after childbirth

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Background
Pregnancy represents a critical period in the life of a woman with diabetes, as it leads to weight gain and alters glycemic control as well as lipid profile. The aim of our study was to determine the evolution of glycemic profile of a group of diabetic women after childbirth.
Methods
We conducted a prospective descriptive study in pregnant women treated for pregestational diabetes and followed at the Department of Nutritional Diseases «D» of the National Institute of Nutrition of Tunis. Glycemic profile was monitored during pregnancy and six months postpartum.
Results
We collected 30 diabetic patients with a mean age of 32.2 ± 4 years [ext :23-39]. Most patients had type 2 diabetes (80%). The mean duration of diabetes was 3.6 ± 2.9 years in patients with type 2 diabetes and 13.6 ± 7.3 years in patients with type 1 diabetes. During pregnancy: The mean glycated hemoglobin (A1C) was 7.8 ± 1.6% with a range from 5.9% to 12%. The occurrence of a hypoglycemic episode was reported in 22% of the patients. After six months of childbirth, only 10% of babies were exclusively breastfed, while half were formula-fed. The mean fasting blood glucose level was 10,11 ± 4,5 mmol/l, and the mean A1C was 8,19 ± 2,05%. Only 3 patients reported experiencing hypoglycemic episodes. We observed a lower mean A1C level in cases of exclusive breastfeeding ($P = 0.035$).
Conclusion
Six months after childbirth, we observed an increase in the glycated hemoglobin level and a decrease in the number of hypoglycemic episodes. Further studies on a larger scale might be needed.

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EP403

JOINT2400

A case of insulin antibody-mediated insulin resistance in type 2 diabetes treated by glucocorticoid

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Introduction
Severe insulin resistance (IR), although rare, is clinically significant as it leads to deterioration of glycemic control despite very high insulin doses. One of the rarest etiologies is autoimmunity, particularly the production of insulin autoantibodies (IAA), which can result in extreme insulin resistance and unpredictable glycemic variations.
Observation
We report the case of a 61-year-old woman with a history of type 2 diabetes treated with human insulin for 10 years. She developed insulin resistance and was admitted to our hospital. She has reported a deterioration of her glycemic control despite an increase in the dose of insulin up to 200 U/day. Clinical examination was unremarkable, with no history of drug intake. A high titer of insulin antibodies was detected in the serum (77.6%). Prednisolone was administered with a dose of 0.5 mg/kg/day for one month. The dosage was tapered by 5 mg at 15-day intervals until reaching 5 mg/day. Insulin requirement decreased by 66% and glycemic control was reached."
Discussion and Conclusion
Insulin resistance is defined as a state (of a cell, tissue, or organism) in which there is a decrease of the biological response to insulin. Clinically, it manifests as a deregulation of glycemic homeostasis. IAA-mediated IR is a rare autoimmune disorder characterized by high titers of insulin autoantibodies, leading to excessive insulin binding and sequestration, resulting in postprandial hyperglycemia and nocturnal hypoglycemia. The treatment of antibody-mediated IR is not standardized; corticosteroid therapy often gives good results. Immunosuppressive therapy, insulin analogs, and plasmapheresis have been proposed in refractory cases. Although uncommon, this condition can cause significant metabolic disturbances and increased morbidity. However, if the diagnosis is early recognized and the treatment is well-conducted, the prognosis can be improved.

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EP404

JOINT3022

Diabetes as a major risk factor for pharyngostoma: influence of comorbidities on postoperative outcomes

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Introduction
Diabetes is a major risk factor for the development of pharyngostoma, a severe postoperative complication that significantly impairs healing. Other contributing factors include poor nutritional status, radiotherapy history, and infection, all of which further compromise tissue regeneration and wound closure.

Objective
This study aims to evaluate the impact of diabetes and other associated risk factors on the incidence, progression, and management of pharyngostoma.
Methods
A retrospective analysis was conducted on patients who developed pharyngostoma, comparing diabetic and non-diabetic cases while considering additional risk factors such as malnutrition, prior radiotherapy, and infections. Data on healing time, complication rates, and clinical outcomes were analyzed.
Results
The average age of our patients was 60 years. The sex ratio was 19.5. 95.1% of patients were smokers, and 51.2% were alcoholics. Some patients had associated comorbidities; diabetes was noted in 7.3% of cases, hypertension in 8.9% of cases, heart disease in 0.8%, and chronic obstructive pulmonary disease in 2.4% of cases. Ten (8.1%) patients had a history of laryngeal cancer. In 3 cases (2.4%), partial laryngeal surgery was performed, and in 7 cases (5.7%), initial non-surgical treatment included radiotherapy. Radiotherapy was exclusive in two cases and combined with chemotherapy as part of a laryngeal preservation protocol in the remaining 5 cases. For locoregional and distant staging, all patients underwent panendoscopy and cervical thoracic CT scan. Total laryngectomy was performed in all patients, extended to neighboring structures in 35.8% of cases. Postoperatively, pharyngostoma occurred in 11 (8.9%) of our patients. Univariate analysis found a statistically significant relationship between the occurrence of pharyngostomy and a history of diabetes ($P = 0.034$), preoperative radiotherapy ($P = 0.016$), total laryngectomies extended to the hypopharynx ($P = 0.017$), and postoperative parietal infection ($P = 0.000$). Preoperative albumin and hemoglobin levels, initial tracheostomy, advanced tumor stage, and suture type were not associated with an increased risk of pharyngostomy in our series.
Conclusion
Diabetes significantly increases the risk of pharyngostoma, particularly when combined with other risk factors. Optimized glycemic control, along with appropriate nutritional support, infection prevention, and careful surgical planning, is essential to improving postoperative outcomes in high-risk patients.
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EP405

JOINT2511

An unusual cause of hypoglycemia: insulin autoimmune syndrome

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Introduction
Insulin autoimmune syndrome (IAS) is a rare cause of hypoglycemia characterized by elevated serum insulin levels and autoantibodies against endogenous insulin that cause spontaneous hypoglycemic episodes. The aim of this case is to emphasize the significance of evaluating IAS in individuals with recurrent hypoglycemia.
Case
A 64-year-old man who had hypoglycemia episodes for 2 months was referred to our endocrine clinic with a suspicion of insulinoma. The patient has no known disease other than choledocholithiasis. In blood tests performed due to hypoglycemia, fasting serum glucose (FSG) was 42 mg/dL, insulin level was 1523.5 mU/l, c-peptide was 6.11 µg/l, and HbA1c was 6.3%. We conducted a 72-hour fasting test to confirm the diagnosis of endogenous hyperinsulinemia. After 14 hours, hypoglycemic symptoms emerged, and FSG was 40 mg/dL, insulin was 212.9 mU/l, and C-peptide was 4.9 µg/l. There was no blood glucose response after glucagon administration. MRI of the abdomen, Gallium-68 Dotatate scintigraphy, and endoscopic ultrasonography (EUS) failed to detect the tumor. The anti-insulin antibody was 91.5% (<8.2). Autoimmune hypoglycemia was considered in the patient. We reviewed the patient's recent prescriptions to determine the triggering factor, as he had been describing hypoglycemia for the last few months. We saw prescriptions for dexketoprofen, paracetamol, and erdosteine. We adjusted the patient's diet regimen and performed close blood sugar monitoring. All of the patient's medications were discontinued, and agents that could trigger hypoglycemia were avoided. During follow-up, the patient's episode frequency decreased, and hypoglycemia was not at a level that would affect his daily life.
Conclusion
Insulin autoimmune syndrome is a rare syndrome that causes episodes of hypoglycemia. This case highlights the importance of considering IAS as a differential diagnosis in patients presenting with recurrent hypoglycemia secondary to hyperinsulinemia. The standard diagnostic test for IAS is the measurement of insulin autoantibodies. Clinicians should keep in mind patients with atypical hypoglycemia, which enables timely diagnosis and eliminates the necessity for expensive imaging methods or invasive surgical interventions. The primary treatment for IAS is a diet consisting of low glycemic index foods. Additionally, steroids may be utilized as an adjunctive therapy.
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EP406

JOINT482

On the evaluation of the significance of hyperuricemia from the position of belonging to the metabolic syndrome

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Metabolic syndrome (MS) is cluster of risk factors for cardiovascular diseases. None of the available versions of recommendations for the diagnosis of MS hyperuricemia (HU) is not recognized as a criterion of MS, although some MS and HU are quite common.
The aim Analysis of the relationship of HU with the components of the MS in a random population sample.
Materials and Methods
The group of subjects ($n = 727$) was formed according to the generally accepted epidemiological approaches by the method of random sampling from among the workers and employees of the industrial enterprise (average age (38.13 ± 5.1) years). Statistical processing of the results was performed using Package for Social Sciences v.16.0 (SPSS Inc, Chicago, Il, USA).
Results And Discussion.
HU was diagnosed in 16.2% of people. It has been established that in people with HU the probability of diagnosis of impaired of glucose homeostasis (IGH) increases by 5.1 times, type 2 DM by 3.7 times, obesity by 2.9 times, arterial hepertension (AG) by 2.3 times and dyslipidemia by 1.7 times, respectively. It is determined that almost every second case of HU in a random population sample is associated with at least two more components of MS (AG + obesity), in every fourth case – with three components (AG + obesity + dyslipidemia), in every eighth case – with four components (AG + obesity + dyslipidemia + IGH). It was found that in every fourth representative of the random population sample, who was diagnosed with impaired of glucose tolerance and type 2 DM, has a "complete" MS; the probability of diagnosing MS in people with IGH increases 10 times compared with the population.
Conclusions
If the verification of "complete" MS is not limited to the mandatory inclusion of HU, the frequency of diagnosis in one member of a random population sample of the quartet of symptoms (obesity + AG + dyslipidemia + hyperinsulinemia) doubles and is already 4.0% of the total random population sample. Under this condition, every second representative of the random population sample of IGH is diagnosed with "complete" MS.
Keywords
hyperuricemia, metabolic syndrome, impaired of glucose homeostasis, impaired glucose tolerance, type 2 diabetes mellitus.
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EP407

JOINT2022

Diabetes mellitus in acute exacerbation of chronic obstructive pulmonary disease. retrospective study

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Background
The relationship between Type 2 Diabetes Mellitus(T2DM) and Chronic Obstructive Pulmonary Disease (COPD) is known to be bidirectional. Diabetes Mellitus (DM) and hyperglycemia are important risk factors for poor outcomes in hospitalized patients with acute exacerbation of COPD (AECOPD). There is limited data regarding specific outcomes in diabetic patients with AECOPD and still many issues need to be clarified about the impact of T2DM in this patient population.

Objective
This study aimed to evaluate the impact of previously known and newly diagnosed DM, on outcomes of hospitalised patients with AECOPD.
Methods
A total of 100 hospitalized patients diagnosed with AECOPD, during the interval January-March 2024, in e tertiary Hospital Center in Albania, were included in the present study. Outcomes of diabetic- AECOPD patients were compared with non-diabetic AECOPD patients. Markers associated with development of type 2 DM were identified. At the same time we analysed how glycemic control during the hospitalization period could influence final outcomes regarding in-hospital case fatality and in-hospital adverse events.
Results
Of the 100 patients enrolled in this study, the overall prevalence of T2DM was 31%, with average glucose values X = 245 mg/dl (min 93mg/dl —max 556 mg/dl). The T2DM group had higher inflammatory marker levels and a longer hospital stay versus the non-diabetic group. Age, increased inflammatory markers, elevated blood glucose on admission and inhospital were all risk factors for complications like need for assisted ventilation and mortality in hospitalized AECOPD patients.
Conclusions
AECOPD patients had a higher prevalence of T2DM than the general population; T2DM comorbidity caused longer hospital stays, and increased risc of inhospital complications in AECOPD hospitalised patients. Poor blood glucose control may increase the risk of mortality in AECOPD patients.
Keywords
Type 2 diabetes mellitus, COPD, Acute exacerbation of COPD, Glycemic control, Outcomes.
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EP408

JOINT1266
Post-surgical biliary pancreatitis and GAD positive diabetes: a rare case of type 3c DM with autoimmune features
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Background
Diabetes mellitus is primarily classified as Type 1(autoimmune origin, mainly by GAD antibodies), and Type 2 (insulin resistance with B-cell dysfunction); however, a clinically significant subtype, Type 3c diabetes, develops due to chronic pancreatitis, pancreatic surgery, or trauma. While type 3c DM typically results from exocrine damage, the presence of GAD antibodies raises the possibility of distant autoimmune mechanisms contributing to B cell loss. Disguising between T3cDM and autoimmune diabetes is crucial in determining optimal treatment strategies.
Case Report
A previously healthy 22-year-old male with a family history of diabetes and autoimmune disease underwent elective laparoscopic fundoplication for a hiatus hernia, with post-operative complications of severe abdominal pain with steatorrhea, nausea, shortness of breath, insomnia, and fatigue. Pain control due to opioid intolerance (hallucinations on morphine and nausea with oxycodone) required PCA fentanyl 20 mg bolus, paracetamol, and diclofenac supplement. Imaging and laboratory findings confirmed biliary pancreatitis with peri-pancreatic inflammatory changes - Amylase 768U/l (n 25-125U/l) and Lipase 1234U/l(n < 150U/l), surgical emphysema, mediastinal gas without pancreatic necrosis. MRCP revealed multiple tiny gallstones and a distal common bile duct calculus. Persistent hyperglycemia ranging from 16-22 mmol/l, HbA1c - 78 (n - 7.5%), and autoimmune screening confirmed for GAD antibodies < 200 IU/ml (n < 5 IU/ml) and lower C peptide at 0.3mg/ml (n 0.9-4 ng/ml), which raised suspicion of surgical type 3c induced diabetes consistent with exocrine-derived. The patient was managed with basal-bolus insulin (Lantus 28 units nightly, Novorapid 8-14 units per meal) and sliding scale correction for blood glucose 10 mmol/l. The patient was discharged with a management plan of Creon 250,000 units and Humalog 12-20 units with a meal. Tresiba long-acting double strength 84 units at night. The patient claims the symptoms of fatigue, night sweats, diarrhea, and severe unknown origin left upper quadrant radiating to left shoulder abdominal pain.
Conclusion
This is an atypical instance of type 3c diabetes accompanied by post-surgical pancreatitis, biliary blockage, and a rapid onset of GAD-positive diabetes. Acute pancreatitis has been known to elevate GAD-antibody levels, which can result in insulin-dependent diabetes. The presented case is rare as GAD antibody levels are typically lower in autoimmune diabetes (less than 100 U/ML). We suggest that post-surgical pancreatitis caused by gallstones triggered an increase in autoimmune cells, resulting in damage to the islet cells and insulin deficiency. This complex case underscores the necessity of a collaborative approach in both diagnosis and treatment.
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EP409

JOINT1087
Working time and metabolic syndrome- analysis of indian data
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Introduction
There has been a recent debate on the relation between work time and metabolic syndrome. The aim of this study is to see whether there is any association between state-wise work time and state-wise prevalence of diabetes and hypertension.
Methods
We compared published data of average working minutes/day in India state-wise from 2019 Time Use Survey, with diabetes, hypertension and dyslipidemia prevalence state-wise, and looked for a correlation with diabetes, and hypertension data state-wise. We collected data from the ICMR-INDIAB study and the latest published literature. We used the Shapiro-Wilk test, skewness and kurtosis to check for the normality of data. We used the Pearson r correlation test for parametric and the Spearmen rho test for nonparametric data to check for correlation between state-wise working time, state-wise diabetes, hypertension and dyslipidemia prevalence. We also evaluated rural and urban data separately whenever available. Statistical analysis was done using JASP (University of Amsterdam).
Results
In our findings, the Average time spent on paid activities by individuals per state positively correlated with state-wise Diabetes mellitus prevalence rate. (Spearman rho 0.412, $P = 0.024$). This relationship was sustained in the urban/rural divide. Average time spent on paid activities in the urban region positively correlated with urban diabetes prevalence state-wise. (Pearson r 0.5, $P = 0.05$). Similarly, rural work time is also correlated positively with the rural prevalence of diabetes mellitus. (Pearson r= 0.595, $P = 0.019$). Average time spent on paid activities was not significantly correlated with diagnosed hypertension at the time of the survey ($P = 0.812$), but it was positively correlated with undiagnosed hypertension at the time of the survey. (Spearman rho 0.358, $P = 0.041$). Work time also correlated positively with cholesterol levels > 200 (spearman rho 0.372, $P = 0.047$), Ldl > 130, (spearmen rho 0.367, $P = 0.05$). However, no significant correlation was found between triglyceride levels > 150 and HDL levels < 40.
Conclusion
In India, the state-wise prevalence of metabolic syndrome components like diabetes, hypertension and dyslipidemias correlated positively with average working minutes/ day, suggesting the need to define optimal working time to find a balance between economic growth and health.
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EP410

JOINT3321
Durability of glycemic response with FDC of sitagliptin and metformin in treatment naive T2DM indian patients from a real-world retrospective EMR based study
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Background and aims
We conducted a real-world, retrospective, observational, electronic medical records (EMR) based study to understand the effectiveness of sitagliptin and sitagliptin + metformin fixed-dose combination (FDC) in Indian patients with type 2 diabetes mellitus (T2DM). The data here presents a subgroup analysis of treatment naïve T2DM patients who received sitagliptin + metformin FDC.
Materials and methods
Aggregated and anonymised EMR data of adult (age ≥18 years) male and female patients having T2DM, who were prescribed with sitagliptin or sitagliptin + metformin FDC, with or without other oral anti-diabetic medicines and had data

available for baseline and follow-up visits from 2017 to 2023 was retrieved. Patients who were on insulin or any other injectable antidiabetic medication like Glucagon-like peptide-1 agonists were excluded. This subgroup analysis assessed the effectiveness of sitagliptin + metformin FDC on glycosylated haemoglobin (HbA1c) levels of naïve patients from baseline to 3 months and 9 months. The study was registered on Clinical Trial Registry – India (CTRI/2023/10/058366)
Results
EMR data was available for 986treatment-naive patients with HbA1c $\geq$7%, who received sitagliptin + metformin FDC. The follow up data for 315 patients was available at 3 months and for 118 patients at 9 months. Mean HbA1c at baseline was 8.94 $\pm$ 1.78 in patients with 3 months' data (n =315) and it was 8.71 $\pm$1.60 in patients with 9 months' data (n =118). Mean change from baseline (CFB) in HbA1c at 3 months (8.94 $\pm$ 1.78 to 7.33 $\pm$ 1.05; CFB: -1.61 $\pm$ 1.83, P<0.0001) was statistically significant. Mean CFB in HbA1c at 9 months (8.71$\pm$ 1.60 to 7.45 $\pm$ 1.29; CFB: -1.26 $\pm$ 1.90, P<0.001) was also statistically significant. Proportion of patients achieving HbA1c <7% in sitagliptin + metformin FDC arm was 40.32% at 3 $\pm$ 1 month and 44.07% at 9 $\pm$ 1 month.
Conclusion
This subgroup analysis of EMR based study in India demonstrated effectiveness of sitagliptin and metformin FDC, in significantly improving HbA1c and providing durable control over 9 months in treatment-naïve T2DM patients in a real-world setting with more proportion of patients achieving HbA1c <7% over time.

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EP411

JOINT2741

Hybrid closed loop in a residential setting: it takes a village but it is worth it

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Hybrid closed loop (HCL) insulin pumps represent a significant advancement in diabetes management and has shown to improve glycaemic outcomes, reduce diabetes-related distress, and improve quality of life. However, its application in residential environments is not well studied. This case study explores the effectiveness of using a HCL insulin pump in a residential setting in a 27-year old woman with Type 1 diabetes (T1D) who is unable to self-care diabetes. She has Trisomy 21, T1D for five years, total hypoglycaemia unawareness, primary hypothyroidism, coeliac disease, and oesophageal achalasia. She lives in residential care and has very limited vocabulary and sensory issues with insulin injections. Oesophageal achalasia deteriorated over the years despite pneumatic dilatations, and only minimal oral food intake became possible. Therefore, percutaneous endoscopic gastrostomy (PEG) tube was inserted to administer the nutrition. Despite being on basal bolus regimen with insulin aspart and detemir and wearing real-time continuous glucose monitoring, her glycaemic ranges were suboptimal (average sensor glucose 14.5mmol/l, GMI 9.6%, Time-in-Range 15%, Very High-Above-Range 57%, High-Above-Range 28%, HbA1c 61mmol/mol). She required multiple hospital admissions due to hyperglycaemic and hypoglycaemic episodes and her quality of life was affected due to recurrent and prolonged hospital admissions. There was also a significant weight gain with BMI 43 kg/m^2. Considering all above, the diabetes MDT explored the option of Metronic MiniMed^{TM} 780G HCL insulin pump with the patient's family and caregivers. Initially, 22 residential staff were trained using a virtual insulin pump platform to familiarize them with pump functions. This was followed by practical, in-person sessions, where staff learned to perform tasks such as set insertions and changes. Smartguard technology was integrated into the training to enhance the staff's ability to manage glucose levels effectively. The diabetes MDT followed up very closely with the patient and caregivers in-person and virtually to adjust the PEG feeding plan and HCL system. The patient has been on HCL system for the past eight months and glycaemic ranges have improved significantly (average sensor glucose 9.3mmol/l, GMI 7.3%, Time-in-Range 55%-67%, Time-below-Range 0-1%, HbA1c 53mmol/mol). Since HCL system, the patient had only two short hospital admissions, is energetic, participating in daily activities and her weight has reduced by 5 kg. Our case suggests that HCL system together with a skilled diabetes MDT support offers promising benefits for residential use. Continued research is necessary to optimise the functionality of HCL system for this cohort.

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EP412

JOINT2351

Role of pre-pregnancy weight and weight gain during pregnancy on maternal and fetal outcomes: real word data from an italian centre

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Gestational diabetes mellitus (GDM) refers to glucose intolerance of variable severity that begins or is diagnosed for the first time during pregnancy and resolves immediately after birth. Although this condition often resolves after giving birth, it can increase the risk of developing type 2 diabetes in the future. The primary aim of our study was to evaluate the possible determinants of maternal-neonatal outcomes in women diagnosed with GDM, in our center between 2021 and 2024.A secondary objective was to evaluate whether the type of birth, spontaneous, or induced, could determine a different risk of neonatal complications or a different category of neonatal weight, classified as adequate weight for gestational age (AGA), small for gestational age (SGA) or large for gestational age (LGA). We initially evaluated 150 women attending our outpatient clinic. Only those who had at least one follow-up visit after birth were included, for a total of 59 women included in the study. We used multivariable regression models to identify clinical predictors of materno-fetal outcomes, namely post-pregnancy maternal weight and glycemia, and offspring birthweight and perinatal complications. Maternal baseline weight, weight gain during pregnancy, treatment for GDM, breastfeeding, assisted fertilization were included as possible predictors. The correlations between postpartum fetal complications, offspring birth weight and weight category, and type of delivery were also evaluated.A total of 59 women were included in the analysis (age 34$\pm$ 5,3 years, BMI 25$\pm$7,2 kg*m$^-$2). Higher pre-pregnancy weight (β 0.850 P = 0.000) and greater weight gain during pregnancy (β 0.889 P = 0.016) were the best predictors of post-pregnancy weight. Similarly, regarding neonatal weight, the determinants that emerged were the mother's pre-pregnancy weight (β 16.88 P = 0.035) and maternal weight gain during pregnancy (β 58.18 P = 0.019); lastly, earlier diagnosis of GDM (β -0.37, P = 0.057) and insulin treatment during pregnancy (β -5.677, P = 0.061), were associated with a tendency to have higher post-partum fasting glycemia When comparing different birthing methods, these appeared to have no influence on fetal perinatal complications or weight. Our study highlights how the mother's pre-pregnancy weight is a fundamental determinant of weight gain during pregnancy, post-pregnancy weight and fetal weight. This calls for public health interventions aimed at avoiding overweight in childbearing age. Women with an early diagnosis of GDM and the use of insulin during pregnancy might be at a greater risk of postpartum impaired fasting glucose. Routinely inducing labor at 39 weeks of pregnancy is not supported by our data but this needs to be confirmed in larger samples.

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EP413

JOINT120

Nephroprotective treatment with dapagliflozin in patients with diabetic kidney disease

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Background and Aims
Albuminuria in patients with diabetes presents a higher risk for adverse renal and cardiovascular (CV) outcomes. Sodium glucose co-transporter 2 (SGLT2) inhibitors demonstrate improved albuminuria and reduces the risk of end-stage renal disease in patients with chronic kidney disease. The study aim was the impact of the SGLT2 inhibitor dapagliflozin on urine albumin-to-creatinine ratio (UACR) and GFR decline.
Method
In the single center trial, total 132 participants with CKD and type 2 diabetes (T2D) were randomly assigned to dapagliflozin (n = 78) 10 mg once daily or placebo (n = 54). Kidney inclusion criteria were eGFR 30–-60ml/min/1.73 m2 and any UACR. The primary end point was a composite of sustained decline in

eGFR >50%, end-stage renal disease, or kidney or cardiovascular death. Percentage treatment difference was estimated by geometric mean ratio for the overall cohort and by eGFR and UACR subgroups. Progression/regression of UACR were assessed. Hazard ratios, 95% confidence intervals (CI), and p-values were estimated by Cox proportional hazards model.
Results
Median baseline eGFR was 42.3ml/min/1.73 m2, with 5% at <30ml/min/1.73 m2. At baseline, median UACR was 103 mg/g, and 1/4 of patients had normoalbuminuria, 2/4 had micro, and 1/4 had macroalbuminuria. Median follow up was 18 months. The UACR difference for dapagliflozin vs placebo was -25.1% (95% CI -27.5, -23.2; $P < 0.001$). Reductions were similar across eGFRs. In UACR 30-299mg/g and >300mg/g, reductions were significant in dapagliflozin ($P < 0.001$). Progression risk was lower and regression risk higher in dapagliflozin vs placebo ($P < 0.001$).
Conclusion
Dapagliflozin significantly slowed long-term eGFR decline in patients with CKD with T2D compared with placebo, and significantly reduced UACR and had favorable effects on UACR progression and regression.

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EP414

JOINT3973

Predictive factors for the use of insulin therapy in gestational diabetes

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Introduction
In diabetic patients, planning conception is essential to prevent embryofetopathy and the progression of diabetes complications in the mother.
Study Objective
The aim of our study is to analyze the clinical and metabolic profile of a group of pregnant women with Gestational Diabetes (GD) and to determine the predictive factors for the use of insulin therapy.
Materials and Methods
This is a retrospective study conducted in our Department, including 368 patients with gestational diabetes. Statistical analysis was performed using SPSS software.
Results
The average age of the patients was 32 years. The average term for diagnosing gestational diabetes was 25.2 weeks of amenorrhea. 22% had a history of GD. Insulin therapy was required in 27% of cases. The average total insulin dose required was 0.5 units/kg/day at the end of third trimester. A regimen with three rapid insulin injections was prescribed for 20 pregnant women. For the remaining patients, a basal-bolus regimen was necessary to achieve targets. The need for insulin therapy was more frequent when GD was diagnosed earlier (<24 weeks) ($P = 0.02$), in patients older than 35 years ($P = 0.02$), and with higher fasting blood glucose levels and average glycated hemoglobin levels ($P = 0.01$).
Conclusion
This study demonstrated that earlier diagnosis of GD, advanced maternal age, and elevated fasting blood glucose levels are predictive factors for insulin therapy, consistent with previous studies. However, a history of macrosomia, recurrence of GD, and diabetic heredity were frequently associated with patients treated with insulin but without statistically significant results.

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EP415

JOINT1477

The use of hybrid closed-loop systems in a pediatric population with type 1 diabetes mellitus- a real-world retrospective study

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Introduction
Hybrid closed-loop (HCL) systems consist of three essential components: a continuous glucose monitoring (CGM) sensor, an algorithm that analyzes data from the CGM, and an insulin pump capable of delivering varying doses of insulin based on this information, alongside doses administered by the user. These technologies aim to improve metabolic control and reduce hypoglycemia risk, enhancing patients' quality of life.
Material and methods
We conducted a retrospective study involving children with type 1 diabetes (T1D) who were admitted to our department to initiate HCL insulin pump therapy. We evaluated the patients at two key points: at baseline, when the insulin pump was first initiated, and during a follow-up visit at least six months later. We assessed glycated hemoglobin (HbA1c) levels at both time points and downloaded CGM reports documenting the previous 90 days. These reports included various parameters: time in range (TIR: 70-180 mg/dL), time in tight range (TITR: 70-140 mg/dL), time below range (TBR) categorized as <70 mg/dL, 54-70 mg/dL, and <54 mg/dL, time above range (TAR) categorized as >180 mg/dL, 180-250 mg/dL, and >250 mg/dL, and the coefficient of variation (CV). This research aimed to assess the effectiveness of HCL therapy in improving glycemic control in children with T1D.
Results
Thirty-two children (68.8% female) participated in the study. Participants had an average age of 11.5 years ($\pm$2.8) and a mean diabetes duration of 5.8 years ($\pm$3.7), with an average follow-up time of 11.9 months ($\pm$4). At follow-up, HbA1c decreased significantly (7$\pm$1% vs 6.6$\pm$0.6%, $P = 0.01$). CGM reports were available at baseline and follow-up for 27 patients. The results revealed a significant increase in TIR (69.2$\pm$15.7% to 79.4$\pm$7.9%, $P<0.001$). Additionally, TITR rose from 48.4$\pm$16.9% to 57.9$\pm$10.1% ($P<0.001$). TBR <70 mg/dL and between 54-70 mg/dL significantly decreased: TBR <70 decreased from 5.4$\pm$3.6% to 3.2$\pm$2.3% ($P = 0.008$), and TBR 54-70 decreased from 4.2$\pm$2.2% to 2.7$\pm$1.9% ($P = 0.007$). TBR <54 mg/dL decreased also, but this change was not statistically significant (1.2% vs. 0.5%, $P = 0.06$). Furthermore, TAR and its subintervals showed significant reductions: TAR >180 mg/dL dropped from 25.3$\pm$16.2% to 17.2$\pm$8.1% ($P = 0.02$), TAR 180-250 mg/dL decreased from 18.1$\pm$9.3% to 13.8$\pm$5% ($P = 0.003$), and TAR >250 mg/dL fell from 7.2% to 3.3% ($P = 0.006$). The CV also significantly decreased, changing from 37.4$\pm$7.3% to 34.3$\pm$5.3% ($P<0.001$).
Conclusions
HCL systems enhance metabolic control in children with T1D, helping them achieve targets for glucose variability and increasing time spent in normoglycemia, thus reducing the risk of short-term and long-term complications.

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EP416

JOINT1463

Congenital hyperinsulinism: same parents, different genetics. regarding two cases

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Introduction
Congenital hyperinsulinism is the most common cause of recurrent hypoglycemia in children <2 years of age.
Aim
To show two cases of brothers with consanguineous parents in order to spread the disease and its evolution and management
Case 1
Girl who showed at 24 hours of age febrile seizure, hypoglycemia (21 mg/dl), and subependymal hemorrhage. She required glucose intake (21mg/kg/day), antic-onvulsant, IV calcium, vitamin D, phenylbutyrate, benzoate, arginine, lactulose, carnitine, glycosade (150ml/kg/day), dextrinomaltose, cornstarch and feeding by NGT. Two critical samples were carried out. Lactic acid (5.6), cholesterol (217), ammonium (287), CK (2689), GOT (377), GGT 342), insulin (40 and 48.57), acids fatty (5), were elevated, while acylcarnitine 6 (C6), C-peptide (7 and 7.76), calcium (8.8), and vitamin D were decreased. Ketone bodies were negatives. She was diagnosed with congenital hyperinsulinism, and PET was performed, finding a diffuse pattern with doubtful focality in the pancreatic tail. Normal genetic panel for hyperinsulinism and K-ATP channels. In expanded exome she was carrier of ABCC8, POMC and TNNI3 mutations. She started treatment with diazoxide without response. She was treated with octreotide (27mg/kg/day), sirolimus (3mg/m2/day) and hydrocortisone. She showed hypertriglyceridemia and swallowing disorders. Currently being treated with Lanreotide 60mg sc every 2 months. Diagnosed with dilated cardiomyopathy with EF 30% and thrombosis at 2 years, requiring EMO and heart transplant. After transplant, lanreotide was withdrawn due to hyperglycemia, and reintroduced a few months later.

Case 2
Male who at birth showed severe non-ketotic hypoglycemia that required glucose intake (>8mg/kg/minute). Critical sample compatible with hyperinsulinism (C peptide >0.6, glucose 25 mg/dl), treated with diazoxide, dextrinomaltose, and more glucose, with hypoglycemia persisting, so he started octreotide 60 mg/dose + glycosade and raw starch (cornstarch), controlling himself. Genetics detected SUR1 DEFICIENCY. At 1.5 years of age he was diagnosed with dilated cardiomyopathy. He developed severe left ventricular dysfunction and moderate/severe mitral insufficiency. After 2 years, the ejection fraction worsened and produced decompensated heart failure, requiring external ventricular assistance. He showed instability and continuous febrile processes that only improved after hydrocortisone. In brain MRI, marked diffuse cerebral atrophy and established infarcts. He progressively worsened, evolving to cardiorespiratory arrest and death
Conclusions
- In case of negative genetics and high suspicion, complete exome may be a diagnostic possibility.
- In case of no response to diazoxide, the next therapeutic steps would be both oral and subcutaneous somatostatins, in that order.
- Hypertriglyceridemia and swallowing disorders are reported side effects of somatostatins and sirolimus.

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EP417

JOINT1781
Role of dedicated DSN: improving outcomes through intervention and support
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Presentation
We report a case of a 40-year-old male admitted in April 2023 with left foot infection and an ulcer on lateral aspect of 5th toe. Past medical history of Type 2 Diabetes Mellitus diagnosed age 25, Hypertension and Hypercholesterolaemia. Current medication Metformin 1g BD, Gliclazide 160mg BD, Canagliflozin 100mg OD, Ramipril 10mg OD and Atorvastatin 20mg OD. On admission HbA1c was found to be 138mmol/mol, patient was therefore referred to the in-patient diabetes nurses. Medication compliance was noted as an issue, considering foot infection insulin was commenced. Basic education and diet advice was given, patient was referred for additional support in the community. Patient declined insulin following discharge stating he would improve his diet and oral medication compliance to achieve better glucose control. At 12 weeks post discharge review in diabetic foot clinic and having been on oral antibiotics the foot infection had settled, and the ulcer was improving. HbA1c had reduced to 90mmol/mol. Patient advised to re-consider insulin but declined. At 18 weeks review, HbA1c rose to 110mmol/mol, patient admitted poor compliance with both diet and medication. Plan to start insulin at next clinic visit in 6 weeks as no Diabetes specialist nurse (DSN) available at the time. At 24 weeks review by DSN in diabetic foot clinic he had very limited blood glucose readings, patient still refusing insulin but agreed to a freestyle libre trial and close DSN phone follow-up. Patient again reported poor compliant with medication, high carbohydrate, sugar, and fat diet. Education was given regarding diabetes complications, diet and exercise impacts on blood glucose levels and the importance of medication compliance. At 25 weeks review we had further detailed discussion regarding glucose results, diet and lifestyle considering freestyle libre data in relation to post meal peaks and subsequent review with DSN 1 week later showed glucose to be 78% within target (4-10mmol/mol). Therefore, no changes to medication, patient to continue to work on improvements with lifestyle modifications. Further weekly phone support with DSN was scheduled. At 31 weeks review in joint foot clinic revealed foot infection fully resolved; foot wound completely healed with an HbA1c of 54mmol/mol.
Conclusions
Dedicated intensive input from DSN with freestyle libre improved challenging compliance issues. Thus, achieved significant improvement in glucose control, leading to complete wound healing while avoiding the need for insulin.

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EP418

JOINT3745
Two cases of wolfram syndrome in bulgarian children from pleven region
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Wolfram syndrome (WS) is a rare autosomal recessive disorder (ORPHA:3463, OMIM# 222300) caused by mutations in the WFS1 genes (Wolfram syndrome type 1 = WS1) or CISD2 genes (Wolfram syndrome type 2 = WS2), with a global prevalence of less than 1 in 1 000 000. These patients often present with diabetes mellitus, diabetes insipidus, optic atrophy, and sensorineural deafness (DIDMOAD). In addition, abnormal urinary tract function or neuropsychiatric disorders could be observed. An Autosomal Dominant Wolfram-like syndrome with similar clinical features, caused by heterozygous mutations of the WFS1 gene, is also reported. We report two patients with Wolfram syndrome, diagnosed more than 10 years after the onset of diabetes mellitus. First patient is a 14-year old boy with diabetes mellitus, bronchial asthma and optic atrophy, genetically proven for WS1. Second patient is 16-year old girl with diabetes mellitus, diabetes insipidus, epilepsy and severe urological abnormalities, suspected for WS. Multiple systemic organ involvement with different and highly heterogeneous clinical features makes WS a diagnostic challenge. Early genetic testing could confirm the diagnosis and improve individual therapeutic approach and outcomes for patients.

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EP419

JOINT493
A favorable factors influencing glycemic control in pediatric type 1 diabetes patients
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Backgrounds
To prevent short-term and long-term complications in pediatric type 1 diabetes patients, optimal glycemic control in essential. However, there is a lack of information about the factors that can predict future blood sugar level control among the patients. Through this article, we aim to investigate predictive factors for optimal blood sugar regulation and identify adverse prognostic factors.
Methods
Retrospective chart analysis was conducted on 92 pediatric and adolescent patients with type 1 diabetes mellitus who visited the Department of Pediatrics at Ajou University Hospital from 2000 to the present. The patients were divided into two groups based on their average HbA1c levels over the past year: the well-controlled group (WC, HbA1c < 7.5) and the poorly controlled group (PC, HbA1c ≥ 7.5). Data collection included all possible factors that may be associated with glycemic control of type 1 diabetes.
Results
Out of the total 92 patients, there were 41 patients in the Well-Controlled (WC) group and 51 patients in the Poorly-Controlled (PC) group, with average HbA1c levels of 6.23 ± 0.41 and 8.62 ± 1.53, respectively. The PC group tended to have a higher current age compared to the WC group (156.85 ± 44.834 vs 175.86 ± 36.718 months, $P = 0.035$). The HbA1c measured after starting insulin treatment was lower in the WC group ($6.587 \pm 0.872\%$ vs $7.259 \pm 1.242\%$, $P=0.003$). When using continuous glucose monitoring(CGM) or insulin pump, the chance of being in the PC group was lower (CGM: Odds ratio 0.396, $P = 0.036$; Insulin Pump: Odds ratio 0.197, $P = 0.009$). No significant differences in sex, BMI, diabetes duration, initial HbA1c and C-peptide level, and DKA history were noted between WC and PC groups.
Conclusions
Older age and higher HbA1c levels after starting treatment suggest a higher likelihood of poor blood sugar control, requiring intensified care. Furthermore, since the use of CGM and insulin pumps aids in blood glucose control, we should encourage patients to use these.

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EP420

JOINT916
Trends and outcomes in pediatric diabetes management after universal coverage expansion: a single tertiary care experience in Thailand
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Background
The global incidence of pediatric diabetes, including type 1 (T1D) and type 2 (T2D) diabetes, has been rising. Modern diabetes therapies have become widely accessible in the past decade, supported by Universal Coverage (UC) policies aimed at improving treatment outcomes.
Objective
To evaluate the clinical outcomes and complication screening trends in childhood-onset diabetes following the implementation of modern therapies.
Methods
A retrospective review was conducted using medical records from pediatric-onset diabetes patients (diagnosed before age 18) treated between 2018 and 2024 at King Chulalongkorn Memorial Hospital in Bangkok, Thailand.
Results
A total of 141 patients were analyzed in 2024, comprising 115 with T1D (81.5%), 11 with T2D (7.8%), and 15 with other types (10.6%). Intensive insulin therapy adoption in T1D reached 100% by 2024. Self-monitoring of blood glucose (SMBG) adherence remained at 56.52%, while the use of continuous glucose monitoring (CGM), reimbursable under UC since August 2023, rose from 8 users in 2022 (5.7%) to 20 users in 2024 (14.2%), marking a 150% increase. The proportion of T1D patients achieving HbA1c levels below 7% has shown a gradual increase, rising from 18.8% in 2018 to 29.1% in 2024. However, this remains below the expected target. The mean HbA1c levels in 2024 were 9% in T1D and 8.13% in T2D. Complication screenings revealed gaps: diabetic retinopathy was screened in 39.7% of patients, diabetic nephropathy using urine albumin-to-creatinine ratio in 59.6%, and serum creatinine in 60.9%. While dyslipidemia screening via LDL measurement was completed for all patients, only 19.9% had LDL levels below 100 mg/dL, suggesting treatment inertia in pediatric patients.
Conclusion
Despite improvements in therapy adoption, including intensive insulin therapy and DSMES programs, glycemic control in pediatric diabetes remains suboptimal. The significant increase in CGM users and the rising trend of T1D patients achieving targeted HbA1c levels indicate progress, yet further adoption of CGM and insulin pump technologies is needed. The shortage of diabetes educators continues to hinder effective management. Strengthening screening strategy and integrating educators into care teams is vital for better outcomes.
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EP421

JOINT3518
Parotid lithiasis revealing previously undiagnosed diabetes mellitus: a case report
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Introduction
Parotid lithiasis, or sialolithiasis, is an inflammatory condition of the parotid gland caused by a stone obstructing its excretory duct. Representing 4-10% of salivary gland lithiasis, it rarely reveals underlying diabetes mellitus, as in the case we present here.
Observation
A 44-year-old man with a family history of type 1 diabetes, who consulted for a right parotid swelling evolving for 2 days in a febrile context. Physical examination revealed a firm, approximately 3 cm, right parotid swelling with overlying inflammatory signs. Purulent discharge was observed from the opening of the right Stensen's duct, associated with a 1 cm trismus, but no facial paralysis was present. Cervical ultrasound showed a heterogeneous, enlarged right parotid gland with a stone in a dilated Stensen's duct. The patient was admitted in our department and started on Amoxicillin-clavulanic acid. The initial Lab results revealed a biological inflammatory syndrome and elevated blood glucose levels, along with a disturbed glycemic profile and a glycated hemoglobin of 6%. An endocrinology opinion was requested and he was placed on insulin therapy with good education regarding his incidentally discovered diabetes. The patient's condition improved significantly, and he was discharged on the 7th day with antibiotic coverage and a follow-up appointment with the endocrinology department for diabetes management.
Conclusion
This observation underlines the importance of looking for diabetes mellitus in patients with lithiasic parotiditis, particularly when associated risk factors are present. Early recognition of diabetes allows for timely intervention and prevention of long-term complications.
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EP422

JOINT626
Diabetes associated with childhood lipodystrophies: clinical characteristics and management
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Introduction
Lipodystrophy syndromes are rare and highly heterogeneous disorders characterized by partial or complete loss of adipose tissue.
Objective
To evaluate the genetic, clinical, metabolic, and therapeutic characteristics of cases diagnosed with childhood lipodystrophy and diabetes.
Materials and Methods
Six cases diagnosed with lipodystrophy and diabetes were included. The demographic and clinical characteristics of the cases, metabolic parameters, nutritional profiles microvascular complications, treatment models, and outcomes were retrospectively analyzed.
Results
The mean age of the patients was 13 years (10–14)(5 female, 1 male). HbA1c levels and treatment modalities are given in Table 1. In Case 1, HbA1c reduced from 9.9% to 5.9% with insulin pump therapy. In case 3 HbA1c reduced from 8.5% to 5.4% with metreleptin therapy only. In case 4 HbA1c reduced from 13.3% to 6.3% with an AID system. In case 5 HbA1c reduced from 9.9% to 8.1% with regular metreleptin use, but increased to 10.7% becuse inconsistent treatment. Case 6 became insulin-independent through a clinical research intervention. The details of this therapy will be disclosed after the publication of research findings. Nephropathy was seen in 67% ($n = 4$), polyneuropathy in 17%($n = 1$) and retinopathy in 17% ($n = 1$).
Conclusion
In four cases, diabetes was diagnosed before lipodystrophy, suggesting that diabetes may be an early manifestation of lipodystrophy syndromes. The use AID system was effective in maintaining glycemic control. Metreleptin therapies improved insulin resistance, resulting in significant reductions in HbA1c levels and, in some cases, eliminating the need for insulin therapy. The effective use of advanced diabetes technologies and targeted therapeutic strategies contributed to improvements in glycemic regulation.
Keywords
Diabetes associated with lipodystrophy, Metabolic control, Insulin infusion pump, Metreleptin, Pediatric and adolescent diabetes
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EP423

JOINT3804
Mody: when to consider? when should genetic tests be performed?
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Introduction
Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes that results from genetic defects that lead to β-cell dysfunction. Due to the heterogeneity of its clinical features and the lack of a single diagnostic criterion, MODY can often be misdiagnosed as type 1 or type 2 diabetes, and therefore its diagnosis is mostly based on genetic testing. Correct diagnosis of monogenic diabetes can significantly change treatment. This study aimed to evaluate the relationship between the clinical features of the cases and the detected genetic variations and to examine the effect of early diagnosis on diabetes management.
Material and Methods
The results of patients who were followed up in Tekirdağ Dr.İsmail Fehmi Cumalıoğlu City Hospital, Department of Pediatric Endocrinology between August 2023-December 2024 and studied the gene panel associated with monogenic diabetes were evaluated. Genetic analysis was performed using the Next Generation Sequencing Analysis (NGS). Variants classified according to the ACMG 2015 Guideline criteria were retrospectively examined.

Abstract EP422

Table 1: Metabolic, Glycemic Control, and Treatment Approaches

Category	Attribute	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Mean/Median
General Information	Lipodystrophy Type	Syndromic Lipodystrophy(MINGIE)	Acquired Generalized Lipodystrophy(Panniculitis-related)	Congenital Generalized Lipodystrophy(-Type 1)	Progeroid Type Lipodystrophy(Mulvihill Smith Syndrome)	Familial Congenital Partial Lipodystrophy(FPLD2, Dunnigan Type)	Congenital Generalized Lipodystrophy(CGL Type 2, BSCL2)	
	Diabetes Diagnosis Age	14	14	13	10	13	14	13/13.5
	Lipodystrophy Diagnosis Age	17	13	14	16	14	6	13.33/14.0
Glycemic Control	HbA1c-At Diagnosis(%)	7.5	12.4	8.5	9.2	9.9	8.5	9.3/8.85
	HbA1c-Final(%)	5.9	12.1	5.7	6.3	10.7	6.0	7.78/6.15
Insulin Treatment Model	Insulin Therapy	Aspart-Glargine	Aspart-Glargine		Aspart-Glargine	Glulisine-Glargine	Glargine	
	Insulin Delivery System	Continuous Insulin Delivery System			Automatic Insulin Delivery System			
Additional Treatments	Oral Antidiabetic		Metformin	Metformin	Metformin	Metformin	Metformin	
	Metreleptin			Metreleptin		Metreleptin		

Results

Mutations were detected in 11/16 (68%) cases that underwent genetic analysis with a preliminary diagnosis of MODY. Among the cases in which mutations were detected; heterozygous mutations were detected in the GCK genes(5/11), HNF1A(3/11), ABCC8(2/11) and G6PC2(1/11). The cases in which GCK mutations were detected applied with a complaint of coincidental hyperglycemia and were followed only with diet and lifestyle changes. Cases 1 and 2 with HNF1A mutations were female twins (15.4 years old) and applied with hyperglycemia. Case 3 (HNF1A mutation) was male (16.3 years old) and applied with diabetes symptoms. Diabetes antibodies were negative. Hba1c values of the cases at the time of application were 9.4%-11%-12%, respectively. Subcutaneous insulin treatment was started. In the genetic analysis of the patients, heterozygous c.685C>T (p.Arg229*) (in twin cases) and c.391C>T (p.Arg131Trp) (case 3) variants were detected. The cases were switched to oral sulfonylurea (gliclazide) and subcutaneous insulin treatments were stopped. One of the cases with mutation detected in the ABCC8 gene presented with diabetic ketosis and insulin treatment was continued.

Conclusion

Based on these clinical cases, the importance of early recognition and awareness of the signs and symptoms of MODY has been emphasized. In clinical practice, strict screening criteria should be established to balance cost-effectiveness and identification. The results of diabetes autoantibodies, family history of diabetes, age at onset, and endogenous insulin secretion should be taken into account to determine whether genetic testing is necessary. When suspicion arises, genetic testing should be performed to diagnose MODY and ensure early treatment and accurate family screening.

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EP424

JOINT1295

A very rare case of MODY 12: inactivating ABCC8 mutation causing sulfonylurea-resistant diabetes

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Introduction

Maturity-Onset Diabetes of the Young (MODY), is a rare monogenic form of diabetes mellitus, comprising 1-2% of cases. Disguised by its atypical clinical features, it is commonly misdiagnosed, with an estimated 80% of MODY patients presumed to have type 1 (T1DM) or type 2 diabetes (T2DM). We hereby present a unique case of MODY, diagnosed in adulthood due to an inactivating mutation of the ABCC8 gene, with no history of neonatal hypoglycaemia, and a lack of clinical response to sulfonylureas.

Case Report

A 22-year-old female was incidentally diagnosed with diabetes in 2017 after presenting with lower abdominal pain and symptoms of urinary tract infection. Urinalysis showed significant glucosuria. She lacked osmotic symptoms, and never experienced diabetic ketoacidosis. She was presumed to have T2DM. Initially treated with gliclazide and metformin, gliclazide was discontinued due to lack of clinical response, and replaced with metformin/empagliflozin combination therapy. She was referred to our pre-pregnancy clinic in 2024. Her BMI was 25 kg/m2, and HbA1c was 69 mmol/mol. Her atypical presentation, lack of insulin resistant features, and strong family history, prompted MODY probability testing, predicting 75%. T1DM serology, including GAD, IA2, and ZnT8 autoantibodies, was negative. C-peptide was 357pmol/l. Subsequent genetic testing identified a heterozygous inactivating ABCC8 mutation, p.Arg1353His (c.4058G>A), previously associated with Congenital Hyperinsulinism (CHI). The patient has no medical history of neonatal hypoglycaemia.

Discussion

The genes commonly associated with MODY include HNF1A, HNF4A, and GCK. While GCK-MODY and HNF1A-MODY account for 90% of cases, ABCC8-MODY makes up only 1%. The ABCC8 gene encodes Sulfonylurea receptor 1, a subunit of K-ATP channels in β-cells, modulating insulin release. Activating ABCC8 mutations are associated with Neonatal Diabetes and MODY. Inactivating ABCC8 mutations typically cause CHI. Only a handful of cases have reported inactivating ABCC8 mutations causing MODY, with even fewer being unresponsive to sulfonylureas. Gliclazide therapy proved unsuccessful, with her HbA1c reaching 97 mmol/mol, and the development of symptoms suggesting peripheral neuropathy. A trial of metformin/empagliflozin significantly reduced HbA1c, suggesting alternative therapeutic pathways may be necessary for cases involving inactivating ABCC8 mutations. To our knowledge, this is the first reported case linking this specific mutation to diabetes demonstrating a poor response to sulfonylureas. This case highlights the phenotypic heterogeneity of ABCC8-MODY, underscoring the importance of genetic testing in young patients with atypical diabetes presentations. It should inform future research into the precise pathophysiological mechanisms linking inactivating ABCC8 mutations to diabetes and their variable treatment responses.

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EP425

JOINT3320

Single center study on evaluating and mitigating key factors associated with extended hospitalisation in patients admitted for hypoglycaemia

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Introduction

Hypoglycemia, defined as blood glucose below 70 mg/dL, is a serious diabetes complication linked to higher mortality, cardiovascular risks, and prolonged hospital stays. Severe episodes are more frequent in type 1 diabetes but also occur in type 2. Effective management is key to improving outcomes. Prolonged hospital stays for hypoglycemia may arise from factors like age, underlying conditions, hormonal issues, diabetes type, and discharge protocols requiring support assessments. Timely care, medication adjustments, and monitoring can help minimize delays. This audit examines factors contributing to longer hospital stays for hypoglycemic patients and identifies barriers to efficient care and discharge. It aims to improve hypoglycemia management and reduce hospitalization times.

Objectives and Methodology

Objectives

- Analyze factors prolonging hospital stays in hypoglycemia.
- Assess management and discharge practices.
- Recommend strategies to reduce hospital stays.

Methodology

A retrospective review of 25 hypoglycemia patients (April–October 2024) was analyzed. Review included demographics, comorbidities, glucose levels,

interventions, care delays, and discharge times. The goal was to identify patterns and improve management and discharge processes for hypoglycemic patients.
Results
The study involved 25 patients, with 64% male and 36% female. Most were aged 60–80 years, followed by 81–100 years and 20–60 years. Of the 25, 11 had type 1 diabetes and 14 had type 2. Nineteen patients were on insulin, and 16 used oral hypoglycemic agents, including 4 on sulfonylureas. At admission, 14 patients had blood glucose below 2.5 mmol/l, and 10 had levels above 2.6 mmol/l. Specialist referrals were made for 15 patients, with most reviewed within 24 hours of admission.
Discussion
Hospital stays ranged from 2 to 22 days, with half discharged within 7 days and the other half requiring longer stays. Prolonged hospitalizations in 3 out of 10 patients were due to factors like fluctuating blood glucose and rest 6 out of 10 were due to comorbidities (e.g., infections, kidney injury), and 1 out of 10 due to delay in discharge planning. Additional complications, such as pneumonia, acute kidney injury and pleural effusion, required extra interventions thus highlighting need for effective management of comorbidities and reduce hospital stay.
Conclusion
Hypoglycemia management involves resolution of factors that prolong hospital stays. Early interventions, efficient discharge plans, glucose monitoring, and regular audits are crucial to improving care and reducing hospitalizations.

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EP426

JOINT1730

Case series of patients with euglycemic diabetic ketoacidosis

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Introduction
Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes, typically characterized by severe hyperglycemia. However, with the increasing use of sodium-glucose linked transporter 2 inhibitors (SGLT2i) now widely prescribed for type 2 diabetes as well as chronic kidney disease and heart failure, there has been a rise in euglycemic diabetic ketoacidosis (euDKA). Unlike classical DKA, euDKA presents with only mild to moderate hyperglycemia, typically defined as a blood glucose level below 250 mg/dL (13.9 mmol/l).
Case series
We present a series of eight patients diagnosed with euDKA during inpatient endocrinology consultations at our institution between 2019 and the end of 2024. The median patient age was 62 years [range 43–74]. At presentation, the median blood glucose level was 189 mg/dL (10.5 mmol/l) [range 92–241 mg/dL; 5.1–13.4 mmol/l], and the median arterial pH was 7.21 [range 7.04–7.29]. All patients had a pre-existing diagnosis of type 2 diabetes mellitus. Half of the patients were hospitalised for major surgical procedures, while the other half presented with severe infections. All patients received standard DKA treatment and were subsequently discharged. Upon discharge, three patients remained on insulin therapy, while the rest continued oral treatment, either alone or in combination with glucagon-like peptide-1 (GLP-1) receptor agonists.
Conclusion
SGLT2i presents a major new contribution in the therapy of patients with type 2 diabetes as well as patients with chronic kidney disease or heart failure without type 2 diabetes. However, given their expanding indications, clinicians must remain vigilant for potential adverse effects, including euDKA. SGLT2i therapy should be temporarily discontinued during severe infections and at least three days before the major surgery to reduce the risk.

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EP427

JOINT3899

Determination of antioxidant activity in seminal plasma of diabetic and non-diabetic individuals

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Introduction
Diabetes Mellitus (DM) is a chronic disorder of glucose metabolism with serious cardiovascular, endothelial, neurological consequences. In patients with DM, it appears that oxidative stress in the testicles is particularly high, which can cause significant impairment of testicular function including fertility or libido problems. Indeed, patients notice visible changes in testicular tissue as well as changes in hormonal balance.
Purpose
The present research work aims to evaluate *in vitro* antioxidant activity in the seminal plasma of diabetic and non-diabetic individuals.
Methods
9 samples from non-diabetics and 6 samples from diabetic patients were collected (License from the Society for Ethics and Conduct No. 49947, 21/06/2024). Statistical analysis was performed using the SPSS statistical software v.29 (academic license). The total antioxidant capacity in seminal fluid was measured with FRAP method. The ferric-reducing antioxidant power (FRAP) assay involves reduction in Fe3+-2,4,6-tripyridyl-s-triazine (TPTZ) complex while taking absorbance at 593nm. The FRAP reagent is prepared by taking acetate buffer pH: 3.6, 10 mmol of TPTZ solution in 40 mmol of hydrochloric acid (HCl), and 20 mmol solution of iron (III) chloride in 10:1:1 (v/v) ratio. The standard curve was made with FeSO4.7 H2O and the results were expressed in μM FeSO4.7 H2O.
Results
Antioxidant activity in seminal fluid of diabetic was found statistically significant lower in diabetic compared to non diabetic men (1631,5 ± 151,7 μM FeSO4.7 H2O versus 3355,3 ± 640,1 μM FeSO4.7 H2O), p: <0,001.
Conclusions
Diabetes mellitus has a clear influence on antioxidant activity of the seminal plasma, since the normal values appear to be reduced, as already reported by other researchers.

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EP428

JOINT1970

Severe acute pancreatitis secondary to major hypertriglyceridemia associated with diabetic ketoacidosis

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Introduction
The triad of ketoacidosis, acute pancreatitis and hypertriglyceridaemia is a very rare phenomenon. The metabolic origin seems to be the cause of this hypertriglyceridaemia(HTG) responsible for pancreatitis(PA).
Observation
A 48-year-old woman was admitted to hospital with abrupt onset of abdominal pain. She had a 2-year history of diabetes and was taking oral antidiabetics. Clinical examination revealed grade 2 obesity with abdominal obesity and acanthosis nigricans. Biological tests revealed metabolic acidosis, hyperglycaemia of 5.6 g/l, triglycerides of 10.2 g/l, lipasemia of 1000 IU/l, and HbA1c of 13%. Abdominal CT confirmed stage E pancreatitis. The diagnosis of ketoacidosis was made in the context of type II diabetes and associated BP. The outcome was favourable within a few days on insulin, with disappearance of pain and regression of ketoacidosis. At the same time, triglyceride levels and other biological parameters rapidly returned to normal.
Discussion
In our case, several mechanisms appear to be interrelated. The high triglyceride level at the time of diagnosis and the rapid reduction after correction of ketoacidosis are in favour of the metabolic origin of this HTG linked to CAD itself. However, it has been shown that major HTG can trigger BP, which usually progresses quite severely.
Conclusion
In conclusion, when significant abdominal pain appears in a patient with AD, we believe it is appropriate to suggest a lipasemia assay. If this assay is three times normal, the diagnosis of PA is likely and an abdominal CT scan should be ordered. Triglyceride levels should be measured at the same time to confirm that the BP is indeed secondary to HTG.

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EP429

JOINT3501

Allergic reaction following the injection of human insulin

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Introduction
Insulin allergy is a rare complication whose clinical manifestations can range from localized skin reactions to more generalized reactions. We report a case of localized urticarial reaction in a diabetic patient treated with human insulin.
Case Report
This is a 23-year-old patient, diagnosed with diabetes one year ago, initially placed on human intermediate-acting insulin (twice daily) and rapid-acting insulin (preprandial), and currently on human mixed insulin (two injections daily). The patient was admitted to the endocrinology department of CHU Mohamed VI for further management of his diabetes. Upon examination, the patient presented with pruritic urticarial lesions localized to the site of injection of the mixed human insulin. The biological tests did not reveal eosinophilia. In our institution, the patient received an injection of long-acting insulin analogue (glargine) and rapid-acting insulin analogues before meals. The clinical course was marked by the resolution of the urticarial reaction at the insulin injection site.
Discussion
Insulin allergy is not always directly related to the insulin molecule itself. It may result from a reaction to one of the excipient components, such as hydrochloric acid, water for injection, glycerol, meta-cresol, phenol, disodium phosphate dihydrate, protamine sulfate, sodium hydroxide, or zinc chloride. It can also be caused by an element used in the injection, such as the nickel in the needle. Thus, insulin can act as an allergen, inducing a pathological reaction, although the exact mechanisms of this response are not fully understood. The use of a different type of insulin allowed for better clinical tolerance.
Conclusion
Allergic reactions to insulin, although rare, remain an important complication, especially in type 1 diabetics. These reactions can disrupt glycemic control, making disease management more challenging. It is therefore crucial to diagnose these allergies promptly and provide appropriate management to ensure the safety and efficacy of the treatment.

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EP430

JOINT3533

Clinical management and outcomes of diabetic foot ulcers: a study of 322 cases

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Introduction
Diabetic foot ulcers (DFUs) are a public health issue with severe consequences that are frequently encountered in our daily practice.
Objectives
To evaluate the demographic data, therapeutic approaches, healing rates, recurrence rates, and amputation rates in patients with DFUs.
Patients and Methods
This is a retrospective cohort study involving adult diabetic patients with DFUs treated in our department from January 2018 to December 2024. Data were analyzed using IBM SPSS Statistics 27.0.
Results
A total of 322 patients with DFUs were treated in our unit. The average patient age was 56 years, with a male-to-female ratio of 1.82. Among them, 27 patients (8.4%) had Wagner grade 1 lesions, 147 (45.7%) had grade 2, and 148 (46%) had grade 3. Treatment involved medical management, including offloading, local wound care, and antibiotic therapy for infections. Healing was achieved in 302 patients (93%), with an average healing duration of 51 days. In 20 cases, complications such as soft tissue abscesses or necrosis necessitated surgical intervention. The recurrence rate among healed patients was 4.9% at the 12-month follow-up.
Conclusion
DFUs remain a common health concern. Early and effective management leads to good outcomes and prevents progression to severe lesions requiring limb amputation.

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EP431

JOINT3569

Diagnosis and therapeutic management of infected diabetic foot: insights from 278 cases

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Introduction
Foot infections in individuals with diabetes represent a major public health issue. They are not only responsible for numerous hospitalizations but can also compromise both functional and vital prognoses.
Objectives
To analyze the epidemiological, clinical, and therapeutic characteristics of infected diabetic foot.
Patients and Methods
This is a retrospective cohort study involving patients hospitalized for diabetic foot infections in our department from January 2018 to September 2024. Data were analyzed using IBM SPSS Statistics 27.0 software.
Results
Our study included 278 patients with a mean age of 56 $\pm$ 11.63 years and a male-to-female sex ratio of 1.28. Type 2 diabetes was observed in 85% of patients, with an average disease duration of 14 years and a mean HbA1c of 14.48%. The most common types of lesions were: dermohypodermitis (DHD) in 24.5%, diabetic foot ulcers (DFUs) complicated by osteitis in 24.5%, DFUs complicated solely by DHD in 23.74%, and DFUs complicated by both DHD and osteitis in 23.74%. The primary trigger was inappropriate footwear in 50.4% of cases. Management included offloading, daily wound dressing, adapted antibiotic therapy, and specialized education. Third-generation cephalosporins were the most prescribed antibiotics (91%), followed by ciprofloxacin (77%), metronidazole (66.9%), and amoxicillin-clavulanic acid in 8.2%. Outcomes were favorable in 85.6% of cases, with a mean healing time of 43.5 $\pm$ 23.76 days.
Conclusions
This study highlights the complexity of managing diabetic foot infections. It underscores the importance of a multidisciplinary approach combining local care, rigorous medical follow-up, and tailored patient education.

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EP432

JOINT2608

Impact of glycemic profile on severe hypoglycemia recurrence in diabetic patients

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Introduction
The recurrence of severe hypoglycemia in diabetic patients poses a significant clinical challenge. Identifying predictive factors for repeated episodes is crucial to improving patient outcomes. Continuous glucose monitoring (CGM) provides detailed insights into glycemic profiles, allowing for the assessment of glucose fluctuations and their potential role in hypoglycemia recurrence. This study evaluates the association between CGM-derived metrics and the likelihood of recurrent severe hypoglycemic episodes in diabetic patients.
Objective
To analyze how variations in glycemic profiles influence the recurrence of severe hypoglycemia in diabetic patients.
Methods
This retrospective observational study included 66 diabetic patients who underwent CGM monitoring. Patients were categorized into two groups based on the presence or absence of recurrent severe hypoglycemia. CGM metrics analyzed included the percentage of time spent in hyperglycemia ($>$180 mg/dL), hypoglycemia ($<$70 mg/dL and $<$54 mg/dL), and the number of hypoglycemic events. The Mann-Whitney U test was used to assess significant differences between groups.
Results
Patients experiencing recurrent severe hypoglycemia demonstrated increased glycemic variability and a lower percentage of time in range. A trend toward an association between higher time spent $<$54 mg/dL and hypoglycemia recurrence was observed (median 2.8% vs. 1.6%, $P = 0.13$), although it did not reach statistical significance. Additionally, the group with recurrent episodes had a higher number of total hypoglycemic events (median 21 vs. 15), yet this difference was also not statistically significant ($P = 0.47$). Other CGM parameters, including time in hyperglycemia and overall glucose variability, suggested an increased risk profile in patients with recurrent hypoglycemia but did not show definitive statistical differences.
Conclusions
Although increased glycemic variability and reduced time in range have been associated with adverse metabolic outcomes, their role in predicting recurrent severe hypoglycemia remains uncertain. The findings of this study suggest a potential trend toward an association between increased time spent $<$54 mg/dL and hypoglycemia recurrence; however, statistical significance was not achieved, likely due to sample size limitations. Larger prospective studies are needed to further investigate these

associations and determine their clinical implications. Future research should focus on refining CGM-based predictive models to enhance hypoglycemia risk stratification and improve patient management strategies.

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EP433

JOINT3224

Use of automated insulin delivery systems in pregnant women with type 1 diabetes: real-world data

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Introduction

The use of commercially available automated insulin delivery (AID) systems during pregnancy remains controversial. In this retrospective study, we evaluated the glycemic and pregnancy outcomes, and AID parameters of 13 women who received AID therapy (9 Minimed 780G and 4 Control-IQ) at our hospital between 2021 and 2024. We obtained CGM and insulin pump data from online platforms and assessed diabetes complications, maternal, and fetal outcomes using the medical records.

Results

The median age was 34 years (IQR: 31–39), with a median diabetes duration of 22 years (IQR: 16-29) and a median BMI of 23 kg/m^2 (IQR: 22-32). 62% of the pregnancies were planned. TIR $>70\%$ was achieved in 9/12 (1st trimester), 9/13 (2nd trimester), and 7/13 (3rd trimester) pregnancies. Insulin dose, daily carbs and number of meals increased throughout pregnancy whereas the carbohydrate-to-insulin ratio gradually declined (Table 1). At delivery, gestational age was 37.3 weeks (37–38). 7/13 women had a cesarean section and 2/13 had mild pre-eclampsia. 7/13 newborns were large for gestational age and 4/13 were admitted to the neonatal intensive care unit (one spontaneous preterm birth and one spontaneous hemoperitoneum).

Conclusion

AID systems help maintain glycemic control during pregnancy without increasing the rates of hypoglycemia.

Table 1: Glycemic parameters and pump data through the pregnancy.

	Initial (First visit)	First Trimester (4-15 weeks' gestation)	Second Trimester (16-27 weeks' gestation)	Third Trimester (28-delivery)
HbA1c (%)	6.3 (6.3-6.6)	6.3 (6.2-6.5)	5.9 (5.8-6.1)	6.0 (5.9-6.3)
glucose management indicator (%)	6.6 (6.5-6.8)	6.4 (6.3-6.7)	6.4 (6.3-6.5)	6.3 (6.2-6.4)
Mean sensor glucose (mg/dL)	136 (126-144)	129 (126-139)	128 (125-134)	125 (123-130)
Coefficient of Variation (%)	29 (28-32)	31 (29-33)	30 (29-31)	28 (27-30)
63-140 mg/dL (%)	60 (56-66)	66 (58-70)	67 (59-71)	70 (65-77)
$>$ 140 mg/dL (%)	39 (33-44)	33 (29-41)	32 (27-38)	29 (23-35)
$<$ 63 mg/dL (%)	0.2 (0-1)	1 (1-2)	2 (1-2)	1 (1-2)
Total daily insulin dose (UI)	40 (32-46)	41 (30-52)	45(34-63)	59(44-72)
Total insulin per body weight (UI/kg)	0.56 (0.50-0.69)	0.61 (0.53-0.68)	0.58 (0.52-0.79)	0.71 (0.61-0.80)
Daily Carbs (g)	133(116-159)	160 (130-171)	175(148-186)	175 (162-181)
Number of meals/day	4.7 (4.3-5.2)	5.3 (4.7-6.2)	6.1 (4.6-7)	6.4 (4.8-6.5)
ICR breakfast (g/UI)	6.6 (4.2-7.9)	6.2 (4-7.7)	4.8 (3.2-6.8)	4.4 (3.3-5.9)
ICR lunch (g/UI)	6.2 (5.2-7.9)	6.4 (4.8-7.5)	5.6 (4.6-7.4)	4.8 (4.1-6.6)
ICR dinner (g/UI)	6.6 (5.2-9.2)	7.6 (4.9-8.7)	6.4 (5.0-7.1)	5.2 (4.2-6.2)

Data are presented as median (IQR); ICR, insulin-to-carbohydrate ratio

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EP434

JOINT2369

Influence of socioeconomic factors on breastfeeding adherence in a group of diabetic women

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Introduction

Several international programs support breastfeeding among the general population and vulnerable groups, such as diabetic women, in order to increase the prevalence of breastfeeding. The aim of our study was to determine the impact of socioeconomic factors on breastfeeding adherence among diabetic women.

Methods

We conducted a descriptive observational cross-sectional study involving 52 patients with type 1 or type 2 diabetes who attended the Nutrition "D" Department at the National Institute of Nutrition of Tunis, two months after childbirth. We asked each patient about their socioeconomic conditions and breastfeeding practices.

Results

The mean age of our patients was 35 ± 0.4 years [ext: 23-44]. The majority (80%) had type 2 diabetes, while 20% had type 1 diabetes. Two months after childbirth, the rates of exclusive and partial breastfeeding were found to be 44% and 33%, respectively. Most women (63%) had a moderate socioeconomic level, while 31% had a low socioeconomic level. Rural residency was found in 10% of cases. Sixty-three percent of the patients were unemployed. Only 42% of those who were working had returned to work two months after childbirth. Husband encouragement of breastfeeding was observed in 77% of cases. Not returning to work and receiving support from the husband for breastfeeding were associated with higher breastfeeding rates ($P = 0.007$ and $P < 0.001$, respectively).

Conclusion

In summary, socioeconomic factors are crucial in determining whether diabetic women can successfully adhere to breastfeeding practices. Addressing these factors through policy interventions and community support programs could improve breastfeeding rates among this population.

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EP435

JOINT4006

Epidemiology of type 1 diabetes in children: a 5-year study

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Introduction

ype 1 diabetes (T1D) is a chronic autoimmune disease with a constantly increasing incidence worldwide, including in children. Its early and effective management is essential to avoid acute complications, such as diabetic ketoacidosis (DKA), and long-term complications. In our region, few studies have been conducted to analyze the epidemiological and clinical characteristics of pediatric T1D, hence the need for a retrospective study to better understand the factors influencing the onset and evolution of this disease in children. The aim of this study was to analyze the epidemiological, clinical, biological, and immunological characteristics of Type 1 Diabetes (T1D) in children.

Patients and Methods

A retrospective study of T1D cases in children under 14 years old, hospitalized at CHU Hédi Chaker, Sfax, between January 2018 and December 2022.

Results

We collected 207 cases with an average hospital incidence of 41.4 children per year. The mean age of the children was 7.35 ± 3.74 years, with 82 children under 6 years old and 125 between 6 and 14 years old. A winter predominance was observed (31.4%). Diabetic ketoacidosis (DKA) at presentation was noted in 58.5% of cases, more frequently in children under 6 years old ($P = 0.02$); it was severe in 45.2% of cases. The mean blood glucose was 23.63 ± 8.23 mmol/l. Autoantibodies were positive in 88% of children, mainly anti-GAD (71.9%). After a mean follow-up of 2.25 ± 1.5 years, 35.7% of children were readmitted, primarily for DKA (12.6%), severe hypoglycemia (10.6%), and diabetes imbalance (23.2%). A satisfactory metabolic control was observed in 17.6% of cases.

Conclusion

The incidence of pediatric T1D is increasing, particularly in young children. Despite awareness programs and diagnostic advances, in our region, inaugural DKA remains common, highlighting the need to strengthen prevention and early screening.

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EP436

JOINT3136

Diabetic ketoacidosis (DK) in the context of COVID-19: epidemiological and clinical insights

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DKA is a potentially life-threatening complication of DM with an increased incidence over the last few decades. Coronavirus disease(COVID-19) has been incriminated in the pathophysiology of new-onset diabetes mellitus via the development of islet autoimmunity. The aim of this work is to compare the epidemiological and clinical characteristics of new onset DKA before COVID-19 with those during the pandemic. This is a cross-sectional analytical study carried out in the Diabetology&Endocrinology department of Farhat Hached University Hospital of Sousse. The study population included all the patients who had been hospitalized for new onset DKA between the year 2018 and 2022, divided in two groups: Group1(G1):patients hospitalized before COVID-19 since the first of March of 2018 until first of March 2020 and Group2(G2):patients hospitalized during COVID-19 since second of March 2020 until 28thFebruary 2022. A metabolic, renal, hormonal, and immunological assessment has been requested. A total of 340 patients were evaluated:137 were registered in G1, while 203 were registered in G2. The mean monthly incidence of DKA before COVID-19 pandemic was statistically different from that observed during COVID-19 with a mean of 5.75±4.29 DKA per month in G1 vs 8.42±4.87 DKA per month in G2(***P* = 0.049).**The study of the temporal trend of hospital cases of DKA showed a significant upward trend with a change in the average monthly percent change of +0.2, with ***P* = 0.037.**The sex ratio(H/F) remained comparable before and during COVID-19($P = 0.287$). The median age of the two populations was 39 [Q1-Q3]=[25–53] years old and 41 [Q1-Q3]=[27– 57] years old with a $P = 0.531$. Familial history of auto-immunity was comparable between the two groups. The median duration of polyuria and polydipsia before DKA was comparable in the two groups with a median period of 30 [Q1–Q3]=[20.75–60] days in G1 vs 30 [Q1–Q3]=[15–90] days in G2 ($P = 0.171$). The median weight loss in kilograms before the diagnosis was estimated at 8 [Q1–Q3]=[5–13] Kg in G1 vs 10 [Q1–Q3]=[6–15] Kg in G2($P = 0.688$). Clinical presentation of DKA including signs of intracellular and extracellular dehydration, weight loss, blood pressure, heartbeat were comparable between the two groups. Goiter was more significantly reported in G1 with 11.6% in G1 vs 3.4% in G2($P = 0.018$). The emergence of COVID-19 occurred amidst a backdrop of an already existing pandemic that is DM, creating a multitude of challenges for the healthcare system worldwide and adding to the burden of an already overstretched health system.

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EP437

JOINT3467

Hyperuricemia : is it a cardiovascular risk factor?

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Introduction

Hyperuricemia is common in diabetic subjects, especially type 2, particularly in obese patients. Our aim was to investigate the prevalence and risk factors of hyperuricemia in diabetics subjects.

Methods

It was a descriptive cross sectional study conducted in department A of the institute of Nutrition of Tunis which included patients with type 2 diabetes. Hyperuricemia was defined by a uric acid level that exceed 360mg/l.

Results

The total number of patients who participated in the study was 112. The characteristics of the patients were respectively : age 49±9.8 years, Body mass index (BMI) 31± 3.7Kg/m^2, HbA1c 9.8±1.57%. The mean waist circumference was 119.1 ± 18.5 cm. The mean duration of diabetic patients was 9±7 years. Hyperuricemia was present in 32.8%, with a mean level of 408 ± 22.6mg/l. A history of stroke, coronary artery disease and arteriopathy were found respectively in 12.4%,14.5% and 34% of cases. Also 75% of subjects presented microangiopathic complications, with 43% having a diabetic neuropathy, 26% with diabetic nephropathy. As for the metabolic profile, 98.1% with low HDLc, high LDLc in 59.7%, high triglycerides in 76.4 %. Hyperuricemia was positively correlated with BMI ($p = 0.007$), waist circumference ($p = 0.01$) and duration of diabetes ($p = 0.009$). Hyperuricemia was significantly more frequent with diabetic nephropathy ($p = 0.031$) and with dyslipidemic patients ($p = 0.001$). Thus, 89% of patients met the International Diabetes Federation definition of metabolic syndrome.

Conclusion

In conclusion, Hyperuricemia was common in our study. It was positively correlated with BMI, waist circumference, length of diabetes, diabetic nephropathy and dyslipidemia, making it a cardiovascular risk factor.

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EP438

JOINT1193

Generalized lipodystrophy masquerading as obesity and insulin resistance

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A 14-year-and-8-month-old girl presented with a primary complaint of rapid weight gain. She had a history of progressive enlargement of her hands and feet since childhood. Excessive hair growth on her body was noted at the age of 10. Menarche occurred at 13 years, but no subsequent menstrual cycles were reported. One year prior, the patient had been diagnosed with obesity and insulin resistance, for which Metformin was prescribed; however, she did not adhere to the prescribed treatment regularly. The patient was born to consanguineous parents. Her family history revealed that two male siblings had died shortly after birth, while one female and one male sibling were healthy. On physical examination, her weight was 67.6 kg (+1.71 SDS), height 169.5 cm (+0.58 SDS), and BMI 23.5 kg/m^2 (+0.96 SDS). Distinct facial features were noted, including a large mandible, triangular facies, and an acromegaloid appearance. Additionally, she had large hands and feet, muscle hypertrophy, acanthosis nigricans, hirsutism, hepatomegaly, and labial hypertrophy. Her physique was characterized by excessive fat accumulation in the upper back, reduced fat tissue in the pelvic region, and subcutaneous fat loss in the lower extremities, giving her a pronounced muscular appearance. Laboratory evaluations revealed the following abnormalities: Fasting glucose :86.2 mg/dL, insulin :132.4 µU/mL, HbA1c:7.6%, ALT:139 IU/l, AST :73 IU/l, FSH:3.76 µg/dL, LH:5.25 mIU/mL, total testosterone :1.43 ng/mL, IGF1:0,7 and leptin :3.9 ng/mL. The lipid panel and other tests were within normal limits (Table 1). Imaging studies demonstrated grade 3 hepatosteatosis on abdominal ultrasound, nephrolithiasis on renal ultrasound, and polycystic ovarian syndrome (PCOS) on pelvic ultrasound.

Table 1. Laboratory values of cases

Paramater	Value	Reference Range
Fasting glucose (mg/dl)	86.2	74-106
Fasting Insulin (µu/ml)	132.4	2.6-24.9
C-peptide (ng/mL)	9.42	0.78-5.19
Two-hour postload glucose (mg/dl)	180	74-106
Two-hour postload insulin (µu/ml)	905	2.6-24.9
HbA1c (%)	7.6	4-6
ALT (IU/l)	139	6-33
AST (IU/l)	73	10-32
Total cholesterol (mg/dl)	147	<170
Triglycerides (mg/dL)	99	35-130
HDL (mg/dl)	50.8	
	35-75	
LDL (mg/dl)	76	100-129
Leptin (ng/mL)	3.9	4.4-24.5
fT3 (pg/dl)	3.65	2.56-5.01
fT4 (ng/dl)	1.2	0.98-1.63
TSH (µIU/mL)	1.5	0.35-5.60
ACTH (pg/mL)	33	2-49
Cortisol (µg/dL)	8.6	3-21
FSH (µg/dL)	3.7	2-10
LH (mIU/mL)	5.2	0.61-16.3
E2 (pg/Ml)	26	36.5-196
Total Testosterone (ng/mL)	1.4	0.02- 0.4
DHEA-S (µg/dL)	107.9	51-321
İGF-1(ng/mL)	0.7	153-485

Echocardiography findings were normal. Based on the clinical findings, generalized lipodystrophy type 2 was suspected, prompting genetic testing. Metformin therapy was reinitiated.

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EP439

JOINT2448

Measurement of insulin secretion during oral glucose tolerance test for prediction of obesity treatment success

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Background
Oral glucose tolerance test (OGTT) is used for diagnosis of diabetes and insulin resistance. There are different modifications of OGTT with measurement of glucose and insulin level on 0, 30, 60, 120 and additional minutes. But weather OGTT is presenting information for treatment effect.
The aim of our study is to assess the importance of measurement of insulin secretion during oral glucose tolerance test for predicting obesity treatment success.
Materials and methods
Our survey include 109 patients (59 women, 50 men, mean age 40.01 ± 11.80years). Patients were divided into three groups and were assigned to treatment with diet, metformin or GLP-1 agonist. All patients underwent OGTT with measurement of glucose and insulin, which was performed on minute 0, 60 and 120. The groups did not differ by gender, weight, BMI or age. Assessment of weight and BMI was done in six months period. The treatment effect was defined as more than 10% weight loss.
Results
Satisfactory treatment results were found in patients with increased insulin level at 0 min (15.2 ± 3.5 vs 11.3 ± 3.1mU/l, $P < 0.05$) and 60 min (145.2 ± 26.5 vs 87.3 ± 25.1mU/l, $P < 0.05$). There was no difference between insulin levels on 120 min in responders and non-responders (45.2 ± 12.5 vs 39.3 ± 9.1mU/l, $P > 0.05$). Insulin levels of 0 and 60 min demonstrated moderate positive correlation with percentage of weight loss ($r = 0.564$) in group only on diet or metformin, but not in GLP1 agonist treated group.
Conclusion
Measurement of insulin level during OGTT presents information about insulin secretion curve and could be used for prediction of treatment effect in obese patients receiving only diet or metformin, but not in GLP1 agonist treated patients

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EP440

JOINT2876

Screening for celiac disease in children with type 1 diabetes, is it necessary? twenty-five years of experience in a single center

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Patients with type 1 diabetes (T1D) have an increased risk of developing additional autoimmune diseases. The risk of developing celiac disease (CD) is 3-4 times higher in children with T1D. Guidelines recommend regular screening for transglutaminase antibodies (TgAb) in T1D children. CD could be an additional burden for T1D children as both diseases affect food intake. We describe the screening practice for CD during the last 25 years in our outpatient clinic in children with T1D. Methods: We retrospectively analysed the development of CD-specific antibodies in our patients with T1D (diabetes onset since 1998). We did not always recommend endoscopy when CD-specific antibodies (TgAb, endomysium (EAb), gliadin) were positive and patients had no CD-specific symptoms. Results: We analysed 304 patients. 122 had CD-specific antibodies. In 98 of them, they disappeared after a short time or were only slightly elevated. The diagnosis of CD was confirmed in 12. All 12 showed CD-specific symptoms such as failure to thrive, anaemia, hypoglycaemia or gastrointestinal problems. In 6 patients, even severely elevated EAb and/or TgAb disappeared on average after 7.1 years (range 4.9 to 13.5 years) on gluten-containing diet. The remaining 6 had antibodies without CD-specific symptoms by the end of the observation period. The time with antibody-positivity was 4 years (range 1.8 to 11.6 years).
Conclusion
We conclude that even highly elevated CD-specific antibodies can disappear in children with T1D and therefore screening for CD-specific antibodies is only useful in symptomatic children with T1D.

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EP441

JOINT3393

Development of disease-modifying therapies for early-stage type 1 diabetes: insights from the EDENT1FI project

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Background and Objectives
The EDENT1FI project aims to advance early diagnosis and intervention for Type 1 Diabetes (T1D), focusing on reducing the progression of the disease and delaying insulin therapy. This project involves screening 200,000 children in Europe for islet autoantibodies, identifying early-stage T1D, and offering targeted disease-modifying therapies (DMTs) to preserve beta-cell function. WP4, dedicated to developing protocols or administering DMTs, investigates interventions aimed at halting or slowing beta-cell destruction, with the potential to dramatically alter the clinical course of T1D.
Methods
The EDENT1FI initiative includes six work packages (WP). WP1 handles screening programs across Europe, WP2 explores psychosocial impacts, WP3 establishes follow-up protocols, WP4 focuses on the development and testing of DMTs, WP5 manages communication strategies, and WP6 ensures project governance. WP4's adaptive trial designs aim to test multiple DMTs, incorporating biomarkers such as C-peptide and glucose tolerance to evaluate efficacy in preserving beta-cell function and delaying progression to insulin dependency. The data is collected from multiple countries, ensuring a comprehensive understanding of the disease progression.
Results
WP4 is developing innovative therapeutic strategies using adaptive trials to assess the efficacy of DMTs for T1D. Key biomarkers, including C-peptide and glucose levels, will be used to identify children and adolescents who are at risk of rapid disease progression. Preliminary results suggest that DMTs can potentially preserve beta-cell function, delaying the onset of insulin dependence. By using adaptive trial designs, WP4 can provide insights into the most effective interventions for managing early-stage T1D.
Conclusion
EDENT1FI, through WP4, establishes the framework to support future disease-modifying therapy trials that could revolutionize the treatment of early-stage T1D. By delaying insulin therapy and preserving beta-cell function, these therapies have the potential to improve long-term health outcomes for children and adolescents with T1D. This collaborative effort leverages advanced biomarkers, adaptive trial designs, and international expertise to offer a more personalized and effective approach to managing early-stage T1D.
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EP442

JOINT366

HbA1c measurement: comparison of biorad D10 (Hplc) and sebia capillarys 2 methods

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Background
HbA1c test provides information on metabolic control in diabetes and could also be used for its Diagnosis, it is essential to have accurate and precise HbA1c

methods covering a range of measurement principles. We report an evaluation of the Biorad D10 kit (Hplc) versus Sebia capillarys 2 Kit (capillary electrophoresis).
Methods
Measurements of HbA1c were carried out in whole blood samples (K3edta tubes) from 111 patiens from different departments in Ziv medical Center- Israel using both Sebia Capillarys 2 Flex piercing (Capillary Electrophoresis) and analyzers Biorad D 10 (HPLC method).
Results
There was a good concordance between the results of capillary electrophoresis and HPLC (R2 = 0.97, *P* 0.0001) There is no significant difference between the results obtained from both technique.
Conclusions
both technique suitable for the clinical application in the analysis of HbA1c. it is concluded that the results obtained after testing samples in Sebia capillarys Flex Piercing II and Biorad D10 are in a good concordance and there is no significant difference in the results obtained. The advantage of using Biorad D10 has benefit of shorter testing time Whereas Sebia capillarys can detecte underlying hemoglobinopathies and high throughput.
Biography
Medical lab scientist, BSc in medical lab science from Biology faculty in Technion, Haifa Israel. MSc in medical sciences (cancer research) from Medicine faculty in Technion, Haifa Israel. Working as a head of immunology lab in Ziv Medical Center, Israel.
Keywords
HbA1C, diabetes, capillarys, D10, diabetes diagnosis
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EP443

JOINT512

Factors associated with gestational weight gain in pregnant women with gestational diabetes mellitus

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Background
Studies disagree that higher pre-pregnancy body mass index (pre-BMI) is associated with more significant weight gain during pregnancy. We aimed to assess factors associated with GWG in women with gestational diabetes mellitus (GDM).
Methods
The study involved 215 singleton pregnant women diagnosed with GDM who delivered at Vilnius University Hospital Santaros Klinikos from 2019 to 2023. Based on pre-BMI, women were categorized into group 1 - BMI < 18.5- 24.9 kg/m^2; group 2-BMI 25-29.9; group 3 - BMI ≥ 30. According to the Institute of Medicine, the cut-off points for weight gain were set at ≤16 kg, ≤11.5 kg, and ≤9 kg for groups 1, 2, and 3, respectively. The association of pre-BMI, fasting plasma glucose up to 14 weeks of gestation (FG14w), FG, fasting insulin (FI), HOMA-IR, lipid profile, and CRP at weeks 24-28 with GWG was analyzed.
Results
There were 123 (57.2%),52 (24.2%) and 40 (18.6%) women in group 1, 2 and 3 respectively. The mean age was 31.9 ± SD 4.05 and did not differ between the groups. Excess weight gained 22 (17.9%), 14 (26.9%), and 12 (30%) of women in groups 1, 2, and 3, respectively. The biggest GWG was in group 1 – 12.5 ±4.9 kg, followed by groups 2- 8.9±5.5 and 3 - 5.7±5.5 (*P*<0.001). HOMA IR was 2.0 ± 1.4, 3.0 ± 2.4, and 4.4 ± 3.4 (*P*<0.001); HDL chol - 2.0 ± 0.4, 1.9 ± 0.4 and 1.7 ± 0.3 (*P*<0.001) in group 1, 2 and 3 respectively. FG14w, FG24-28w, hCRP, triglycerides (TG), and FI differed significantly between the groups (*P*<0,001 for all). Pre-BMI, HDL chol, and FG24-28w explained 24% of GWG variance in the whole group (R2 adjusted = 0.24, *P*<0.001). Only HDL chol correlated significantly with GWG in group 2, explaining 13% of the variance (R2 adjusted = 0.13, *P* = 0.005) and resulting in a significant OR of 19.2 (95% CI 2.2-166.4) and AUC of 0.81 (95% CI 0.6 - 0.9). None of the variables demonstrated a statistically significant association with GWG in groups 1 and 3.
Conclusions
GDM women with the highest pre-BMI gained the least weight during pregnancy. Pre-BMI, HDL chol, and FG24-28w were significant determinants of GWG in the whole group, but only HDL chol remained significant in women with pre-pregnancy overweight. Further research is needed to explore other possible factors related to GWG in women with GDM.
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EP444

JOINT3851

Diabetic foot in patients with type 1 diabetes : a challenging complication (a study of 56 patients)

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Introduction
Diabetic foot is a high-risk complication of type 1 diabetes, poorly described but responsible for severe morbidity and amputations.
Objectives
To analyze the epidemiological, diagnostic, therapeutic, and evolutionary characteristics in type 1 diabetics with diabetic foot.
Patients and Methods
This descriptive retrospective study was conducted among patients with type 1 diabetes hospitalized for diabetic foot in our department from January 2018 to September 2024. Data were analyzed using IBM SPSS Statistics 27.0.1.
Results
Our study included 56 patients, with an average age of 37.71 years (range: 17-68 years). Males predominated with a sex ratio of 3.3. The average duration of diabetes was 19 years. The mean HbA1c was 11%. For insulin therapy: 65% were on a premixed regimen and 35% on a basal-bolus regimen. 62.5% of the patients were at very high cardiovascular risk: dyslipidemia in 34%, hypertension and smoking in 21.4%, and obesity in 14.2%. Macroangiopathy was dominated by peripheral artery disease in 32% of cases. Microangiopathy was dominated by diabetic retinopathy and peripheral neuropathy in 66.1% and 58.2% of cases, respectively. The initial cause of the lesions was inappropriate footwear in 59% of cases. The most common type of lesion was diabetic foot ulcer in 84% of cases: 29.7% associated with dermohypodermitis, and 42% complicated by osteitis. Management was medical in 91% of cases, with 8.9% requiring surgical treatment, and 3.5% undergoing amputation.
Conclusions
The occurrence of diabetic foot in patients with type 1 diabetes is linked to glycemic imbalance and the presence of degenerative complications, notably peripheral artery disease, retinopathy, and peripheral neuropathy. The evolution is favorable in most cases.
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EP445

JOINT3876

Impact of glycemic imbalance on diabetic foot ulcer healing

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Introduction
Diabetic foot is a major public health concern, with a high rate of amputations. The complications of diabetic foot disease (DFD) are mainly due to diabetic neuropathy, arteriosclerosis, and infections of ulcers. Offloading of wounds is essential for treating high-risk ulcers. Preventing recurrences relies on patient education, proper foot care, and appropriate offloading.
Objective
To assess the impact of glycemic imbalance on clinical indicators such as delayed wound healing and progression to amputation.
Patients and Methods
A descriptive statistical study was conducted on 276 patients with poor glycemic control (HbA1c > 8%) followed at the diabetic foot consultation in the Endocrinology and Metabolic Diseases Department at Ibn Rochd University Hospital, Casablanca.
Results
The average age was 57 years, with a male predominance of 64.86%. The average duration of diabetes was 14.5 years, and the average HbA1c was 13%. Of the patients, 80.28% were treated with insulin therapy, while 19% were on oral antidiabetic drugs (OAD). The main reason for consultation was diabetic foot ulcers (59.12%) and diabetic ulcer with dermohypodermatitis (40%). The majority of patients had poor footwear as the main trigger factor (68%), followed by post-traumatic causes (11.54%), ischemia (10%), and others. Among the 276 patients with poor glycemic control (HbA1c > 8%), 108 had osteitis. Delayed

healing (> 15 days) was observed in 247 patients (89%), and 34 of these patients underwent amputation.
Conclusion
It is well established that glycemic imbalance is a factor associated with delayed wound healing. In particular, the benefit of systematic insulin therapy in these patients leads to improved healing outcomes.
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EP446

JOINT3983
Microbiological spectrum of diabetic foot infections (a study of 46 cases)
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Introduction
Diabetic foot infections are common and serious, leading to prolonged hospitalizations and increased morbidity and mortality. Understanding the bacteriological profile of these infections is essential to improve patient management. The aim of our study is to establish the microbial flora found in these lesions.
Patients and Methods
This is a descriptive retrospective study conducted on 46 patients hospitalized in our department for diabetic foot who underwent bacteriological sampling. Data were analyzed using Python with the Pandas library.
Results
Our cohort included 46 patients with an average age of 54 years, 76% of whom were over 40 years old. Males predominated with a sex ratio of 6.6. The average delay in management was 45 days. More than half of the lesions were classified as stage B Texas University (54.3%), with 41% classified as Texas 3B. The treatment duration exceeded 6 weeks in more than 80% of cases. The infections were dominated by Gram-positive cocci (47.8%), Gram-negative bacilli (21.7%), and Enterobacteriaceae (13%). The most frequently implicated bacteria were Staphylococcus, Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, followed by Pseudomonas aeruginosa, Morganella morganii, Proteus mirabilis, and Streptococcus. The absence of bacteria in some samples may be due to inadequate sampling or prior antibiotic use.
Conclusions
Diabetic foot infections are common, often managed late, and require prolonged antibiotic therapy. This study provides a detailed profile of the bacteria involved to guide antibiotic selection and improve management.
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EP447

JOINT3577
Lipid profile and micro and macrovascular complications in LADA diabetes at hospital universitario de canarias, spain
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Introduction
Latent Autoimmune Diabetes in Adults (LADA) constitutes the most prevalent form of autoimmune diabetes in adults. Its estimated prevalence ranges from 2% to 12%, although this figure can vary depending on demographics (higher in Northern Europe and China) and the diagnostic criteria used, as these are not yet definitively established. Patients with LADA exhibit an intermediate range of characteristics between type 1 (DM1) and type 2 (DM2) diabetes. In metabolic syndrome, they have a frequency similar to or higher than DM1, but lower than DM2 (with lower dyslipidemia, insulin resistance index, and better blood pressure control). At the onset, they have a lower risk of microvascular complications compared to DM2 patients. However, this risk progressively increases as the glycemic profile worsens. Regarding the lipid profile, there are no detailed descriptions or specific recommendations for managing dyslipidemia in this type of diabetes. However, in general, for diabetic patients with dyslipidemia, the American Diabetes Association (ADA) recommends initiating treatment with moderate or high-potency statins, as well as interventions targeting lifestyle habits.
Material and Methods
A descriptive and cross-sectional study was conducted to assess the lipid profile and the presence of micro and macrovascular complications in patients with LADA diabetes. A sample of 42 patients, aged between 26 and 77 years (mean age 50.9 years), with 42.8% being male, was evaluated between 2022 and 2024 in the Endocrinology Department of the Hospital Universitario de Canarias, Spain. 92.8% of patients had the mentioned parameters assessed in 2024, while the rest were evaluated in 2023.
Results
A retrospective evaluation was conducted for the following: total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, use of lipid-lowering treatment, percentage of LDL target achievement (according to the SCORE2 guideline), presence of microalbuminuria, use of ACE inhibitors/Angiotensin II receptor blockers (ARBs), and the presence of micro and macrovascular complications (acute myocardial infarction, diabetic retinopathy, or diabetic neuropathy).
- Total cholesterol: 177.95 mg/dL
- LDL cholesterol: 98.05 mg/dL
- HDL cholesterol: 59.15 mg/dL
- Triglycerides: 99.5 mg/dL
  - Average values of variables:
  - Micro/macrovascular complications: 14.28%
  - Positive microalbuminuria: 7.14%
  - Percentage of patients reaching LDL target: 31.70%
  - Treatment with ACE inhibitors/ARBs: 26.19%

Conclusion
Given the importance of cardiovascular risk factors and the presence of micro and macrovascular complications, larger and more specific studies are necessary to assess the lipid profile, its management, and the prevalence of complications in patients with LADA diabetes.
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EP448

JOINT397
Correlation between visceral fat, insulinrésistance and age in type 1 diabetes patients
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Introduction
The prevalence of metabolic syndrome (MS) and insulin resistance (IR) increases with age. This association is poorly studied in patients with type 1 diabetes (T1D). The aim of our study was to evaluate the association between IR, MS and age in young adults with T1D.
Methods
We conducted a cross-sectional study including 68 patients with T1D. The study subjects were young adults, aged between 18 and 45 years. Each patient underwent a physical examination (anthropometric parameters and blood pressure), a fasting biological sample collection for the measurement of HbA1c, lipid parameters and C reactive protein (CRP), an evaluation of body composition by DXA Scan to measure the visceral fat mass (VFM). Visceral fat mass proportion (%VFM) was calculated by the formula: [VFM (g)/Weight (g)] x 100. High visceral fat mass (HVF) was defined by a %VFM > 1,1 in men and > 0,7 in women. MS was diagnosed according to the International Federation of Diabetes (IDF) criteria.
Results
The study population consisted of 29 men (42.6%) and 39 women (57.4%). The mean age was 29.4 ± 7.23 years. The median duration of diabetes was 11 years (4.2–17.0), with a range from 1 to 29 years. MS was observed in 14 patients (20.6%). HVF was present in 15 patients (23.4%). MS was not associated with age in T1D patients ($P = 0.621$). T1D patients with HVF were significantly older than T1D without HVF (34.3 ± 8.38 vs 28.3 ± 6.40; $P = 0.005$). An age above 30 years old was significantly more observed in T1D patients with HVF than patients without HVF (73% vs 40,8%; $P = 0.027$).
Conclusion
In our study, age was not associated with MS in patients with T1D. This could be explained by the young age of our population. Yet an age above 30 was associated with visceral fat which is correlated with IR and can increase cardiovascular risk.
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EP449

JOINT354
Association between diabetes mellitus and severity of epistaxis: a retrospective study
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Introduction
Epistaxis is a common condition encountered in otorhinolaryngology, generally benign, but it can occasionally present as a severe and life-threatening event. For patients with diabetes mellitus (DM), epistaxis may be a sign of underlying vascular complications. This study aims to evaluate the relationship between diabetes and the severity of epistaxis and its implications for management strategies.
Methods
A retrospective cross-sectional analytical study was conducted at the Department of Otolaryngology–Head and Neck Surgery of Farhat Hached University Hospital, encompassing patients consulting and/or admitted for epistaxis between January 2015 and December 2022.
Results
A total of 720 cases were analyzed. Of these, the majority (87.9%) were classified as benign and managed on an outpatient basis, while 12.1% of patients presented with severe epistaxis necessitating hospitalization. A significant prevalence of cardiovascular diseases was observed, including hypertension (32.9%), diabetes (12.8%) and dyslipidemia (6.9%). Other noteworthy medical conditions included chronic kidney disease ($n = 19$; 2,6%) and haematological pathologies ($n = 11$; 1,5%). Despite the prevalence of diabetes (12.8%), no statistically significant correlation was found between diabetes and the severity of epistaxis. Contrary to previous studies suggesting a direct association between DM and severe epistaxis, our findings suggest that diabetes may act as a predisposing factor by inducing vascular changes such as endothelial dysfunction and impaired hemostasis. Additionally, diabetes mellitus may contribute to atherosclerotic changes in the nasal vessels, increasing their fragility and susceptibility to bleeding. The coexistence of cardiovascular conditions, such as hypertension and dyslipidemia, which are frequently associated with diabetes, may further exacerbate the risk of epistaxis in this population.
Conclusion
Diabetes mellitus may increase the risk of epistaxis through its effects on vascular integrity, though its role in determining the severity of the condition remains uncertain. Further large-scale, prospective studies are needed to elucidate the underlying pathophysiological mechanisms and refine management strategies for diabetic patients presenting with epistaxis.
Keywords
Epistaxis – Bleeding – Diabetes Mellitus - Severity criteria - Risk Factors – Management.
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EP450

JOINT2810
Electroconvulsive therapy and the onset of diabetes: a rare but critical complication in children
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Objective
Electroconvulsive therapy (ECT) was approved for adolescents with severe conditions under specific conditions since 2004. However, its use in children and adolescent populations is less common. Studies on ECT's impact on blood sugar in adults have highlighted its diabetogenic effects. It is recommended that glycemic control be achieved before ECT in diabetic patients, while in non-diabetic patients, consecutive blood glucose monitoring is advised following ECT sessions. In pediatric populations, however, data and experience in this area are limited. This case report presents a 13-year-old male with normoglycemia before ECT who was subsequently diagnosed with diabetes mellitus. The aim is to raise awareness of this potential complication in children and adolescents undergoing ECT.
Case Presentation
A 13-year-old boy with early-onset psychosis and treatment-resistant ADHD had been on medication, including fluoxetine, olanzapine, quetiapine, and mianserin for the past two months. Due to treatment failure, ECT was planned. Two days before starting ECT, the patient had HbA1c of 5.5% and blood glucose level of 94 mg/dL. After undergoing 3 ECT sessions (10,25, and 35 joules, spaced 3 days apart) and a final session 15 days later (50 and 65 joules), the patient developed polyuria, polydipsia, and weight loss over the past week. Physical examination showed a height-SDS of -0.88, BMI-SDS of -0.34, and Tanner Stage 4 puberty without syndromic findings. Upon admission to our deparment, the patient's had blood glucose: 441 mg/dL, HbA1c:9.1%, insulin level :38.68 uIU/mL, and C-peptide : 2.72ng/mL (0,6-4). No acidosis or ketosis was present. Ophthalmic examination showed no optic atrophy. Antibodies tested positive for Anti-glutamic acid decarboxlyse level with 5.4 (positive$>$5) and moderate islet cell antibodies 0.7(0,7-1.0), while anti-insulin antibodies were negative. Further investigations investigations showed normal lactate, ammonia, lead, mercury, copper levels and aryl sulfates A and tandem mass and amino acids in urine and blood. Measles IgG/IgM were negative. No mutations were found in the MODY and WFS-1 and 2 gene panels. Despite basal insulin and oral antidiabetic treatment, glycemic control was not achieved. After 34 ECT sessions, the patient's C-peptide decreased to 0.49, and he is now on basal-bolus insulin at 1.1 units/kg/day.
Conclusion
Considering the uncertainty surrounding the etiology of childhood psychiatric disorders and the potential impact of ECT on glycemic control, the effect of ECT on beta cell reserve in children should be further evaluated. A multidisciplinary approach is essential during the ECT treatment process in children, with careful attention to hyperglycemic complications and more frequent monitoring of blood glucose levels.
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EP451

JOINT476
Atezolizumab-induced autoimmune diabetes mellitus: clinical case
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Background
Atezolizumab, a PD-L1 inhibitor, has significantly improved outcomes in advanced bladder cancer. However, immune checkpoint inhibitors (ICIs) can cause immune-related adverse events, including autoimmune diabetes mellitus (ADM). Although immune-related T1DM is a rare complication, it has been increasingly reported with ICIs, including nivolumab, pembrolizumab, and atezolizumab. The estimated incidence of ICI-induced diabetes ranges from 0.2% to 1.4%, with most cases occurring within 1–6 months after initiation of therapy.
Case Presentation
A 46-year-old military officer with stage IV bladder cancer (pT4pN0M0, G3) was hospitalized on **March 6, 2024**, due to progressive fatigue, polyuria, polydipsia, and severe hyperglycemia (29.8 mmol/l). He had previously undergone multiple transurethral resections (TURs), radical cystectomy with Bricker urinary diversion (July 2023), and four cycles of gemcitabine-cisplatin chemotherapy (July–October 2023). In January–February 2024, he received two cycles of atezolizumab (T-centrix). Within weeks, he developed worsening hyperglycemia. Laboratory tests confirmed new-onset T1DM: glucose 26.65 mmol/l, ketonuria 3.9 mmol/l, and positive autoimmune markers—glutamic acid decarboxylase antibodies (GADA: 85.1 U/mL) and islet cell antibodies (ICA: 43.7 U/mL). The C-peptide level was markedly reduced (0.33 ng/mL), indicating β-cell destruction. No prior history of diabetes or autoimmune diseases was noted. The patient was started on basal-bolus insulin therapy and intravenous hydration. Over the hospitalization period, glycemic control improved, with glucose levels stabilizing (7.5–15 mmol/l). He was discharged after treatment with recommendations for endocrinology and oncology follow-up, regular HbA1c monitoring, and continued glycemic management. Atezolizumab-induced diabetes has been documented in several case reports. A systematic review of ICI-related diabetes cases found that median onset occurs within 6–12 weeks of therapy initiation, often presenting with diabetic ketoacidosis (DKA). Atezolizumab-related cases remain less frequent than those linked to PD-1 inhibitors, but the mechanism is believed to involve T-cell–mediated β-cell destruction, similar to classic autoimmune diabetes.
Conclusion
This case highlights atezolizumab's potential to induce autoimmune diabetes, likely via immune-mediated β-cell destruction. The onset of hyperglycemia within weeks of ICI therapy underscores the importance of regular glucose monitoring in patients receiving immune checkpoint inhibitors. Early detection and timely intervention can prevent life-threatening complications.
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EP452

JOINT988

Use of diabetes app to help improve management of adolescent type 1 dm patients

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Introduction
Patients use technology based platforms for most daily activities, including managing their health. This is especially true of most adolescents, who prefer to use health based websites and text messaging platforms that involve health management. The management of Type 1 DM in adolescents can be challgening, given that many of these patients have poor diabetes control during this time period. Providers have been trying to find new and innovative ways to manage these patients, in order to improve their diabetes control. Given that adolescents prefer to use app based technology for their health management, they would benefit from an app to help in their diabetes care. Our group previously did a pilot study, where adolescent Type 1 DM patients received a smartphone with pre-loaded apps to help manage their diabetes care. In review of the data, most participants in the study had improvements in their diabetes outcomes. However, the partcipants preferred to have one app that they could download to their own phone to help manage their diabetes.
Objectives and hypotheses
Use of an app to improve the management of adolescent Type 1 DM patients.
Methods
Our group has a created an app with the aid of Equiva Health. Within the app, we have included a communication tab, where the participants can send HIPAA protected texts to providers, as well as have appointments via Zoom; an education tab with different modules that reviews diabetes education; a glucose monitoing tab, which has embedded CGM and glucometer monitoring apps; a fitness and nutrition tab that includes apps for carbohydrate counting. The study will focus on adolescent Type 1 DM patients, 12-22 years of age. Patients will have a baseline HbA1C or GMI and repeat HbA1C or GMI 3 months after using the app. Calls to the office, admissions to the hospital and hypoglycemia episodes will also be tracked at baseline and after using the app. The study team will include a physician, an advanced practice nurse and a social worker.
Results
Results acquisition is in process.
Conclusions
Given the preference of adolescents to use technology to manage their health, as well as our previous study data, we anticipate that this app will help improve diabetes management in adolescent Type 1 DM patients. The acquisition and analysis of the data obtained from this study will lead to continued app improvements and development of additional app features.

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EP453

JOINT3919

Parenting style and glycemic control in adolescents with type 1

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Introduction
The role of parents in the management of adolescents with type 1 diabetes (T1D) is crucial, as it can significantly influence the management of the disease in our young patients. The way parents interact with their child can affect the adolescent's motivation to maintain good blood sugar control.
Objective
Our study aims to examine the role of parenting style in achieving metabolic control in adolescents with type 1 diabetes.
Materials and methods
This is a descriptive cross-sectional study including parents of children with type 1 diabetes (T1D) aged 15–18 years, followed in our department, who attended consultations with their children. Glycemic control was assessed by HbA1c, and parental educational style was evaluated using a questionnaire. Parental Authority Questionnaire and Parental Helplessness Questionnaire.
Results
The study included 100 patients, with a sex ratio (F/M) of 1.5. The average age of the population was 16 years, and the mean duration of diabetes was 5 years. The average HbA1c was 10.6%. Among the patients, 86% were treated with analogs, while 14% used human insulin. Overall, the permissive educational style was dominant, accounting for 80%, followed by the authoritarian that counted for 11%. For patients with HbA1c within the target range, 85% of parents adopted a cooperative educational style. Meanwhile, among patients not achieving HbA1c targets, the majority of parents adopted permissive educational style.
Conclusions
In line with our hypothesis, a cooperative parenting style is associated with better glycemic control in adolescents, while a permissive and authoritarian parenting style predicts worse outcomes.

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EP454

JOINT289

Higher prevalence of mental health impairment in youth with diabetes and association of higher HbA1c with physical complaints

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Introduction
An increased prevalence of mental health impairments has been reported for adolescents with type 1 diabetes (T1D). Although psychosocial factors bear the potential to have a detrimental impact on glycemic control, health professionals are insufficiently trained to recognize and accommodate problems in this field.
Objectives
We aimed to determine the prevalence and the type of mental health impairment in adolescents in our outpatient diabetes clinic and to assess the relationship between mental health problems and glycemic control.
Methods
YSR11-18R assesses the scales: anxious/depressive, regressive/depressive, physical complaints, social problems, thinking, and repetitive problems, attention problems, rule-breaking and aggressive behaviour and measures socially desirable behaviours. Student's t tests were used to compare the results in two groups, patients with good (HbA1c $< 7.7\%$), and less good glycemic control (HbA1c $> 7.7\%$).
Results
In 29 adolescent patients (15 girls, 14 boys), aged 14.9 years (range: 13-18), median HbA1c was 7.8% (range 6.1-14.3%). In 3 questionnaires manifest psychiatric comorbidities were detected, while 3 showed less severe psycho-pathologies, thus 10 percent of YSR tests in our cohort were abnormal. The individual problem scales showed that highest T-values (means $\pm$ SD) were achieved in the fields regressive/depressive (T 55.7 $\pm$ 9), anxious/depressive (T 55.79 $\pm$ 9) and attention problems (T 55.6 $\pm$ 6.4). HbA1c $< 7.7\%$ was associated with significantly less ($P = 0.03$) physical complaints; adolescents with HbA1c > 7.7 had a tendency towards rule-breaking behaviour ($P = 0.08$). High scores were obtained in the socially desirable responses (Highest score 2, mean 1.53 $\pm$ 0.30 SD). Good glycaemic management was associated with fewer physical complaints, while adolescents with impaired glycemic control showed a tendency towards rule-breaking behaviour.
Conclusions
There is an increased prevalence of psychosocial impairment in T1D adolescents but poor glycemic control is mainly associated with physical complaints. YSR testing allows for detection of psychologic problems in adolescents with T1D and thus could allow for targeted interventions.

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EP455

JOINT230

Beyond blood sugar: body composition changes in children with T1DM

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Background
Type 1 Diabetes Mellitus (T1DM) is characterized by insulin deficiency, leading to a catabolic state at diagnosis. While intensive insulin therapy facilitates a rapid and complex reshaping of body composition, the effects on body fat and lean mass, particularly in children, remain underexplored, especially in the Indian context. This study aims to evaluate the impact of insulin therapy on body composition in children with newly diagnosed T1DM over a 10–12-week period and compare it with healthy controls.

Methods
42 children with newly diagnosed T1DM (aged 5–18 years) and 42 healthy controls were included. Clinical assessments, anthropometry, and Body Impedance Analysis (BIA) were performed at diagnosis and after 10–12 weeks for cases, and once for controls. BIA parameters analysed were body fat mass (FM), fat-free mass (FFM), percent fat mass (%FM), percent fat-free mass (%FFM), fat mass index (FMI), and fat-free mass index (FFMI).
Results
At diagnosis, children with T1DM had significantly lower weight Z-scores (-0.58), BMI Z-scores (-0.87), and Triceps skinfold thickness (TSFT) (-4.31) compared to controls. BIA revealed reduced FM (-2.90), FMI (-1.71), and %FM (-9.13%) in the T1DM group. The FFM and FFMI showed no significant difference between the groups, though %FFM was higher in T1DM children indicating a relatively lower proportion of fat mass in cases. After 10-12 weeks of insulin therapy, children with T1DM demonstrated significant increases in weight Z-scores (0.44), BMI Z-scores (0.59), TSFT (0.35 mm), FM (0.77 kg), FMI (0.44 kg/m^2), and %FM (2.07%). FFM (1.03 kg) and FFMI (0.59kg/m^2) also increased, while %FFM decreased, suggesting a shift towards increased fat storage On follow-up, T1DM children matched controls in weight and BMI-Z-scores but had lower FM (-2.13 kg), FMI (-1.28 kg/m^2), and %FM (-7.06%) with higher %FFM (6.77%).
Conclusion
Children with newly diagnosed T1DM exhibit lower body fat mass and BMI at diagnosis, primarily due to insulin deficiency. Insulin therapy leads to an increase in both fat and fat-free mass, with a greater impact on FM, but could not match healthy controls by 10–12 weeks, particularly in terms of fat mass. These findings highlight the importance of addressing body composition changes in children with T1DM to mitigate long-term cardiovascular and skeletal health risks. Future studies with longer follow-up periods are needed to better understand the long-term effects of insulin therapy on body composition in children with T1DM, particularly in the Indian population.

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EP457

JOINT1877

Unilateral ptosis in a patient with graves' disease and multiple sclerosis: a diagnostic challenge

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Introduction
Ptosis can indicate a variety of conditions, including neurological, muscular, or vascular disorders. In patients with autoimmune or inflammatory diseases, establishing a diagnosis can be challenging. We present the case of a sudden unilateral ptosis in a woman with Graves' disease (GD) and Multiple Sclerosis (MS).
Case Presentation
A 53-year-old woman, was being monitored for GD, (TSH $<$ 0.005 µUI/l, FT4: 28 pmol/l, mild bilateral Graves' orbitopathy without symptoms of activity, and positive TSH receptor antibodies) treated with methimazole. She had type 2 diabetes, hypertension, and MS. The patient presented with sudden onset of left eyelid ptosis over two months. Clinical examination revealed ptosis with exotropia of the left eye, suggesting oculomotor nerve (III) palsy, without pupillary involvement. Other cranial nerves were intact, except for the known left abducens nerve palsy (VI). The right eye showed a subconjunctival haemorrhage, with no other abnormalities. Laboratory tests showed a slightly low TSH (0.09 µUI/l) with a normal FT4 level (16.9 pmol/l). Other biological parameters were within normal limits. A cerebral CT angiography ruled out aneurysm or carotid dissection.
Discussion
The ptosis in this patient presents a diagnostic challenge due to her multiple systemic conditions. Mechanical or traumatic origin was excluded based on imaging and patient history. MS could explain third cranial nerve involvement, but the gradual onset, lack of visual disturbances, and the absence of other typical symptoms make this less likely. Myogenic origin (myasthenia gravis), While autoimmunity is a risk factor, the sudden onset, non-fluctuating nature of the ptosis, and lack of worsening with exertion argue against this diagnosis. Vascular origin remains possible due to the patient's vascular risk factors, but the absence of an internal carotid aneurysm on angiography reduces this likelihood. Further investigations are planned, including brain MRI with MR angiography, anti-acetylcholine receptor, anti-MuSK antibody testing, and electromyography.
Conclusion
This case underscores the diagnostic complexity of ptosis in patients with multiple comorbidities. A multidisciplinary approach is essential to identify the underlying cause.

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EP458

JOINT572

Microbiota profiling in diabetic foot infections at oran university hospital: a study from the endocrinology-diabetology department

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Introduction
Foot infections in diabetic patients represent a critical turning point in the progression of the disease, significantly contributing to the development of diabetic foot disease. These infections are often characterised by a multitude of bacterial strains, which are frequently multi-resistant. Recognising the bacterial flora responsible for foot infection is crucial to ensure the effectiveness of antibiotic treatment. The aim of our study is to determine the microbial flora present in these lesions.
Materials and Methods
A retrospective descriptive analysis was carried out over a period of 2 years on a sample of 102 patients hospitalised for diabetic foot in the Endocrinology-Diabetology Department of Oran University Hospital. Based on the clinical manifestations seen, various sampling techniques were employed, including swab sampling, needle aspiration, tissue biopsies and curettage of the lesion.
Result
The results showed that 48 patients (47%) had overt foot infection, with an average age of 61 years. The average length of hospitalisation was 51 days. Bacteriological samples were positive in 43 cases (89.6%). Of these, gram-negative bacilli were found in 31 cases (72.1%), dominated by proteus mirabilis and vulgaris (11 cases) and Escherichia coli (7cases). There were four cases each of Serratia marcescens and Enterobacter, three cases each of Klebsiella pneumoniae and oxytoca, and two cases of Pseudomonas. Regarding Gram-positive cocci, 12 cases were identified, including Streptococcus species (8 cases) and Staphylococcus aureus (4 cases). The patients received targeted antibiotic therapy based on the antibiogram results, along with additional treatment to cover anaerobic pathogens. Osteitis was diagnosed in 34 patients, representing 71% of the cases. Complications led to minor amputations in 15 patients (31.3% of cases) and major amputations in 7 patients (14.6% of cases). The remaining patients experienced a positive clinical outcome.
Conclusion
A comprehensive understanding of the microbiology of diabetic foot infection is essential. It plays a key role in guiding the selection of targeted antibiotic therapy and contributes to optimizing the overall management of this condition.

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EP459

JOINT3832

Beliefs and eating habits in pregnant diabetic women

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Introduction
The pregnant woman with diabetes may face overeating and a reduction in physical activity, two factors responsible for glycemic imbalance. The objective of this study is to evaluate the eating behaviors and beliefs of pregnant women with diabetes in order to improve their management.
Materials and Methods
A prospective descriptive study conducted at the Endocrinology and Metabolic Diseases department of Ibn Rochd University Hospital in Casablanca, involving

patients followed for gestational diabetes who completed a questionnaire to assess their eating beliefs.
Results
We included 64 patients in our study, with an average age of 32.3 years, 47.1% had gestational diabetes and 52.9% had type 1 or type 2 diabetes. The average BMI before pregnancy was 29.8 kg/m^2. Regarding treatment, 74.3% of patients were on insulin and 25.7% followed hygiene-dietary rules. Glycemic control was perfect in 61.2% of patients. Regarding eating behavior, 72.4% of patients had an excessive intake of slow sugars, 62.8% had an excessive intake of fats, and 36.4% consumed rapid sugars, 70.8% ate at fixed times, while 20% skipped at least one meal. Regarding food beliefs, 68% of patients think they should eat less to be healthy, 30% think they can eat the foods they want, 45% think they must eat for two, and 34% think weight gain should not be limited. Regarding physical activity, 28.4% of patients practiced it, with 75.2% believing it helps control blood sugar levels, while 22% think it could harm their pregnancy.
Conclusion
Our study highlights the eating beliefs and behaviors of pregnant women with diabetes and emphasizes the need for better information and improved dietary education for these patients.

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EP460

JOINT3908

Gestational diabetes: clinical profile, screening methods, and management approach

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Introduction
Gestational diabetes represents a public health issue due to its increased frequency, which has significantly risen since the revision of its diagnostic criteria, as well as its impact on both maternal and fetal health.
Objective
The objective of this study is to identify the clinical profile, screening methods, and management approaches for gestational diabetes.
Materials and Methods
A retrospective descriptive study conducted in the Endocrinology and Metabolic Diseases Department of Ibn Rochd University Hospital – Casablanca, among patients monitored for gestational diabetes.
Results
We included 227 patients in our study, all followed for gestational diabetes, with an incidence of 30% of diabetic pregnancies. The average age was 33.1 years, the average gravidity was 2.9, while the average parity was 2.08. The average BMI before pregnancy was 29.6 kg/m^2. Screening for gestational diabetes was conducted in the presence of overweight or obesity in 48.8% of patients, a personal history of macrosomia in 12.3% of cases, and a family history of diabetes in 29.5% of cases. Screening for gestational diabetes was carried out through fasting blood glucose in 73% of patients and the oral glucose tolerance test in 17%. The average gestational age at diagnosis was 22.5 weeks. Regarding management, 66.6% of patients were following hygiene-dietary rules, and 33.4% were on intensified insulin therapy with biweekly consultations. Glycemic control was perfect in 53.3% of patients. As for obstetric complications observed: 14.6% had gestational hypertension, 16.7% had macrosomia, 7.2% had a risk of preterm birth, and 4.3% had malformations.
Conclusion
The results of our work highlight the need to improve the screening of gestational diabetes and the management of patients diagnosed with gestational diabetes.

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EP461

JOINT2620

Educational factors and their impact on metabolic management in diabetic patients

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Introduction
Diabetes management requires active patient participation, including adherence to treatment regimens, dietary modifications, and glucose monitoring. Several sociodemographic factors, including educational attainment, may influence a patient's ability to manage their condition effectively. Patients with lower educational levels may have reduced access to health information, lower health literacy, and greater difficulties in implementing diabetes self-management strategies. Severe hypoglycemia, a life-threatening complication requiring external assistance, can result from inadequate metabolic control, medication mismanagement, or unrecognized hypoglycemia symptoms. Understanding the relationship between education and metabolic management is crucial. This study investigates whether educational attainment is associated with an increased risk of severe hypoglycemia.
Objective
To evaluate the impact of educational level on the frequency of severe hypoglycemia in diabetic patients and explore whether lower education levels are linked to an increased risk of poor glycemic control and hypoglycemic events.
Methods
A retrospective analysis was conducted on a cohort of 66 patients diagnosed with diabetes. Data were collected on their highest level of education and history of severe hypoglycemia. Patients were stratified into different educational groups, ranging from no formal education to higher education. Statistical analyses, including non-parametric tests, were performed to compare the frequency of severe hypoglycemia among groups and determine whether educational level influenced diabetes self-management.
Results
Patients with lower educational attainment exhibited a higher frequency of severe hypoglycemic episodes than those with higher education levels. Although the difference did not reach statistical significance ($P = 0.07$), a clear trend was observed, suggesting that lower education levels may be associated with an increased risk of severe hypoglycemia. Additionally, these patients demonstrated a higher likelihood of incorrect insulin administration, lack of adherence to glucose monitoring recommendations, and limited awareness of hypoglycemia symptoms. These findings suggest that health literacy plays a key role in diabetes self-management and metabolic stability.
Conclusions
Educational background appears to influence diabetes management, with lower education levels potentially predisposing patients to severe hypoglycemic episodes. These results highlight the need for tailored educational interventions addressing varying literacy levels to improve self-care practices and enhance metabolic control. Structured diabetes education programs that simplify complex medical concepts and promote individualized learning strategies may help reduce the risk of severe hypoglycemia and improve overall patient outcomes. Future studies with larger sample sizes are needed to confirm these findings and guide targeted educational policies in diabetes care.

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EP462

JOINT3499

Do we consider cardiovascular risk in patients with type 1 diabetes mellitus? a cross-sectional observational study at the canary islands university hospital complex (CHUC)

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Introduction
Type 1 diabetes mellitus (T1DM) is a chronic metabolic disease with a high cardiovascular risk (CVR). In addition to maintaining good glycemic control, it is essential to manage other CVR factors to reduce the risk of chronic microvascular and macrovascular complications.
Objectives
- To determine whether patients followed up in Endocrinology consultations at CHUC have LDL levels within the target range according to their CVR group and whether they have been prescribed statins.
- To collect descriptive data on the population (age, sex, and years since T1DM diagnosis).

Materials and Methods
A cross-sectional descriptive study was conducted on 89 patients followed up in outpatient Endocrinology consultations at the Canary Islands University Hospital Complex (CHUC). The latest consultation and laboratory results of a sample of patients who attended consultations between January and May 2024 were analyzed.
Results
- The study population had a mean age of 40.87 years, with 52.8% being women and 47.2% men, and a T1DM duration of 22.4 $\pm$ 1.2 years.

- According to European guidelines, CVR stratification was as follows: very high in 61.8%, high in 25.8%, and moderate in 12.4% of patients.
- The LDL levels recorded in the latest laboratory tests were: <55 mg/dL in 4.5%, 55-69 mg/dL in 12.4%, 70-99 mg/dL in 30.3%, 100-115 mg/dL in 19.1%, and $>$ 115 mg/dL in 33.7% of patients.
- The percentage of patients within the target LDL range according to their CVR group was: 5.4% in the very high-risk group, 17.39% in the high-risk group, and 36.36% in the moderate-risk group.
- Only 32.6% of the study population had been prescribed a statin.

Conclusions

- In most cases, patients' LDL levels were not within the target range for their CVR group.
- We propose recording the patient's CVR group in their medical history and addressing lipid-lowering treatment as part of the comprehensive metabolic management of patients with T1DM.

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EP463

JOINT469

Diabetic retinopathy in hospitalized patients: a multicenter tunisian study

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Introduction

Diabetic retinopathy (DR) is a major microvascular complication of diabetes and is currently the leading cause of acquired blindness in many countries. In Tunisia, its prevalence remains poorly documented. This study aims to determine the prevalence and profile of DR in hospitalized diabetic patients.

Patients and Methods

We conducted a descriptive cross-sectional study between February and March 2024 in three Tunisian university hospitals: Hedi Chaker and Habib Bourguiba University Hospitals in Sfax, and Taher Sfar University Hospital in Mahdia. The study included diabetic patients hospitalized in departments other than endocrinology and ophthalmology. Data collected included the history of DR and the results of any available fundus examinations.

Results

Among the 315 patients included, 65% were men, with a median age of 65 years and a median diabetes duration of 8 years. Most patients (87%) had type 2 diabetes, while 5.4% ($n = 17$) had newly diagnosed diabetes during hospitalization. DR was present in 26.5% ($n = 79$) of patients at the time of admission. Notably, 41.9% ($n = 125$) of previously known diabetic patients without a history of DR had not undergone a fundus examination for more than a year.

Conclusion

The prevalence of DR observed in this study is lower than that reported in other international studies, such as one conducted in the United States, where it reached 44% among hospitalized patients. This discrepancy may be attributed to the lack of systematic screening in our cohort, potentially underestimating the true prevalence. Screening for DR in hospitalized diabetic patients is crucial, regardless of the reason for admission, as acute diabetes complications, such as hypoglycemia, frequently occurring in hospital settings, can exacerbate DR through adrenergic discharge and activation of growth factors. This study emphasizes the urgent need to integrate ophthalmological screening into the care protocols for hospitalized diabetic patients.

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EP464

JOINT683

An atypical presentation of malignant otitis externa in a diabetic patient

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Background

External malignant otitis (EMO) is a severe infection often seen in immunocompromised patients, particularly those with diabetes mellitus. Atypical presentations can delay diagnosis and treatment.

Case Presentation

It is about a 62-year-old male with a history of type 2 diabetes who presented with a right earache and hypoacusis evolving for 3months, followed by facial asymmetry that developed 10 days before consultation. Physical examination revealed a Grade III right facial palsy (House and Brackmann classification) and normal otoscopy findings, including a well-calibrated external auditory canal, absence of otorrhea, and intact tympanic membrane. Imaging studies, including CT and MRI of the temporal bone, indicated chronic otomastoiditis with involvement of the second segment of the facial nerve. Initial treatment with corticosteroids and antivirals resulted in complete resolution of facial palsy. Two months later, the patient re-presented with right earache and itching. Otoscopy revealed a stenotic external auditory canal with otorrhea. Microbiological analysis of pus samples identified *Aspergillus flavus*. The patient was treated with voriconazole for six months, leading to a remarkable clinical response.

Conclusion

This case highlights the importance of considering fungal infections in atypical presentations of external malignant otitis in diabetic patients, especially when initial findings are unremarkable. Early recognition and targeted antifungal therapy are crucial for successful management.

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EP465

JOINT2485

Kaposi sarcoma manifesting as leg lesions in a patient with diabetes mellitus: a case report

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Introduction

Kaposi's sarcoma can be defined as a mesenchymal proliferative process involving cells of the blood and lymphatic system, caused by human herpes virus type 8. Diabetic patients are generally prone to pathogenic infections and tumor involvement.

Case Report

Herein, we report the case of Kaposi sarcoma in a Tunisian 52-year-old female with type 2 diabetes progressing for 10 years and managed with insulin therapy, at the stage of chronic macroangiopathic and microangiopathic complications. The current history dates back a few months, when the patient presented to our department with multiple raised violaceous flat patches located on both lower legs. Deep and superficial sensations were preserved and pulses were palpable. The X-ray of legs was unremarkable. A skin biopsy was performed and the immunohistochemical study had shown tumor cells expressing human herpes virus type 8 and CD34. Kaposi's sarcoma associated virus was retained. The etiological investigation of an associated opportunistic infection was negative. There was no evidence of internal organ involvement on whole –body CT scan. Then, the patient underwent treatment with topical alitretinoin 0.1% gel by dermatology. Lesions were remarkably ameliorated. Adjuvant radiotherapy was proposed but refused by the patient.

Conclusion

Our case illustrates the potential association between diabetes and Kaposi's sarcoma and emphasizes the importance of clinical examination in the detection of tumor lesions in diabetics. Rigidly control glucose levels were required allowing for long-term remission and reduction of complications.

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EP466

JOINT2687

Co-occurrence of Ketoacidosis Decompensation and Acute Pancreatitis in Type 1 Diabetic Patients: Clinical and Biological Specificities

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Objective
To describe the clinical and biological presentation characterizing the simultaneous occurrence of acute pancreatitis (AP) and diabetic ketoacidosis (DKA) in type 1 diabetes (T1D).
Patients and Methods
A retrospective descriptive study including 10 T1D patients who presented with a simultaneous episode of DKA and AP.
Results
The average age at T1D diagnosis was 19.7 ± 9.3 years, with a female predominance (60%). T1D was frequently first diagnosed through classic cardinal symptoms (50%) or spontaneous DKA (20%). In 10% of cases, T1D was diagnosed during an AP episode, classified as stage E in 57.1% of cases. The mixed AP-DKA episode occurred at an average age of 26.9 ± 14.9 years. A febrile presentation was frequently reported (30%), along with general state impairment (20%) and severe dehydration (10%). Respiratory and neurological symptoms were present in 20% of cases. Gastrointestinal symptoms were pronounced, particularly epigastric pain (90%), vomiting (50%), and diarrhea (20%). Urinary ketones were markedly elevated in 50% of cases, with an average blood glucose level of 3.2 ± 1.4 g/l. Metabolic acidosis was present in all cases, with mean pH and bicarbonate values of 7 ± 0.3 and 12.3 ± 8.3, respectively. Functional renal failure complicated 10% of cases. An infectious syndrome was observed in 40% of cases, with an average CRP level of 47 ± 72.9 mg/l. All patients showed favorable outcomes after appropriate resuscitation, with insulin requirements estimated at 0.76 ± 0.3 IU/kg/day.
Discussion
The co-occurrence of DKA and AP in T1D is a relatively rare but potentially severe event due to the reciprocal deleterious effects of both conditions. The prognosis of this mixed emergency depends on early diagnosis and prompt resuscitation.

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EP467

JOINT3524

Asymptomatic hyperuricemia: prevalence and risks

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Introduction
Hyperuricemia is a disease, that excess uric acid can lead to precipitation of uric acid into urate crystals. Asymptomatic hyperuricemia is defined as a biological abnormality characterized by elevated blood uric acid levels with no clinical manifestations.
Methods
It was a descriptive cross sectional study conducted in department A of the institute of Nutrition of Tunis which included patients with type 2 diabetes. Hyperuricemia was defined by a uric acid level that exceed 360mg/l.
Results
The total number of patients who participated in the study was 120. The characteristics of the patients were respectively : age 47 ± 9 years, Body mass index (BMI) 29 ± 4.2 Kg/m^2, HbA1c 10.8 ± 2.4%. The mean duration of diabetic patients was 11 ± 7years. Hyperuricemia was present in 34.8%, with a mean level of 411 ± 19.6 mg/l. Twenty two percent have asymptomatic hyperuricemia : 78% of patients have arterial hypertension, 64.1% with microangiopatic complications, 21% with a history of stroke, 22.5% with coronary disease, 67% with arteriopathy. As for the metabolic profile of patients with asymptomatic hyperuricemia, 98% with low HDLc, high LDLc in 79.7%, high triglycerides in 66.4 %. Asymtomatic hyperuricemia was positively correlated with BMI(p = 0.001) and duration of diabetes (p = 0.009) and it was significantly more frequent with coronary disease (p = 0.01) and with dyslipidemic patients (p = 0.007).
Conclusion
Asymptomatic hyperuricemia is common in our population. It is equivalent to symptomatic hyperuricemia in terms of complications and aggravation of comorbidity. It was positively correlated with BMI, duration of diabetes, coronary disease and dyslipidemia.

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EP468

JOINT3553

Association of type 1 diabetes and celiac disease

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Objective
Type 1 diabetes (T1DM) and celiac disease (CD) are autoimmune inflammatory diseases caused by the interaction of genetic and environmental factors. The aim of this study was to determine the prevalence and characteristics of CD in type 1 diabetic patients.
Methods
We conducted a cross-sectional study of 80 type 1 diabetic patients followed up in ward C of the Tunis Institute of Nutrition. Patients were divided into two groups: Group 1 (G1):40 T1DM patients with negative CD serology and Group 2 (G2): 40 type 1 diabetics with positive CD serology.
Results
The mean age of our population was 28 ± 8 years. The mean duration of diabetes was 9 ± 5.6 years. Among G2 patients, 13 had positive Ig A anti-transglutaminase autoantibodies and 30 patients underwent jejunal biopsy with histological confirmation of CD (37.5% of patients). Diabetes imbalance, as evidenced by elevated HbA1c, was associated with the presence of CD (G1: 10.4 ± 3.1%, G2: 11.9 ± 2.1%; P = 0.001). Hypoglycemia was more frequent in patients with CD (G2 of 3.1 episodes/patient/week, G1:1.7 episodes/patient/week, P = 0.01).
Conclusion
The association of CD and T1DM is frequent and exposes this population to diagnostic, therapeutic and psychological difficulties. Appropriate therapeutic education is imperative to preserve the prognosis of these patients.

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EP469

JOINT1654

A complex case of Type 1 DM with history of recurrent severe disabling hypoglycaemia treated with renal and pancreatic transplant

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Hypoglycemia is a common complication in patients with diabetes, particularly in those treated with insulin, sulfonylurea, or glinide. Impairments in counter regulatory responses and hypoglycemia unawareness constitute the main risk factors for severe hypoglycemia. Episodes of hypoglycemia are associated with physical and psychological morbidity, particularly those with pre-existing mental health issues or learning disabilities. Here, we describe a case of 37 years old male, with Type 1 DM, with ESRD on hemodialysis, diabetic proliferative retinopathy, Charcot neuroarthropathy, and diabetic foot. He had repeated episodes of hospital admissions with a history of severe disabling hypoglycemia. He was only on a few units of insulin Tresiba and novorapid to control his blood sugar. Any minor adjustment of insulin doses caused him severe hypoglycemia particularly on the day of hemodialysis. Blood sugar in hospital was between 1.3 to >27.5 mmol/l. We had a multidisciplinary discussion to start HCL insulin pump but as he is having learning disabilities, it was not considered later. Furthermore, reductions of insulin dose to prevent hypoglycemia caused him to develop episodes of DKA. Personally, he is non-smoker and non-alcoholic with no history of taking any illicit drugs. Physical examination was unremarkable except for having features of chronic diabetic Charcot neuroarthropathy. His insulin injections sites were normal. His observations, including NEWS, were stable in between episodes of hypoglycemia. His investigations including blood test showed creatinine about 500umol/l (baseline) after dialysis with normal liver function test. His HBA1c was between 57 and 73 mmol/mol with C peptide level was <50 pmol/l. Then we consulted with tertiary Centre for consideration of renal and pancreatic transplant for him. After discussion of his thorough case history with tertiary Centre, it was decided to proceed for renal and pancreas transplantation for him. He recovered well after the surgery. His diabetes is now on the way to remission after about 3 months of the pancreatic and renal transplant. Recent blood sugar readings in libre sensor showed his target in range of blood sugar was 99% without having any episodes of hypoglycemia with GMI was 43mmol/mol off insulin therapy. This case highlights the importance of involving multidisciplinary teams including diabetologist, DSN, dietitian, transplant surgeon, psychiatrists, and nephrologist for coordinated effort in complex cases of hypoglycemia especially in type 1 DM patients. Those Patients who are not suitable for insulin therapy, considering pancreatic/pancreatic and renal transplants can be life-changing, especially those who are young and fit for surgery.

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EP470

JOINT2318

Refocusing on the implications for management: a case of hyporeninemic hypoaldosteronism in a patient with diabetic nephropathy presenting with severe hyperkalemia

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Background
Diabetic nephropathy (DN) is the most common cause of Hyporeninemic Hypoaldosteronism (HH), which often presents as hyperkalemia. Most of these patients are on Renin-Angiotensin-Aldosterone inhibitors (RAASi) to slow the progression of kidney disease. However, these medications can cause hyperkalemia as a side effect, which can complicate the disease management.
Case presentation
A 65-year-old female with Hypertension and Type 2 Diabetes Mellitus, currently on Lisinopril and Metformin, was brought from the clinic for elevated potassium levels. She denied chest pain, dyspnea, oliguria, or peripheral edema. No family history of hyperkalemia. Vital signs were normal. Physical examination was unremarkable. Laboratory tests showed Potassium 8 mEq/l without EKG changes, Sodium 131mEq/l, Creatinine 1.4 mg/dL (baseline 1.3 mg/dL), urine Protein/Creatinine ratio 4.5 g/g (ref $<$3.5 g/g), HbA1c 13%. Lisinopril was temporarily held, and the patient received calcium gluconate, and dextrose with insulin but remained hyperkalemic. The nephrology team suggested emergent hemodialysis (HD). Because of unexplained hyperkalemia, hormonal testing was added which showed Cortisol 20 mg/dL (ref 5-25 mg/dL), plasma Renin activity 0.4 ng/mL/hr (ref 0.7-3.3 ng/mL/hr), Aldosterone 2 mg/d (ref 3-25 mg/d). After one session of HD, repeat potassium was 3.9mEq/l. She was restarted at a lower dose of lisinopril with daily electrolyte monitoring and her glucose regimen was optimized. She was subsequently discharged with strict outpatient follow-up.
Discussion
DN causes autonomic dysfunction, resulting in decreased renal sensitivity to renin stimulation factors, causing HH and hyperkalemia. RAASi are effective in preventing progression to end-stage kidney disease but are a known cause of hyperkalemia. Withdrawing RAASi based on a diagnosis of HH alone may deprive patients of the cardiorenal benefits of these medications. Therefore, initiation of low-dose RAASi with gradual titration combined with a low potassium diet and avoidance of nephrotoxic medications can be done with close outpatient monitoring. However, the best treatment remains to be the optimization of glucose control.
Conclusion
HH is a complication of DN, and the optimization of glucose control plays a central role in the management. In addition, RAASi are effective means of slowing disease progression, and the benefits of continuing RAASi in patients who develop correctable side effects outweigh the risks, provided that proper patient education with close monitoring of laboratory tests and follow-up can be done.
Reference
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EP471

JOINT57

Newly diagnosed LADA in elderly people: a case study

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Aims and objectives.
To provide a report of an 88- year-old woman who treated for 29 years as T2DM but lately was diagnosed with LADA.
Background
Latent autoimmune diabetes in adults (LADA) is the most common term used to describe slow autoimmune β-cell destruction that occur in adults, leading to a long duration of marginal insulin secretory capacity. LADA often misdiagnosed as type 2 diabetes mellitus (T2DM), because of the resemblance in their clinical presentation. The diagnosis of LADA is similar to type 1 diabetes mellitus (T1DM), by detection of Islet autoantibodies in the blood. However, in most cases of patients with LADA are only glutamic acid decarboxylases (GADA) - positive. Currently, the Immunology of Diabetes Society (IDS) suggests diagnosing LADA at age of onset $\geq$ 30 years. While the threshold age for diagnosis LADA is still a matter of debate.
Design
Case study of one patient with uncontrolled T2DM, visiting a nurse practitioner diabetes Clinic.
Methods
A 88 -year-old Woman with history of T2DM participated in this case study. A full investigation was conducted and described by nurse practitioner diabetes to identifying a misdiagnosis.
Results
A patient treated for 29 years as T2DM was found with positive GADA (1869.6 IU/ml). Due to the newly results the patient was re-diagnosed with LADA and a change in treatment regime performed.
Conclusion
This Case highlights the complexity of investigation LADA among T2DM patients, and the importance to perform it among elderly patient as well. The key components for investigation LADA include: profound anamnesis, GADA testing and C-peptide levels. Relevance to clinical practice. The importance of role of Nurse practitioner diabetes in primary health care setting for a thorough diagnosis among uncontrolled glycemic patients revealing hidden types of this complex disease.

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EP472

JOINT3999

Epidemiological, clinical, and therapeutic profiles of pre-existing diabetes in pregnancy: exploring complications in a moroccan cohort

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Introduction
In Morocco, pre-existing diabetes during pregnancy is a serious public health concern. In addition to placing a significant socioeconomic burden on patients, it is associated with an increased risk of complications.
Objective
Examining the epidemiological, clinical, and therapeutic aspects of pre-existing diabetes during pregnancy is the aim of our research. We also want to evaluate maternal-fetal morbidity and mortality, neonatal outcomes, and pregnancy progression.
Materials and Methods
A retrospective, descriptive study based on a review of clinical records of pregnant women with type 1 and type 2 diabetes, monitored at the Endocrinology, Diabetology, and Metabolic Diseases Department of the Hassan II University Hospital in Fez over a 13-year period, from January 2009 to September 2022.
Results
319 women with pre-existing diabetes were included, of these, 24.1% had type 1 diabetes and 75.9% had type 2 diabetes. The average age of type 2 diabetes was 36.4 $\pm$ 5.45 years. The duration of diabetes was 43 $\pm$ 10.86 months on average. 5.8% of cases had degenerative consequences. The average pre-pregnancy HbA1c was 8.2% $\pm$ 2.6%, and 97.9% of pregnancies were unplanned. The average age of type 1 diabetes was 29.7 $\pm$ 6.29 years. 106 $\pm$ 62 months was the average duration of diabetes. 93.5% of pregnancies were unplanned, with an average pre-pregnancy HbA1c of 8.2% $\pm$ 3.1%. Insulin was used. In the first, second, and third trimesters, the average daily insulin dosage was 35.4 $\pm$ 2.9 IU, 39.9 $\pm$ 3.2 IU, and 47.9 $\pm$ 3.6 IU, respectively. Concerning maternal complications, among those with type 1 diabetes were urinary tract infections (12.3%), severe hypoglycemia (4.2%), ketoacidosis (13.3%), and gestational hypertension (7.8%). Urinary tract infections were the most common consequence among type 2 diabetes (15.5%), followed by ketoacidosis (2.8%). 58.3% of type 2 diabetes and 61.2% of type 1 diabetes had cesarean deliveries. Among the prenatal problems were hydramnios (29.8% vs. 30.1%), fetal abnormalities (9.4% vs. 6.7%), and macrosomia (37% in type 2 diabetics vs. 31.5% in type 1). 5.3% of cases had neonatal complications (4.4% in type 2 diabetics and 6.8% in type 1 diabetics). Of them, neonatal distress accounted for 29.2%, neonatal jaundice for 23.1%, and neonatal hypoglycemia for 20%.
Conclusion
Given these complications and their impact on both maternal and fetal health, whether in terms of vital or functional prognosis, we emphasize the need for a multidisciplinary approach.

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EP473

JOINT2601

Clinical profile of patients with nondiabetic hypoglycemia in a tertiary endocrine center in Nepal

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Nondiabetic hypoglycemia is a challenging condition for diagnosis and management. We retrospectively reviewed the records of the patients diagnosed with nondiabetic hypoglycemia who visited our center from May 2013 to November 2024. Total 36 patients were included in this study. The mean age was 48.33 ± 14.30 years (range 19-75 years). 21(58.33%) patients were male and 15(41.67%) were female. The average weight was 70.27 ± 12.82 (range 47-100) kg and average BMI was 27.65 ± 4.84 (range18.6-37.3) kg/m2. All patients had symptoms of hypoglycemia with positive Whipple's triad. Weight gain was seen in 26(72.22%) patients.1 (2.77%) patient had a history of seizure and 3(8.33%) patients had loss of consciousness. The major cause of hypoglycemia was reactive hypoglycemia in 22 patients (61.11%) followed by hyperinsulinemic hypoglycemia in 7 patients (19.44%). Out of 7 hyperinsulinemic hypoglycemia patients, insulinoma was detected in 6 patients.1 (2.77%) patient had drug induced (carbimazole) hypoglycemia, 1(2.77%) patient had post bariatric surgery hypoglycemia and 1 (2.77%) patient had post gastrectomy (for gastric carcinoma) hypoglycemia. 2 (5.55%) patients had sarcoma-associated hypoglycemia (1 had retroperitoneal sarcoma and other Ewing sarcoma).1(2.77%) patient had purely alcohol induced hypoglycemia.1(2.77%) patient had hemodialysis induced hypoglycemia. In cases of hyperinsulinemic hypoglycemia, the average blood sugar level during hypoglycemia was 42.98 ± 11.0 mg/dl (range 29-57mg/dl), insulin level was 35.07± 53.82 mIU/l (range 5.28 - 156.2 mIU/l) and C peptide level was 4.47 ± 4.24 ng/ml(range 0.6-13.5 ng/ml). In a 72 hour fast, 2 patients had hypoglycemia within 6 hours, 2 patients within 12 hours, 1 patient within 24 hours, 1 patient within 48 hours and 1 patient within 72 hours. All reactive hypoglycemia patients were diagnosed by extended oral glucose tolerance test. Comorbidities like prediabetes were present in 10 patients, diabetes in 3 patients, hypothyroidism in 15 patients, 7 patients had chronic cardiovascular disease, 1 patient had CKD and 1 patient had OSA. Out of 6 patients with insulinoma, 5 patients had tumour located in tail of pancreas and 1 patient had in uncinate process of pancreas. The maximum size of insulinoma was 14.4 mm and the minimum was 1 mm. Enucleation was done in 4 cases of insulinoma and 1 patient underwent distal pancreatectomy. 5 insulinoma cases were cured after surgery. One case of insulinoma was lost to follow up. Out of 22 cases of reactive hypoglycemia, acarbose was used in 15 patients and the rest were managed by dietary modifications.

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EP474

JOINT738

Planned postpartum screening study for cardiometabolic and renal outcomes in women diagnosed with gestational diabetes mellitus in Auckland, new Zealand

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Background
The prevalence of gestational diabetes mellitus (GDM) in New Zealand has increased from 1.4% in 1991 to 6.2% in 2019, comparable to an estimated 7.8% in Europe in 2021, though lower than rates up to 27% reported in Asian and African. National rates of GDM are significantly higher for Māori (12%) compared to European women (around 7%). After GDM, there is up to a 20-fold increased risk of developing diabetes, and an increased age-adjusted risk of major cardiovascular (CV) events and renal disease compared to women who remain normoglycemic during pregnancy. There are few reports on post-partum screening for women diagnosed with GDM in NZ and internationally. One national study reported low post-partum screening rates for type 2 diabetes for women with GDM (56%) and unacceptably low rates for Māori women (38%), which also varied by maternal age, deprivation and region. No recommendations have been identified for screening of CV risk factors (blood pressure, lipids, smoking status) or renal disease in NZ. A large, representative United Kingdom study reported 80% of women were screened for hypertension in the first year post-partum (declining to 48% by the third year), 58% for diabetes, and only 46% and 11% for smoking status and lipids, respectively.
Aim
To identify factors associated with post-partum screening in women with GDM to increase screening and risk management, particularly for Māori and Pacific women.
Methods
Anonymised medical information will be obtained for women diagnosed with GDM in Auckland from a primary health-care provider, covering approximately 50% of the Auckland population, to identify factors associated with post-partum screening for cardiometabolic and renal disease. Approximately 250 of the total women will be randomly selected and complete a self-administered questionnaire and telephone interview to identify facilitators and barriers to screening. Comparisons will be made between women who complete screening and those who do not, utilising chi-square or t-tests for demographic and health-related variables, Cox proportional hazard ratios for calculating time-to-first cardiometabolic events, Kaplan-Meier to generate outcome (survival) curves and logistic regression to generate odds ratios for health outcomes.
Results
Initial results for the total cohort will be presented if available. Findings are expected to translate across diverse populations, identify solutions to increase post-partum screening and improve risk management and health outcomes for at-risk women.

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EP475

JOINT1205

Time in tight range (TITR) stratified by coefficient of variation (CV) in a cohort of patients with type 1 diabetes mellitus and multiple daily injections. a real-life study

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Objetive
To analyze the TITR (70-140 mg/dL) and assess their possible differences according to CV in a cohort of type 1 DM patient with MDI.
Patients and Methods
355 adult users of isCGM with at least a HbA1c during the period October 1, 2023-October 1, 2024, and glucose data in the 90 days prior (or at least 60 days) were included.
Results
Age 46.9 years (SD 13.6); 57.2% male; age at diagnosis 25.6 years (SD 14.3); time of evolution 21.6 years (SD 12.6); HbA1c 7.2% (SD 1.1). Glucometric parameters: glucose 165.9 mg/dL (SD 31.5), TITR 38.4% (20.3% had a TITR ≥ 50%), TIR (70-180 mg/dL) 60.4% (SD 16.5), TBR1 (54-69 mg/dL) 3.3% (SD 2.8), TBR2 (< 54 mg/dL) 0.5% (SD 0.8), TAR1 (181-250 mg/dL) 23.3% (SD 8.4), TAR2 (> 250 mg/dL) 12.4% (SD 12.1), CV 37.1% (SD 6.2), GMI 7.3% (SD 0.8) and GRI 47.8% (SD 21).
Conclusions
The percentage of patients achieving TITR ≥ 50% is higher in patients with lower glycemic variability. The correlation TITR-TIR is high and modified by glycemic variability.

Table 1: Clinical characteristics and glucometric parameters according to the CV.

	CV ≤ 36% (n = 156)	CV > 36% (n = 199)	P
Age (years)	48.3 (SD 13.6)	45.9 (SD 13.5)	0.094
Gender (male) (%)	59.4	56.1	0.534
Age at diagnosis (years)	27.5 (SD 14.7)	24.1 (SD 13.8)	0.029
Time of evolution (years)	21.1 (SD 13.5)	21.9 (SD 11.9)	0.482
Mean glucose (mg/dL)	151.4 (SD 35.1)	169.4 (SD 27.4)	0.022
TITR (%)	40.8 (SD 16.4)	36.4 (SD 10.4)	0.008
TITR ≥ 50% (%)	31.4	11.6	< 0.001
TIR (%)	65.5 (SD 19.8)	56.5 (SD 12.1)	< 0.001
TBR1 (%)	1.9 (SD 2.4)	4.4 (SD 2.6)	< 0.001
TBR2 (%)	0.2 (SD 0.4)	0.8 (SD 0.9)	< 0.001
TAR1 (%)	23.1 (SD 11.1)	23.5 (SD 5.7)	0.667
TAR2 (%)	9.3 (SD 13.3)	14.8 (SD 10.4)	< 0.001
CV (%)	31.5 (SD 3.3)	41.5 (SD 4.1)	< 0.001
GMI (%)	7.2 (SD 0.8)	7.4 (SD 0.7)	0.022
GRI (%)	38.1 (SD 22.8)	55.5 (SD 15.8)	< 0.001
HbA1c (%)	7.1 (SD 1.2)	7.3 (SD 0.9)	0.049

The correlation TITR-TIR was high and differs depending on CV (patients with CV ≤ 36%: β = 0.88; CI 95% 0.83-0.93; R^2 Adjusted 0.89; P< 0.001 – patients with CV > 36%: β = 0.84; CI 95% 0.81-0.87; R^2 Adjusted 0.94; P< 0.001)

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EP476

JOINT3417

Characteristics of diabetic ketoacidosis episodes treated at HUC between 2021 and 2023

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Introduction and Objectives
Diabetic ketoacidosis (DKA) is one of the acute complications of diabetes mellitus. It is more common in patients with type 1 diabetes mellitus (T1DM), although cases have also been reported in patients with type 2 diabetes mellitus (T2DM) and latent autoimmune diabetes in adults (LADA). DKA can be triggered by poor adherence to treatment, new-onset diabetes, or secondary to an infection. The objective of this study is to describe the characteristics of DKA episodes attended at the Hospital Universitario de Canarias (HUC) between 2021 and 2023.
Materials and Methods
A descriptive observational study was conducted on a sample of 41 DKA episodes evaluated by the Endocrinology and Nutrition Department of HUC between 2021 and 2023. Variables analyzed included age, sex, type of diabetes, biochemical parameters (blood glucose, pH, ketonemia, bicarbonate), HbA1c, treatment, and associated comorbidities.
Results
Of the 41 patients, 23 (56%) were women and 18 (44%) were men, with a mean age of 34 years. A total of 28 patients (68%) had T1DM, including 4 newly diagnosed cases, while 8 patients (19%) had T2DM and 5 (13%) had LADA. Among the associated comorbidities, 29% had diabetic retinopathy, and 14% had diabetic nephropathy. The most frequent triggers of DKA were insulin omission and infections (30% each, totaling 60%), followed by undertreatment (17%, more common in T2DM patients), substance abuse (12%), and new-onset diabetes (10%). The average pH upon arrival was 7.11, with a mean blood glucose level of 390 mg/dL, a mean ketonemia of 4.8 mmol/l, and a mean bicarbonate level of 7.75 mmol/l. The mean HbA1c level measured before the event (in most cases, approximately 4 months prior) was 10.92%, while the mean HbA1c after the event was 11.71%. Regarding electrolyte imbalances, the most frequent was hyponatremia (48%), followed by hypokalemia (43%).
Conclusions
DKA has a mortality rate of $<5\%$, which is even lower in our country, likely due to the rapid clinical management facilitated by the availability of appropriate infrastructure and resources. Nevertheless, the incidence of DKA remains significant. The poor metabolic control reflected in the high HbA1c levels prior to the event may have been influenced by loss of follow-up and less strict monitoring secondary to the COVID-19 pandemic.

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EP477

JOINT1589

Association between diabetes mellitus and severity of epistaxis: a retrospective study

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Introduction
Epistaxis is a common condition encountered in otorhinolaryngology, generally benign, but it can occasionally present as a severe and life-threatening event. For patients with diabetes mellitus (DM), epistaxis may be a sign of underlying vascular complications. This study aims to evaluate the relationship between diabetes and the severity of epistaxis and its implications for management strategies.
Methods
A retrospective cross-sectional analytical study was conducted at the Department of Otolaryngology–Head and Neck Surgery of Farhat Hached University Hospital, encompassing patients consulting and/or admitted for epistaxis between January 2015 and December 2022.
Results
A total of 720 cases were analyzed. Of these, the majority (87.9%) were classified as benign and managed on an outpatient basis, while 12.1% of patients presented with severe epistaxis necessitating hospitalization. A significant prevalence of cardiovascular diseases was observed, including hypertension (32.9%), diabetes (12.8%) and dyslipidemia (6.9%). Other noteworthy medical conditions included chronic kidney disease ($n=19$; 2,6%) and haematological pathologies ($n=11$; 1,5%). Despite the prevalence of diabetes (12.8%), no statistically significant correlation was found between diabetes and the severity of epistaxis. Contrary to previous studies suggesting a direct association between DM and severe epistaxis, our findings suggest that diabetes may act as a predisposing factor by inducing vascular changes such as endothelial dysfunction and impaired hemostasis. Additionally, diabetes mellitus may contribute to atherosclerotic changes in the nasal vessels, increasing their fragility and susceptibility to bleeding. The coexistence of cardiovascular conditions, such as hypertension and dyslipidemia, which are frequently associated with diabetes, may further exacerbate the risk of epistaxis in this population.
Conclusion
Diabetes mellitus may increase the risk of epistaxis through its effects on vascular integrity, though its role in determining the severity of the condition remains uncertain. Further large-scale, prospective studies are needed to elucidate the underlying pathophysiological mechanisms and refine management strategies for diabetic patients presenting with epistaxis.

Keywords
Epistaxis – Bleeding – Diabetes Mellitus - Severity criteria - Risk Factors – Management.
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EP478

JOINT3001

The role of chronic diabetic imbalance in increasing the risk of hepatic fibrosis

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Introduction
Non-alcoholic hepatic steatosis has become the leading cause of chronic liver disease in the world. Our aim was to assess the prevalence of hepatic fibrosis by Fibroscan in unbalanced type 2 diabetic (T2D) patients with no known liver disease.
Patients and methods
Prospective cross-sectional study including 30 T2D followed at the endocrinology department CHU Farhat-Hached. A Fibroscan and a hepatic work-up were performed. Patients with known chronic liver disease were excluded.
Results
The mean age was 52.9 ± 11.7 years, 53% of patients were male. The mean duration of diabetes was 9 ± 7.6 years old. Only 23.1% had a normal weight, compared with 46.1% with a BMI >30kg/m2. Android obesity was present in 92.2%, with an average waist circumference of 103 cm. Diabetes was unbalanced in 71.4% of patients, with a mean HBA1c of $9.22\pm2.22\%$. Cytolysis was found in 9.5% and no patient presented with cholestasis. Median elasticity was 6.48 ± 3.63 kPa. Fibrosis was confirmed in 41.4% and 13.8% had advanced fibrosis ($F\geq3$). Among the cohort, 20% of obese patients had hepatic fibrosis, including 10% with severe fibrosis. Unbalanced diabetes was noted in 29.6% of cases of Fibrosis ($P<0{,}001$).
Conclusion
Unbalanced type 2 diabetes and obesity are among the factors that accelerate progression to liver fibrosis in non-alcoholic steatosis.

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EP479

JOINT3029

Metabolic profile of tunisian type 2 diabetes patients at insulin initiation: a retrospective study

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Introduction
Type 2 diabetes (T2D) is a progressive disorder that often necessitates insulin therapy when oral glucose-lowering agents fail to control hyperglycemia. Initiating insulin in T2D patients represents a critical therapeutic escalation, aimed not only at preventing acute and chronic complications but also at reducing cardiovascular risks. This study aimed to evaluate the metabolic profile of Tunisian T2D patients at the time of insulin initiation.
Patients and Methods
We conducted a retrospective descriptive study at the Endocrinology Department of Taher Sfar University Hospital, including 245 T2D patients who commenced long-term insulin therapy due to the failure of oral antidiabetic agents or the presence of signs of insulinopenia.

Results
The study included 245 patients with a mean age of 59.3 ± 9.18 years and a sex ratio (M/F) of 0.67. The median duration of T2D was 10 years [6–15]. Hypertension and dyslipidemia were present in 50.6% and 53.5% of patients, respectively. Most patients (87.7%) were on a combination of metformin and sulfonylureas. Even though 66.4% of patients reported significant weight loss, the median BMI was 27.6 kg/m^2 [25.1–30], with 76% of patients being overweight or obese. Waist circumference, a key indicator of insulin resistance, was 100 cm [91.5–108.7] in women and 102 cm [93.5–107] in men. Glycemic control was suboptimal, with median HbA1c and fasting plasma glucose (FPG) levels of 11.43% [10.5–12.85] and 2.9 g/l [2.3–3.3], respectively. Lipid profiles were also poor, with median levels of total cholesterol, triglycerides, HDL-C, and LDL-C at 1.62 g/l [1.46–2.05], 1.32 g/l [0.9–1.82], 0.44 g/l [0.35–0.5], and 0.96 g/l [0.69–1.23], respectively. Median uric acid levels were 312 µmol/l [243–391].
Conclusion
Our findings underscore the poor metabolic profile of T2D patients at insulin initiation, reflecting a significant delay in therapeutic escalation. The observed dyslipidemia may be attributed to insulinopenia and/or chronic hyperglycemia. Early intensification of treatment, whether through basal insulin or other agents with proven metabolic benefits, could mitigate further cardiovascular complications and improve outcomes.

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EP480

JOINT3285

A rare presentation of type 1 diabetes mellitus: cornelia de lange syndrome presenting with nonketotic hyperosmolar state

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Introduction
Cornelia de Lange syndrome (CdLS) is a rare genetic disorder characterized by growth and developmental delay, typical dysmorphic features, and genitourinary system anomalies. Diabetes mellitus (DM) has been rarely reported in CdLS, and its etiology remains unclear.
Case
A 4-year-old male presented with respiratory distress following a one-week history of fever, cough, vomiting, and fatigue. He was born at 32 weeks of gestation (BW 935 g) via cesarean section due to fetal distress. He remained in the neonatal intensive care unit for 4 months. Dysmorphic features (microcephaly, synophrys, hypoplastic external genitalia) led to a diagnosis of CdLS (NIPBL exon 37, c.6461T>C heterozygous mutation). He required gastrostomy at 4.5 months, developed epilepsy at 1 year, and a cochlear implant was placed for bilateral hearing loss at 14 months. On admission, the patient was lethargic, hypotensive, and tachypneic with dehydration. Height was 82 cm (-5.1SDS), and weight 9.8 kg (-5.7SDS). Laboratory revealed a blood glucose of 1693 mg/dL, sodium 162mEq/l, potassium 4.42mEq/l, creatinine 1.8mg/dL, BUN 79mg/dL, pH 7.28, HCO_3 19 mmol/l, negative urine ketones. He was diagnosed with nonketotic hyperosmolar state. A bolus of isotonic saline (20 mL/kg) was followed by 5% dextrose and 0.45% saline infusion at a rate of 4 L/m^2/day. Regular insulin infusion (0.025 U/kg/h) was initiated two hours after hydration. Persistent respiratory distress and hypotension required intubation and adrenaline infusion. Blood glucose gradually decreased, ketones remained negative. After 17 hours, the metabolic and clinical condition improved, insulin infusion was discontinued. However, hypernatremia persisted for 78 hours, necessitating free water supplementation. Pulmonary edema developed during this period, leading to a reduction in fluid intake. Further evaluation during hyperglycemia revealed low C-peptide (0.466ng/mL) and insulin (2.97mIU/l), an HbA1c of 9.3%, positive anti-GAD antibodies (15U/l). Basal insulin (0.4 U/kg/day) in two doses along with correction boluses was started. During follow-up, insulin was temporarily discontinued. However, hyperglycemia recurred five months later, requiring the re-initiation of basal insulin therapy (0.58 U/kg/day).
Conclusion
Diabetes has been rarely reported in CdLS, and this case represents the first well-documented pediatric Type 1 DM. Hyperosmolar state is an uncommon presentation of Type 1 DM in children. The syndromic condition may have contributed to the atypical clinical course of diabetes in this patient.
Keywords
Cornelia de Lange syndrome, Type 1 Diabetes Mellitus, Nonketotic Hyperosmolar State

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EP481

JOINT1726

Ketotic decompensation revealing early-stage fournier gangrene complicating type 2 diabetes

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Introduction
Fournier's gangrene is a rare and serious bacterial infection of the external genitalia and perineum, causing skin destruction. It generally affects men with a history of immunodepression. It is a medico-surgical emergency due to its rapid evolution, which can lead to sepsis and death. Treatment combines surgical intervention and appropriate antibiotic therapy. We report the case of a patient admitted for diabetic ketosis on Fournier gangrene.
Observation
A 60-year-old patient, diabetic (type 2) 6 years previously, was admitted for management of diabetic ketosis. He presented with a polyuro-polydipsic syndrome with pain in the anal region evolving in a context of chills. Examination revealed a red, warm, painful and indurated swelling on the left perianal area. Biological examination revealed an infectious syndrome with elevated WBC and CRP. Ultrasound of the anal soft tissues revealed extensive infiltration of the subcutaneous and fascial soft tissues, with micro-logetes in the process of collection. Fournier's gangrene was diagnosed on the basis of necrosis of the subcutaneous tissues. Management consisted of surgical debridement, excision of necrotic tissue and drainage, combined with triple antibiotic therapy. Post-operative management was straightforward. On improving, the patient was referred to the plastic surgery department for skin reconstruction.
Discussion/conclusion
Despite its rarity, Fournier's gangrene remains a formidable disease due to its serious complications, and is particularly common in diabetic patients. Diagnosis is mainly clinical. Treatment involves emergency surgical debridement with appropriate antibiotic therapy. Plastic surgery techniques can be used to improve aesthetics. Prognosis is closely linked to rapid diagnosis and intervention.

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EP482

JOINT1795

Diabetes mellitus in equatorial guinea: community-based primary health care intervention

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The last decade has seen a significant increase in cases of diabetes mellitus (DM), a trend that is expected to continue to rise, especially in low- and middle-income countries, where mortality is higher according to the World Health Organisation. On the African continent, DM is positioned as one of the major non-communicable diseases that often go undiagnosed and untreated. This research aims to analyse the situation of DM in Equatorial Guinea, identifying the associated risk factors and evaluating the impact of health interventions in its population. For its development, an educational intervention programme was implemented in the capital of the country, targeting both patients and health personnel, together with a qualitative study that analysed the knowledge on prevention, diagnosis and treatment of DM, as well as the availability of resources. The results of the study revealed that patients with DM simultaneously present the main risk factors: poor dietary habits (98%), high blood pressure (64%), overweight (57.2%) and obesity (49.8%). At the same time, a lack of programmes aimed at the early diagnosis and comprehensive management of this disease was identified, a situation that is increasingly worsening due to the low perception of DM as a health priority among patients and health personnel despite its high morbimortality. In this context, there is an urgent need to design and implement tailored strategies including awareness raising campaigns, specialised training of healthcare workers and the development of diabetes prevention and early detection programmes. In conclusion, it is essential to improve the perception of DM as a health priority through comprehensive and contextualised strategies. It is recommended to establish health checks focused on early detection. It is also proposed to develop educational programmes that address nutrition, self-care and body weight management, as well as to train medical staff and promote outreach campaigns on different digital platforms that are popular among the population are key elements to improve the care and prognosis of diabetes in Equatorial Guinea.

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EP483

JOINT1119

Charming circle between iron and vitamin D deficiencies in women with type 2 diabetes mellitus and heart failure with preserved ejection fraction

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Background and aims

Iron and vitamin D deficiencies are two of the most common nutrient deficits in the world. Frequently when it comes to such significant pathologies as diabetes or heart failure (HF) we simply lose focus on nutritional support, which can improve quality of life and alleviate symptoms that may be caused by nutrient deficiencies rather than the underlying diseases. Aim of the study is to evaluate associations between iron status and vitamin D level with inflammation caused by underlying diseases in females with type 2 diabetes mellitus (T2DM) and HFpEF.

Materials and methods

30 women with T2DM and HFpEF (mean age -58,4±1,3 years; body mass index (BMI)- 33,8± 2,5 kg/m^2, waist circumference (WC) - 103,5±1,9 cm, glycated hemoglobin (HbA_1C)- 7,1±0,1% and duration of T2DM -7,7±0,8 years) were comprehensively phenotyped including physical examination, laboratory (N-terminal pro-brain natriuretic peptide (NTproBNP), ferritin, transferrin saturation (TSAT), glycated hemoglobin (HbA_1C), 25-hydroxycholecalciferol (25(OH)D) and C-reactive protein (CRP)) and instrumental (echocardiography: left ventricular ejection fraction (LVEF) >50%) results.

Results

25(OH)D concentrations <30 ng/mL were presented in 86,7% patients, 3,3% females had 25(OH)D level>30 ng/mL. ID were presented in 23 (76,7%) women against 23,3%. Women with 25(OH)D concentrations <30 ng/ml had reduced ferritin, TSAT levels compared to those with 25(OH)D concentrations >30 ng/ml. The prevalence of ID was in 21 (80,8%) females with 25(OH)D concentrations <30 ng/ml compared to 5 (25%) in those with concentrations >30 ng/mL. Alike the prevalence of low vitamin D level was higher in women with ID 87% against 13% to those who had adequate iron status. Due to fact that inflammation alters of iron status and differs by vitamin D level, we investigated level of CRP and evaluated interactions between inflammation and 25(OH)D concentrations in predicting iron status. In patients with inflammation 36,7% we observed higher 25(OH)D concentrations in combination with lower ferritin level than in those without inflammation 63,3%.

Conclusions

Low Vitamin D level was associated with increased risk of ID in women with T2DM and HFpEF 87%, similarly as iron deficient women with type 2 DM and HFpEF had a higher risk of low vitamin D status. Chronic inflammation inherent T2DM and HF could increased ID which may be inhibiting with high doses of vitamin D.

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EP484

JOINT2700

Gestational diabetes: about an algerian population

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Introduction

Gestational diabetes mellitus (GDM) is a form of hyperglycemia that develops during pregnancy and poses risks to both mother and fetus. Gestational diabetes mellitus is a common complication in pregnancy. The International Diabetes Federation recently estimated that globally, 1 in 6 live births had a GDM diagnosis. Due to its high frequency and its health, social and economic impact, GDM has become a major public health issue. The aim of this study was to analyse the risk factors for gestational diabetes in a population of Algerian pregnant women.

Patients and methods

This is a retrospective descriptive study conducted at the diabetology consultation of the diabetology and endocrinology department of the Tizi Ouzou University Hospital located east of Algiers, during the period 2022-2023 among pregnant women referred for management of gestational diabetes.

Results

The study involved a population of 156 patients with an average age of 32.5 years. 63% of these women were over 35 years of age. The screening method used to diagnose gestational diabetes was fasting plasma glucose with a rate of 53.84% and OGTT with a rate of 30.12%. 20.5% of patients had a personal history of gestational diabetes and 47.4% had a family history of type 2 diabetes. Personal histories of macrosomia, hydramnios and miscarriage were found in 19.9%, 3.8% and 26% of cases respectively. 3.8% of these women had hypertension. Among the obstetric complications observed during the follow-up of these patients, hydramnios represented 7% of cases and macrosomia 5% of cases.

Discussion and conclusion

The identification of risk factors and screening for gestational diabetes highlights the importance of early detection and management to reduce the risk of macrosomia, neonatal complications and long-term impact on the health of the mother and child.

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EP485

JOINT2226

Potential of dietary polyphenols in prevention and treatment of type 2 diabetes and different types of dementia

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Introduction

Type 2 diabetes and different types of dementia including Alzheimer's disease(AD) are widespread diseases that share metabolic defects, such as insulin resistance, impaired glucose metabolism, oxidative stress, neuroinflammation and advanced glycation end products formation. As a result of many studies there is evidence that shows that type 2 diabetes significantly increases the risk of cognitive decline and dementia, particularly AD. Some authors have proposed the term "diabetes type 3" or "diabetes of the brain" for AD because of the similarities found between type 2 diabetes and AD mentioned above. Very important is the presence of brain insulin resistance in AD. For this reason, new approaches to improve glycemic control and restore cerebral insulin function are being investigated that could be of therapeutic benefit to adults with type 2 diabetes and different types of dementia. Besides drugs the use of foods that are rich in polyphenols has been shown to be a promising alternative in the fight against these diseases. It has been shown that dietary polyphenols can reduce blood sugar levels, protein glycation, improve insulin resistance, reduce oxidative stress and inflammation.

Study aim

The study aims to determine whether polyphenols intake can help prevent, improve and slow the progression of diabetes type 2 and therefore AD and other dementias because of the similarities found between these diseases mentioned above.

Methods

To estimate the role of dietary polyphenols, we observed 30 patients (25 women and 5 men) with diabetes mellitus type 2 and different types of dementia including AD who consumed polyphenols-rich foods between 1 December 2023 and 1 December 2024. The patients had poor glycemic control with HbA1c above 8.0%. In addition they had loss of cognitive functioning that included memory loss, reasoning skills, and some of them loss of ability to perform simple tasks.

Results

For one year of dietary polyphenols intake in the observed group we have found out significant reduction of HbA1c to below 7.0%, improvement of glucose variability. Moreover we have found positive effects of polyphenols on improving the cognitive performance in patients.

Conclusions

Phenolic compounds in foods have great therapeutic potential for diabetes management, which is related to their ability to reduce oxidative stress, reduce insulin resistance and AGEs formation. Thus, they can prevent or delay progression of diabetes type 2 and therefore different types of dementia including AD because of the similarities found between these diseases mentioned above.

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EP486

JOINT3931

Marked inflammatory syndrome revealing type 1 autoimmune hepatitis in a young female patient with type 2 diabetes

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Autoimmune hepatitis (AIH) is a progressive, chronic liver disease characterized by unresolving hepatocellular inflammation of autoimmune origin and varied clinical presentation. In type 2 diabetes mellitus (DM), the prevalence of AIH seems to be the same as in general population. Usually, patients with T2DM and AIH have a shorter duration of diabetes, are mostly women with increased liver enzymes and require higher insulin doses. A 42 -years old female with a history of gestational diabetes, hypertension and deep vein thrombosis presented in our service for a consult. At presentation: BMI = 34.52kg/m^2, WC = 112cm; Pulse = 72/min and B*P* = 140/90mmHg. The lab exams showed: marked inflammatory syndrome with CR*P* = 209.58 (NV < 0.5mg/dl), neutrophilic leukocytosis, mild dyslipidemia, low vitamin D and iron levels, hyperglycemia (BG = 186mg/dl) with A1c = 7.3% and mild increased LDH and γ-GGT. The microvascular complication screening revealed peripheral sudomotor dysfunction by Sudoscan testing. Treatment with Metformin 750mg twice daily, Rosuvastatin 10mg/day and vitamin D 5000IU/day for 3 months was initiated and the patient was referred for a gastroenterology consult. The diagnosis of type 1 autoimmune hepatitis was established after exclusion of viral etiology and based on the positive ANA of 1/160 with intense positive anti-DFS70 (dense fine speckle, 70kDa molecular weight) and equivocal anti interferon-inducible protein Ro-52. The thyroid hormones were within normal ranges, but the thyroid antibodies were not measured. The immunosuppressive treatment with Azathioprine 150mg/day was initiated alongside Silymarin. After 6 months, decreases in BMI (-4.41kg/ m^2), WC (-14cm) and A1c (-1.6%) were noted. The inflammatory syndrome resolved, but the LDL cholesterol was above target, so the statin dose was increased. The particularity of this case consists in marked inflammation with mild cholestasis, normal ALAT and ASAT and no symptoms. The treatment with Metformin and lifestyle optimization led to significant weight loss and improved glycemic control.

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EP487

JOINT1747

Prevalence of lipohypertrophy and associated factors among insulin-treated diabetes mellitus patients

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Background
As a consequence of insulin therapy in diabetes mellitus, a variety of local skin reactions may occur, the most common is Lipohypertrophy (LH). This study aimed to determine the prevalence and associated risk factors of insulin-induced LH.
Patients and methods
We performed a cross-sectional study including insulin-treated patients for more than one year from the endocrinology department of Rabta Hospital in Tunis between February and August 2024.
Results
We included 60 patients with a sex-ratio of 0.58 and 75% type 2 diabetes mellitus patients. Mean age, duration of disease and period of insulin therapy were respectively 54.8 ± 16.7; 17.2 ± 9.4 and 11.9 ± 8.4 years. LH prevalence was 60%. Female gender (P = 0.02, OR[CI95%:1.4-13] = 4.3), lack of assistance from a third party (LATP) (P = 0.03, OR[CI95%:1,1-11,7] = 3.7) and concentrating insulin in a small area (P < 0.001, OR[CI95%:9.8-38.9] = 3,7) were associated with higher prevalence of LH. Duration of disease, body mass index, body weight-adjusted dose, duration of insulin use, needle length and reuse, rate of rotating injection site, and cold insulin injection weren't associated with LH. Multivariate analysis revealed that female gender, LATP and not spacing insulin injections were independently associated with LH. The strongest factor associated with LH was failure in spacing injections in the same area (OR_a = [CI95%:3.8-359.5] = 37).
Discussion and Conclusion
Insulin-induced LH is a common complication in diabetes management. Female gender, LATP and not spacing injections are independently associated with LH. The most prominent factor was inadequate spacing of injections within the same area. Based on our and previous studies [1,2], it is important to examine injection sites and educate patients on prevention of lipodystrophy.
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EP488

JOINT2454

Unusual case of pancreatic neoplasm revealed by insulin initiation in a diabetic patient

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Introduction
Pancreatic cancer ranks 12th among the most common malignancies, with type 2 diabetes mellitus (T2DM) increasing the risk by 1.8 times. Paraneoplastic dermatomyositis is a well-documented mode of presentation.
Case Report
We report the case of a 64-year-old female patient with a family history of T2DM and papillary thyroid carcinoma in her two daughters. She had been diagnosed with diabetes three years prior and was managed with oral antidiabetic. She presented with spontaneous ketoacidosis, necessitating the initiation of human insulin therapy. Within 24 hours of the first insulin injection, she developed non-pruritic, ill-defined erythematous plaques on the thighs (injections were administered in the arms) and subsequently on the anterior forearms. Suspecting insulin allergy, insulin therapy was discontinued for 15 days, and oral antidiabetic agents were resumed. However, the progressive worsening of the cutaneous lesions raised suspicion of paraneoplastic dermatomyositis. An abdominal CT scan revealed an intrapancreatic tumor at the cephalo-isthmic junction, measuring 25 × 18 mm. She underwent chemotherapy followed by Cephalic duodenopancreatectomy. Histopathological examination confirmed a moderately differentiated ductal adenocarcinoma. Following surgery, insulin therapy was reintroduced, leading to complete resolution of the cutaneous lesions.
Discussion and Conclusion
Pancreatic adenocarcinomas are frequently associated with dermatomyositis, with an incidence at least three times higher than in the general population. The association with worsening diabetes should prompt clinicians to consider an underlying pancreatic malignancy.

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EP489

JOINT1262

Comparative characteristics of carbohydrate metabolism in patients with different types of autoimmune diabetes

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Introduction.
Autoimmunity is the major cause of classical type 1 diabetes mellitus (T1DM) as well as heterogenic forms – latent autoimmune diabetes in adults (LADA) and latent autoimmune diabetes in youth (LADY). These categories of diabetes share biochemical markers of β-cell–directed autoimmunity with classical T1DM but also have main features of type 2 diabetes (T2DM) like slowly progression and insulin resistance. In clinical practice, autoimmunity in classical T1DM as well as in LADA and LADY is usually documented by antibodies against glutamic acid decarboxylase (antiGAD) to prevent misdiagnosis in these categories of patients.
The aim of the study.
To compare features of carbohydrate metabolism in patients with different types of autoimmune diabetes mellitus (DM).
Material and methods.
71 patients with autoimmune DM were examined: 20 patients with classical type 1 DM (T1DM), 36 – with latent autoimmune diabetes in adults (LADA) (18 – LADA1 phenotype and 18 – LADA2), and 15 patients with latent autoimmune diabetes in youth (LADY). In addition to anamnesis data and general clinical research methods, indicators of carbohydrate metabolism (fasting glycemia, glycated hemoglobin (HbA1c)), and C-peptide level were evaluated.
Results.
The average age of manifestation of classical T1DM was 19 years, while in LADA1 it was 40.5 years, in LADA2 – 41, and in LADY – 20 years. Body mass index was in the normal range in patients with classical T1DM and LADY (21.99

and 23.39 kg/m^2 respectively), while in patients with LADA overweight was registered. Fasting plasma glucose level and HbA1c were recorded in the range from 9.22 to 9.90 mmol/l and 8.5% to 8.85% respectively and did not differ depending on the group. C-peptide level was 0.1 [0.10;0.15] and was significantly lower in patients with classical T1DM: by 6.4, 5 and 6.2 times compared with the LADA1, LADA2 and LADY respectively. HOMA-IR was the highest in patients with LADA2, but did not significantly differ from the LADA1 and LADY levels. AntiGAD level was the highest in classical T1DM and LADY groups (341.75 IU/ml and 270 IU/ml respectively); in LADA1 group the average level was 214.20 IU/ml and 95.50 IU/ml in LADA2, which significantly differ from two previous groups ($p < 0.05$).
Conclusions.
Autoimmunity plays a major role in establishing the correct diagnosis of the type of diabetes mellitus and can prevent a misdiagnosis.

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EP490

JOINT775

Prevalence of autoimmune disorders in pediatric and adolescent patients with type 1 diabetes mellitus: a retrospective cohort study

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Objective
To provide an overview of the epidemiology of concurrent autoimmune conditions in pediatric Type 1 Diabetes Mellitus (T1DM) patients, with a specific focus on investigating sex-specific disparities and evaluating the impact of glycemic control. This research aims to contribute valuable insights to inform the development of screening policies for this patient population.
Methods
This retrospective observational study analyzed data from all patients diagnosed with T1DM who attended the endocrine clinic at Al Jalila Children's Specialty Hospital between 2017 and 2023. The study assessed various variables, including age, gender, glycemic control, thyroid function, and the presence of celiac disease (CD), among others.
Results
346 patients diagnosed with T1DM were included in the study. Our cohort consisted of 166 (48.0%) males and 180 (52.0%) females, stratified into three age groups: $\leq$4 years (14.5%), 5-12 years (56.4%), and 13-18 years (29.3%). 166 (55.1%) patients had a BMI of $<$18.5 (underweight). 206 (59.5%) patients were from the UAE. 233 (75.9%) patients had uncontrolled HbA1C levels. The study focused on two autoimmune disorders: 24 (6.9%) patients with CD and 34 (9.8%) patients with thyroid disease, with 4 (1.2%) patients having both conditions. CD exhibited varying prevalence across age groups, with a statistically significant difference (p-value = 0.043), being more common in children $\leq$4 years (12.0%). The prevalence of thyroid disease was higher in patients from the UAE (12.1%) than those from other countries (6.4%), showing a trend toward significance (p-value = 0.080).
Conclusion
CD showed significant variations in prevalence across age groups, being most common among children aged 4 or younger.. Thyroid disease was notably more prevalent in patients from the UAE than in those from other countries, indicating a compelling trend toward significance. Additional research is needed to validate and further establish the significance of these observed associations.

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EP491

JOINT3873

Severe ketoacidosis and multi-organ failure in a type 2 diabetes mellitus patient: a case report

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Background
Diabetes Mellitus Type 2 (T2DM) is commonly associated with various complications, including cardiovascular, renal, and hepatic dysfunction. Diabetic ketoacidosis (DKA) is a potentially fatal endocrine emergency resulting from uncontrolled diabetes mellitus (DM). We present a case of a T2DM patient who presented in an emergency setting with severe diabetic ketoacidosis and multiple organ failure.
Case Presentation
A 51-year-old male with a history of poorly controlled T2DM in treatment with basal -bolus insulin presented to the emergency department with symptoms of altered consciousness, abdominal pain, and general fatigue. On admission, the patient exhibited severe metabolic acidosis (pH 6.9), elevated serum amylase (550 U/l), lipase (510 U/l), creatine kinase-MB (CK-MB) (80 U/l), and troponin I (0.15 ng/mL) Laboratory findings also revealed significantly elevated liver enzymes (AST, ALT) and renal dysfunction (elevated serum creatinine and urea). Clinical examination suggested signs of multiple organ failure, including hepatic, renal, pancreatitis and cardiac involvement.
Management and Outcome
Initial management focused on correction of ketoacidosis and stabilization of the patient's cardiovascular, renal, and hepatic functions. The patient was treated with intravenous fluids, insulin for blood glucose control and intensive monitoring of organ functions. The patient's clinical condition improved gradually, with normalization of metabolic parameters, organ function, and consciousness over the course of 24-48 hours.
Conclusions
This case highlights the complexity of managing T2DM patients with severe acidosis and multi-organ failure. Acute complications like diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS) can lead to multi organ dysfunction if not promptly recognized and managed. Early intervention and multi-disciplinary management are critical in improving outcomes in such high-risk patients.

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EP492

JOINT2417

"Sweet testosterone" – improved metabolic compensation after starting testosterone therapy in two transgender adolescents

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Transgender people experience gender dysphoria due to incongruence between their gender indentity and the sex they were assigned at birth. Due to many barriers experienced by transgender people there is no accurate data available, but it is estimated that they represent approximately 0,5% of the Poland population. One of the method to reduce the symptoms of gender dysphoria is hormone therapy, the aim of which is to match a person's gender characteristics to their identity. The mainstay of therapy for transgender men is testosterone taken as a gel or in the form of regular injections. Type I diabetes is a chronic autoimmune disease underlying which is a process that leads to the gradual destruction of insulin-producing cells of the pancreas. It accounts for about 10% of all cases of diabetes and most often affects children, adolescents and people before the age of 30. Treatment requires the patient to receive continuous insulin administration and regular blood glucose measurements. In recent years, there have been several research papers indicating an up to ninefold higher incidence of type I diabetes in transgender and gender diverse patients. The reasons for this process are unknown. Despite this, there is very little knowledge about the impact of hormone therapy on the course and control of type I diabetes. The effect of testosterone on diabetes control has been studied primarily in cisgender patients with type II diabetes and metabolic syndrome. Single research papers have indicated an initial improvement in the metabolic control of transgender patients after starting hormone therapy with testosterone. We present a description of the observations of two transgender boys, diagnosed with type I diabetes in childhood, who began testosterone therapy at the age of 16. Control of metabolic compensation was carried out through regular clinic visits through two years until they reached adulthood. Our observations indicate a significant improvement in diabetic parameters after the initiation of hormone therapy, especially in terms of lowering glycated hemoglobin, reducing mean blood glucose, and improving self-monitoring and dietary adherence. More studies are needed to describe the effects of hormone therapy on the course and control of type I diabetes and to create guidelines to create inclusive and multispecialty care for transgender and gender diverse children and adolescents with type I diabetes.
Keywords
transgender, gender dysphoria, gender diverse, testosterone, diabetes, auto-immunity, glucose homeostasis

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EP493

JOINT460

Alpha-lipoic acid-induced insulin autoimmune syndrome: an emerging public health risk

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Introduction
Insulin autoimmune syndrome (IAS), a condition mostly prevalent in East Asia, is a rare cause of spontaneous hypoglycaemic episodes, occurring in the late post-prandial phase and driven by the production of insulin autoantibodies (IAAs). The soaring popularity of food supplements containing Alpha-Lipoic Acid (ALA) and the concomitant surge in the reported cases of IAS have led the European Food Safety Authority to raise a safety concern about this association, especially in the presence of certain genetic polymorphisms in the Human Leukocyte Antigen HLA-DR4.
Case report
A 48-year-old female of Caucasian origin was referred on an urgent basis to an endocrine clinic in Athens, Greece, with a 5-day history of recurrent pre-syncopal episodes occurring two hours after meal ingestion. She had no history of diabetes mellitus and fulfilled the criteria of Whipple's triad on several occasions, with capillary blood glucose as low as 36-43 mg/dl (2.0-2.4 mmol/l). On hospital admission, baseline laboratory evaluation showed hypoglycaemia due to endogenous hyperinsulinism, as evidenced by very high serum insulin (189 mIU/l) and C-peptide concentrations. Its commonest cause, insulinoma, was excluded following detailed imaging. Grossly elevated IAAs of 175 IU/ml (normal range $<$ 20 IU/ml) indicated IAS which, in the absence of exposure to other offending drugs, was attributed to an ALA-containing supplement initiated two months ago for the management of arthralgia. Her management included dietary modification with small, frequent meals of low glycaemic index, oral prednisolone 40 mg, and diazoxide 150 mg daily. She responded rapidly without experiencing further hypoglycaemic episodes on this strict dietary regimen. In the following months, the IAA titre remained significantly elevated despite high-dose glucocorticoids, whilst she developed severe resting tremor, insomnia and depressive symptoms. Three months after the initial presentation, prednisolone was tapered and eventually discontinued, leading to resolution of these neuropsychiatric symptoms. One month later and despite prednisolone withdrawal, a significant decline in the IAA titre was first noted. Six months after presentation, the patient remained symptom-free with gradually declining, albeit still positive, IAA titres, despite discontinuation of both prednisolone and diazoxide, alongside a significant relaxation of dietary restrictions.
Conclusion
IAS is a severe, albeit rare, adverse event of ALA intake, which should discourage the overuse of ALA-containing supplements, and lead to inclusion of a clear warning about this risk in their labelling. This case report also illustrates the challenges in the management of IAS, as well as the often underappreciated neuropsychiatric side effects of glucocorticoids.

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EP494

JOINT1618

Polymorphisms of leptins gene in different types of diabetes mellitus

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Leptin is a protein about 16 kDa size playing a key role in energy intake and expenditure. It is a member of the cytokine family including intraleukin 2 and intraleukin 4 and is one of the most important hormones produced by adipocytes. The gene's function was initially linked to a signaling pathway suppressing food intake. The relationship between genetic variants in the leptin gene and the risk of developing diabetes has not been extensively analyzed. The -2548 G/A polymorphism in the promoter region of the leptin gene shows a genotype-specific association with an increased risk of developing diabetes.
Study Aim
Investigation of allelic and genotypic frequencies of the 2548 G/A polymorphism in the leptin gene in the observed groups.
Methods and materials
A total of 302 individuals were included in the present study, of which 202 patients were divided into five groups according to diabetic type-Diabetes type 1;Diabetes type 2 DT2; Type 2 diabetes with secondary depletion ;Diabetes type MODY; Diabetes type LADA and healthy control group.
Results
Leptin is involved not only in the regulation of food intake and energy balance, but also as a hormone related to glucose metabolism, body mass regulation and functions as an endocrine mediator. In general, in the studied groups, no relationship was found with the studied polymorphism in leptin genes and predisposition to the development of certain diabetic pathology. A certain tendency, which confirms the literature data, was observed only in patients with type 2 diabetes. The population frequency of the 2548 G/A polymorphism in the leptin gene shows great variability. From the present study, it can be seen that the frequency determined for the studied sample from the Bulgarian population is comparable to that of other European populations. When comparing the distribution of genotype G/G (+/+) to the other genotypes, an interesting finding is the higher frequency of genotype G/G (+/+) in patients with type 1 diabetes compared to the control sample ($P = 0.0645$). According to literature data as well as preliminary studies for the Bulgarian population, genotype A/A (-/-) has a relationship to diabetic pathology, which contradicts the data from the present study. It should be noted that predisposition to the disease associated with genotype A/A (-/-) was found mainly in patients with gestational and type 2 diabetes.

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EP495

JOINT3419

Steroid-induced diabetes: when ocular treatment becomes a metabolic threat

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Introduction
Corticosteroids, even when administered topically, are known to induce hyperglycemia or diabetes in predisposed patients. While systemic corticosteroid use is a well-documented cause of diabetes, the risk associated with topical corticosteroids, such as eye drops, is often underestimated. We report a case of diabetes induced by dexamethasone eye drops in a 64-year-old patient admitted for the management of nodular prurigo.
Case Report
A 64-year-old man with no prior history of diabetes was admitted for severe nodular prurigo. Routine laboratory tests revealed elevated fasting blood glucose and HbA1c. The patient had been using dexamethasone eye drops for the past 4 years to treat chronic uveitis. Over the past 2 years, he had gradually developed symptoms of hyperglycemia, including increased thirst, frequent urination, and fatigue. Despite these symptoms, he had not sought medical advice, attributing them to other factors. The patient had no other identifiable risk factors for type 2 diabetes, such as obesity, sedentary lifestyle, or family history.
Discussion
This case highlights the risk of corticosteroid-induced diabetes, even with topical administration. Dexamethasone eye drops, used over an extended period, likely led to systemic absorption, causing insulin resistance and hyperglycemia. The rapid resolution of hyperglycemia following discontinuation of the eye drops supports the diagnosis of medication-induced diabetes. This case also underscores the importance of regular blood glucose monitoring in patients using corticosteroids, particularly in those with prolonged use or additional risk factors.
Conclusion
Topical corticosteroids, including eye drops, can induce diabetes or exacerbate preexisting diabetes due to systemic absorption. Healthcare providers should remain vigilant for this potential complication, especially in patients with long-term use. Regular monitoring of blood glucose and timely intervention can prevent long-term complications.

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EP496

JOINT421

Dietary impact on the onset of MASLD in patients living with type 2 diabetes

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Background
As the prevalence of MASLD rises, understanding the dietary factors contributing to its development is becoming crucial. Diet plays a critical role in metabolic health, yet its precise effect on the development of MASLD remains under-explored. This study aims to evaluate the impact of dietary intake on the onset of MASLD in people with T2DM.
Methods
This retrospective study included 202 T2DM patients, followed up to 2024 at the Endocrinology-Diabetology Department of Hedi Chaker University Hospital in Sfax, Tunisia. Patients were divided into two groups based on the presence or absence of hepatic steatosis on imaging :
- Group 1 : 101 T2DM patients with MASLD
- Group 2 : 101 T2DM patients without MASLD

For each patient, we assessed macronutrient intake, including daily caloric intake in Kcal, as well as the percentage of daily intake from lipids, proteins, and carbohydrates. Additionally, we evaluated the intake of saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids. Thus, We assessed micronutrient intake, including fiber (g/day), iron (mg/day), calcium (mg/day), and cholesterol (mg/day).
Results
The total energy intake was similar between groups 1 and 2 (2125 [1900-2585] versus 2100 [1700-2400] kcal/day, respectively ; $P = 0.251$). In terms of macronutrients, carbohydrate intake was significantly higher in Group 1 compared to Group 2 (53% [50%-57%] versus 52% [48%-54%], respectively; $P = 0.044$). No statistically significant differences were observed for protein intake ($P = 0.080$), fat intake ($P = 0.302$) whether considering saturated, mono-unsaturated, or poly-unsaturated fatty acids ($P = 0.403$, $P = 0.225$, $P = 0.896$, respectively). Regarding micronutrients, daily intakes of iron, calcium, dietary cholesterol, and fiber were comparable between the two groups.
Conclusion
Our study aims to provide insights into potential nutritional interventions for prevention and management of MASLD within T2DM patients, offering avenues for targeted dietary strategies.

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EP497

JOINT2403

Association between neutrophil-to-lymphocyte ratio and metabolic syndrome in diabetic patients: a cross-sectional study

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Introduction
Metabolic syndrome (MetS) is a cluster of risk factors that significantly increase the risk of cardiovascular diseases and type 2 diabetes. Inflammation plays a key role in the pathogenesis of MetS, and the neutrophil-to-lymphocyte ratio (NLR), a marker of systemic inflammation, has been linked to various metabolic disorders. This study aims to investigate the relationship between NLR and MetS, exploring its potential as an early biomarker for risk stratification.
Methods
A cross-sectional study was conducted, including 50 diabetic patients hospitalized at the Endocrinology Department of Mahdia from January to April 2024.
Results
The average age of participants was 54 $\pm$ 21 years, with a predominance of females (79.2%). Two thirds of the patients were diagnosed with type 2 diabetes, 24% were obese, and 23.7% had established cardiovascular disease. Hypertension was present in 28.9% of patients. Metabolic syndrome was observed in 50% of the patients. The average waist circumference was 84 cm. The median values of various metabolic parameters (in mmol/l) were as follows: fasting glucose (11.3), triglycerides (1.41), HDL-C (1.07). NLR did not significantly differ across BMI groups ($P = 0.266$). Additionally, no significant correlation was found between NLR and HbA1c ($P = 0.193$), fasting blood glucose (FBG) ($P = 0.259$), HDL cholesterol ($P = 0.139$), and triglycerides ($P = 0.624$). NLR was significantly higher in patients with hypertension (2.47 [1.78-7.56] vs 1.6 [1.2-2.29]; $P = 0.029$). No significant correlation between NLR and metabolic syndrome was observed ($P = 0.405$).
Conclusion
Our study suggests that while NLR is elevated in patients with hypertension, it does not correlate significantly with metabolic syndrome or other key metabolic parameters. Further research with a larger sample size and longitudinal design is needed to clarify the role of NLR as a potential biomarker for metabolic disorders.

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EP498

JOINT363

Study on sialic acid concentrations in type 1 and type 2 diabetes mellitus

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Sialic acids are the carbohydrate part of glycoproteins presented in the conjugate form on the outer surface of membranes as membrane receptor. They are components of insulin receptors, interferon and serotonin, as well as of various circulation hormones, transporting proteins, lipoproteins, mucopolysaccharides and various exudates. The data on the concentrations of circulation sialic acids in diabetes mellitus (DM) are contradictory. The work was initiated to study concentrations of sialic acids the blood serum of patients with type 1 and type 2 DM.
Materials and methods
Twenty two patients with type 1 DM and 28 patients with type 2 DM aged from 26 to 65 were examined. The control group included 10 healthy persons of the matching age. Periodate-resorcinol method was used to measure concentrations of sialic acids. HbA1c was measured using enzyme-linked immunosorbent assay.
Results and discussion
Concentrations of the serum sialic acids in DM were found significantly increased, while those in erythrocytes and leucocytes were reduced. Our findings demonstrated that the serum sialic acid concentrations were increased in both DM types, as compared to the control ones ($P < 0.05$). In type 1 DM, mean level was 291.7 ± 42.9mg%. Sialic acids were significantly higher in patients with type 2 DM than those in healthy persons (174.5 ± 27.0mg% vs 145.0 ± 10.9mg%). Significant differences were observed in comparison of sialic acid concentrations between two groups of the diabetics ($P < 0.05$). Mean HbA1c was higher in patients with type 1 DM than the one in the controls ($6.7 \pm 1.9\%$ vs $5.4 \pm 0.8\%$). Mean HbA1c in patients with type 1 DM was $7.8 \pm 1.5\%$. Sialic acids are known to be responsible for the formation of various isoforms of transferrin and regarded as a marker of microvascular complications in type 2 DM. Hyperglycemia results in the increase on non-enzymatic glycosylation of many proteins and in the formation of glycation end products. Non-enzymatic glycosylation changes properties and functions of some proteins. The changes in the glycosylation in DM were found by many authors. Most glycosylated proteins add the remains of sialic acids in their carbohydrate chains. The increased sialic acid concentrations may be caused by the generalized cell endothelial dysfunction either by the washout of glycoproteins containing sialic acids from cells into circulation or by the cytokine-mediated acute phase response. Thus, in association with other laboratory data determination of sialic acids may be used for assessment of severity of the disease and the depth of pathological process, as well as for differential diagnosis.

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EP499

JOINT2980

Bilateral femoral head necrosis in early adulthood with pituitary stalk interruption syndrome: need for comprehensive medical education on the impact of growth retardation in misdiagnosis

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Synopsis
We present the case of a 34-year-old female with early onset bilateral femoral head necrosis, diagnosed with pituitary stalk interruption syndrome (PSIS). The patient's medical history includes growth retardation from an early age, hip pain for nearly two years, and impaired consciousness for two weeks prior to admission. She had no history of alcohol use, autoimmune diseases, malignancies, or organ dysfunction.

Purpose
We present a case to highlight the importance of recognizing how growth disorders in children and adolescents can affect long-term health. It emphasizes the need for comprehensive medical education that bridges pediatric and adult specialties to reduce diagnostic delays in complex cases such as PSIS.
Medical history
The patient was diagnosed with growth hormone deficiency due to short stature at age 10.H*er* followed *primary amenorrhea and absence of secondary sexual characteristics during puberty were not thoroughly investigated, obscuring the growth hormone deficiency due to* long-term sex hormone deficiency *and delayed skeletal closure.*Eight years ago, she was diagnosed with hypothyroidism *and began thyroid hormone replacement*. Over the past two years, she *developed* bilateral groin and lower limb pain, initially treated *as sacroiliitis. The pain progressed on the pain scale, leading to a duck-step gait and limited hip movement. Two weeks before hospitalization, she lost consciousness and was diagnosed with hypopituitarism and adrenal insufficiency. After replacement therapies, her consciousness returned, but the hip pain worsened with both hips in flexion and abduction. Upon* admission, her bone age was assessed as 13-14 years, *indicating* delayed skeletal maturation. Frog-position DR and MRI *imaging revealed bilateral femoral head avascular necrosis, with outward and upward displacement of the femoral necks, and pituitary MRI confirmed PSIS.*
Diagnosis and treatment
The patient was diagnosed with PSIS, hypopituitarism, secondary adrenal insufficiency, hypogonadotropic hypogonadism, secondary hypothyroidism, growth hormone deficiency, and bilateral femoral head necrosis. Hormonal replacement therapy and bilateral artificial hip replacement were performed. Upon reevaluation of her medical history and bone age, the condition was likely a misdiagnosed case of slipped capital femoral epiphysis (SCFE).
Conclusion
This case underscores the importance of considering a patient's developmental history, bone age, and hormonal status in diagnosing hip disorders in early adulthood. It highlights the need for improved medical education that integrates pediatric and adult specialties, especially in cases with atypical presentations or complex histories. Early recognition can lead to better outcomes in conditions like SCFE.
Keywords
Early onset avascular necrosis, Slipped Capital Femoral Epiphysis, Pituitary Stalk Interruption Syndrome
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EP500

JOINT1723
Prevalence of sarcopenia in indians with type 1 diabetes mellitus
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Objective
Sarcopenia is an ignored and underdiagnosed condition in patients with diabetes. India houses the largest number of patients with type 1 diabetes but lacks data on sarcopenia prevalence in them. We estimated the prevalence of sarcopenia in type 1 diabetes patients and compared it with age- and sex- matched healthy participants.
Research design and methods
Patients with type 1 diabetes and age $\geq$ 12 years were included and patients with pregnancy, lactation and any condition which can affect skeletal muscle properties were excluded. A total of 93 patients of type 1 diabetes and an equal number of age- and sex-matched healthy participants were included for comparison in a cross-sectional and observational study. For sarcopenia assessment, skeletal muscle mass, strength and function were measured and cutoffs for diagnosis were taken according to the Asian Working Group on Sarcopenia 2019 guidelines.
Results
The prevalence of sarcopenia in T1DM patients was significantly higher than controls (30.1% vs 11.8%) with an odds ratio of 3.2 and was more common in adults compared to adolescents (36.7% vs 12%). Gender, total daily dose of insulin, eGFR and IGF-1 levels did not have a correlation with sarcopenia in T1DM.
Conclusions
This study shows that patients of type 1 diabetes have an approximately three times higher prevalence of sarcopenia when compared to the general population with nearly 1 out of 3 type 1 diabetes patients affected by the condition.
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EP501

JOINT158
HbA1c measurement: comparison of biorad D10 (Hplc) and sebia capillarys 2 methods
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Background
HbA1c test provides information on metabolic control in diabetes and could also be used for its Diagnosis, it is essential to have accurate and precise HbA1c methods covering a range of measurement principles. We report an evaluation of the Biorad D10 kit (Hplc) versus Sebia capillarys 2 Kit (capillary electrophoresis).
Methods
Measurements of HbA1c were carried out in whole blood samples (K3edta tubes) from 111 patiens from different departments in Ziv medical Center- Israel using both Sebia Capillarys 2 Flex piercing (Capillary Electrophoresis) and analyzers Biorad D 10 (HPLC method).
Results
There was a good concordance between the results of capillary electrophoresis and HPLC ($R2 = 0.97$, $P < 0.0001$) There is no significant difference between the results obtained from both technique.
Conclusions
both technique suitable for the clinical application in the analysis of HbA1c. it is concluded that the results obtained after testing samples in Sebia capillarys Flex Piercing II and Biorad D10 are in a good concordance and there is no significant difference in the results obtained. The advantage of using Biorad D10 has benefit of shorter testing time Whereas Sebia capillarys can detecte underlying hemoglobinopathies and high throughput.
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EP502

JOINT2319
Factors impacting glycemic balance in pregnant diabetic women
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Introduction
Diabetic pregnancy is a high-risk pregnancy requiring optimal programming and glycemic balance to avoid maternal-fetal complications.
Objective
To assess factors influencing glycemic balance in pregnant diabetic women.
Materials and methods
This is a retrospective study over a 2-year period conducted at the Endocrinology, Diabetology, Metabolic Diseases and Nutrition Department of the Hassan II University Hospital in Fez. We included all pregnant patients with pre-existing diabetes who agreed to participate. Patients with gestational diabetes were excluded. Glycemic balance was judged by an HbA1c $<6.5\%$ and a glycemic cycle within the target in $>90\%$ (glycemic targets in preprandial between 0.60 and 0.95 and in postprandial <1.2 g/l) Eating habits were assessed by a food diary Statistical analysis was performed using SPSS 26 software. We retained the value $P<0.05$ as the significance threshold.
Results
We collected 80 patients, the average age was 35.56 ± 5.4 years, 27% had type 1 diabetes and 73% type 2 diabetes, the average duration of diabetes was 8.7 ± 3.1 years. Only 9.2% planned the pregnancy. 61.2% had a hbA1c $< 6.5\%$. 89% of patients ate 3 meals per day and 58% ate one to two snacks per day. 56% abused slow sugars and 44% consumed fast sugars. Mean HbA1c was significantly higher in T1D than T2D ($P<0.001$), in patients who had not planned their pregnancies ($P = 0.02$), in patients who made dietary errors ($P<0.01$), and in patients with a long duration of diabetes (0.01)
Conclusion
Our study highlights several factors impacting glycemic balance in diabetic women, particularly in pregnant type 1 diabetic women, with a long duration of diabetes development. Hence the interest in education on programming and optimal balance of diabetes in preconception]
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EP503

JOINT54

Euglycemic diabetic ketoacidosis in a type 1 diabetic: a case without SGLT2 inhibitors

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Background
Euglycemic Diabetic Ketoacidosis is a rare but potentially life-threatening complication of diabetes characterized by ketoacidosis with blood glucose levels typically <200 mg/dL. The absence of hyperglycemia is a conundrum for physicians in the emergency department; it may delay diagnosis and treatment causing worse outcomes. Euglycemic DKA is an uncommon diagnosis but can occur in patients with type 1 or type 2 diabetes mellitus. Usually with the addition of sodium/ glucose cotransporter-2 inhibitors in diabetes mellitus management, euglycemic DKA incidence has increased. We present a case of a 16-year-old male with a history of type 1 diabetes who developed euglycemic DKA following a prolonged poor appetite (fasting). Notably, the patient was not on any SGLT2 inhibitors. This case highlights the importance of recognizing euglycemic DKA in patients with diabetes, even in the absence of significant hyperglycemia or SGLT2 inhibitor use. Euglycemic DKA was first described in 1973 by Munro *et al* [1] among type 1 DM. Euglycemic DKA is an uncommon diagnosis with an incidence ranging between 2.6% to 3.2% of admissions with DKA [2,3].
Case Presentation
A 16-year-old male with a history of type 1 diabetes mellitus presented to the emergency department with a chief complaint of body malaise. The patient reported a 3-day history of body malaise, accompanied by poor appetite for the past week. He also described experiencing burning epigastric pain and nausea. He was compliant with his insulin. He denied any history of infection, fever, cough, or urinary symptoms. On PE, the patient was well-nourished, alert, and oriented with a Glasgow Coma Scale (GCS) of 15. He was not in respiratory distress. Vital signs were within normal limits: blood pressure 100/70 mmHg, pulse rate 98 bpm, respiratory rate 20 cpm, temperature 36.6 °C, oxygen saturation 97%, height 171 cm, and weight 58 kg. Laboratory investigations revealed a blood glucose level of 108 mg/dL, arterial blood gas showing metabolic acidosis with an increased anion gap, and ketonemia. Based on these findings, a diagnosis of euglycemic diabetic ketoacidosis secondary to fasting starvation was established. The patient was promptly started on intravenous fluids, insulin therapy, and electrolyte replacement.
Conclusion
This case report underscores the importance of recognizing euglycemic diabetic ketoacidosis as a potential complication in patients with diabetes, even in the absence of marked hyperglycemia or SGLT2 inhibitor use. Prompt recognition and management of euglycemic DKA are crucial for optimizing patient outcomes and preventing potentially life-threatening complications.

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EP504

JOINT2994

Type 1 diabetes in patients over 50: clinical and biological characteristics

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Objectives
The aim of our study was to describe the clinical and biological characteristics of patients diagnosed with type 1 diabetes after the age of 50.
Patients and methods
This was a descriptive study including 10 patients hospitalized in our department for diabetes mellitus.
Results
10 patients were included: 7 women and 3 men, aged between 52 and 71 years with an average age of 64.1 years. The mode of onset of diabetes was ketosis or ketoacidosis decompensation in 6 patients, incidental in 3 patients and hyperosmolar decompensation in one patient. Six out of 10 patients had no family history of diabetes or cardiovascular disease, and only 4 had a history of autoimmunity. Five patients had hypertension, including 2 with coronary artery disease, and 3 patients had autoimmune disease. The mean weight at diagnosis was 65.9 kg (42 - 103) with a mean BMI of 25.3 kg/m2. Only three patients were obese. The mean HbA1c was 12.4%. Immunological tests revealed positive anti-GAD antibodies in 9 patients and positive anti-IA2 antibodies in one patient. Regarding degenerative complications, 2 patients had diabetic retinopathy, one of whom had associated nephropathy.
Discussion
The incidence of type 1 diabetes in adults is increasing because of the widespread use of immunoassays; where the clinical presentation and the family history may cast doubt, these help to rectify the diagnosis.

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EP505

JOINT1519

The complexity of diabetes management in MELAS syndrome: a personalized approach to glycaemic control

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Introduction
MELAS is a rare genetic disorder with multi-system involvement, marked by myopathy, encephalopathy, lactic acidosis, and stroke-like episodes due to mitochondrial DNA mutations. Mitochondrial disorders are often associated with endocrine abnormalities like diabetes, which results from impaired pancreatic β-cell insulin secretion.
Case Presentation
We present a 63-year-old male diagnosed with MELAS syndrome at the age of 41, following his brother's diagnosis with encephalopathy and MELAS. He has a significant family history of MELAS. His initial management included Ramipril and Amlodipine for hypertension, along with Co-enzyme Q10 for mitochondrial support. Given the known association of MELAS with diabetes, the patient was referred to endocrinology for an oral glucose tolerance test (OGTT) with showed a fasting glucose of 6.6 mmol/l and a 120-minute level of 17.5 mmol/l, confirming Type 2 diabetes. He was started on repaglinide 500 µg three times daily with meals while avoiding metformin due to the risk of lactic acidosis. During follow-up, his HbA1c was 6.8% (50.8 mmol/mol), and additional testing revealed persistently elevated cholesterol at 10.8 mmol/l, HDL of 1.58 mmol/l, triglycerides of 5.74 mmol/l, and a total cholesterol-to-HDL ratio of 6.8. His creatinine was 124 µmol/l, with an eGFR of 54 mL/min. Despite medication adjustments, his hypertension and diabetes remained sub optimally controlled, necessitating further medications adjustment, His renal function progressively declined, with nephrotic-range proteinuria and creatinine levels rising to 165 µmol/l. Referred to nephrology, he underwent a nephritic workup, renal ultrasound, and biopsy, revealing severe glomerulosclerosis associated with long-term hypertension and diabetes. With CKD progressing to stage 3 (GFR 14 mL/min), he required haemodialysis and, eventually received a left renal transplant. Post-transplant, his glycaemic control became challenging due to persistently elevated glucose levels. He was initiated on Insulatard insulin (18 units in the morning, 16 units in the evening) along with gliclazide 80 mg twice daily. Given the need for frequent glucose monitoring—six times daily—and difficulty using fingerstick testing due to a left-arm fistula, he qualified for the Freestyle Libre continuous glucose monitor. This device significantly improved his quality of life and glycaemic control, with an HbA1c of 55 mmol/mol, glucose levels ranging between 4.9–12 mmol/l, and 63% time-in-range.
Conclusions
This case illustrates the complex challenges of managing diabetes and hypertension in patients with mitochondrial disorders. It emphasizes the importance of early recognition and proactive management of renal and endocrine complications which are essential for improving outcomes.

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EP506

JOINT272

Psychosocial experience of gestational diabetes in a population of tunisian women

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Introduction
Gestational diabetes (GD) is a condition that causes significant concern and stress, which can have repercussions on maternal and fetal health. However, there is

limited research on patients' experiences regarding GD care. The objective of this study was to identify the psychosocial experiences triggered by a GD diagnosis to improve healthcare services.
Methods
This cross-sectional study explores the experiences of 53 women diagnosed with GD, followed up at our GD unit in Service C of the Tunis Institute of Nutrition. Data were collected through in-depth interviews.
Results
The average age of the participants was 33.79 ± 4.8 years. Smoking and sedentary lifestyles were observed in 5.7% and 54.7% of cases, respectively. Their medical history included hypertension (7.5%), dyslipidemia (3.8%), and hypothyroidism (7.5%). The majority of women were overweight, with a preconceptional body mass index (BMI) averaging 28.82 ± 5.02 kg/m^2. Their diabetes was well-controlled, with an average HbA1c of 5.55 ± 0.67%. Difficulty accepting GD was reported by 49.1% of patients, while 30.2% experienced feelings of self-devaluation. Additionally, 17% felt that society reduced them to their disease, whereas 54.7% perceived GD as a socioeconomic burden. Adapting to new dietary habits was a major challenge: 52.8% of women struggled to modify their diet, and 35.8% found preparing varied and balanced meals burdensome. This adaptation led to frustration and deprivation for 47.2% of the patients. The psychological impact of GD was also significant, with 52.8% of women reporting recent stress. Support from their social circle played a crucial role in their experience, yet 22.6% felt unsupported, and 33.21% believed that their entourage was unaware of GD's implications. Furthermore, 11.3% of patients themselves lacked knowledge about the disease's implications. Regarding pregnancy weight gain, 39.6% of women had insufficient weight gain, 32.1% had normal weight gain, and 28.3% experienced excessive weight gain. No statistically significant association was found between pregnancy weight gain and recent stress or feelings of frustration and deprivation (P = NS).
Conclusion
Based on the experiences of this group of Tunisian women, it is evident that healthcare services need to be restructured to improve pregnancy experiences and ensure that women are actively engaged and attentive to their own health.
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EP507

JOINT2360
Blood lipid profile of patients with diabetes mellitus of various degrees of severity
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Diabetes mellitus (DM) is characterized by a global metabolic disorder, not only of carbohydrate but also lipid metabolism. Consumption of high-calorie diets and lack of physical activity in the long term lead to the accumulation of very low-density lipoprotein cholesterol (VLDL-C), which accelerates the development of atherosclerosis and is a major risk factor for cardiovascular diseases. The purpose of the work was to study the indicators of lipid metabolism in the blood of patients with diabetes of varying severity. The mild form is characterized by a glucose level of up to 8 mmol/l on an empty stomach, the moderate form is up to 14 mmol/l, the severe form of diabetes is over 14 mmol/l. Indicators of total blood lipids in the control were 5.20±0.33 g/l and significantly increased at all degrees of severity ($P<0.05$). Total cholesterol in the control was 4.89±0.10 mmol/l; in diabetes it significantly increased to 6.0±0.17 in mild form, to 5.95±0.11 in moderate form, to 5.79± 0.16 mmol/l ($P<0.05$) in severe cases. The level of triglycerides in the control was 1.56±0.21 mmol/l, with mild diabetes it was significantly increased to 1.84±0.05, with moderate severity - 2.25± 0.04, with severe diabetes - 2.98±0.34 mmol/l ($P<0.05$). VLDL and LDL cholesterol in the control corresponded to 10.47±1.24 mmol/l. In the mild form, this indicator was increased to 26.36±3.51 ($P<0.01$), in the moderate form – to 26.41±2.04, in the severe form – to 15.35±0.31 mmol/l. At the same time, HDL cholesterol significantly decreased in all groups. The lipid spectrum of patients with diabetes shows a significant increase in atherogenic lipoproteins and a decrease in antiatherogenic lipoproteins.
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EP508

JOINT1744
Growth assessment during puberty in children and adolescents with type 1 diabetes mellitus
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Introduction
Adequate linear growth and final height are major aims during treatment of type 1 diabetes (T1D) in children. Such items could be influenced by suboptimal glycemic control. Modern intensified insulin therapies are fundamental tools to reach adequate metabolic control.
Aim
To evaluate growth during puberty in children and adolescents with T1D followed up at a Pediatric Endocrinology center, HIAEP Sor María Ludovica, Buenos Aires, Argentina.
Material and methods
Forty-four children with T1D were evaluated (54.5% Male), regarding mean age, height, mean target height, HbA1c at T1D onset, at the start of puberty (thelarche stage ≥ 2 or testicular volume ≥ 4 ml), at the end of puberty (menarche or testicular volume ≥ 15 ml), at pubertal growth peak, and at discharge, clinical condition at T1D debut and diabetes duration. Quantitative variables were analyzed using the Shapiro-Wilk test. Growth and HbA1c levels were compared (Student's/Mann-Whitney tests). Correlations between anthropometrics and HbA1c were estimated (Pearson/Spearman coefficients).
Results
Median age at diagnosis was 8.49 (4,82; 9,97) and mean HbA1c at onset was 12,56±2,76. Mean height SDS was 0.52±1.34 at diagnosis and 0.47±0.97 at the end of puberty, mean height gain was 16.63±6.29 cm in males and 14.97± 5.92 cm in females. At discharge, mean height SDS was 0.22±0.96 in males and -0.74± 1.05 in females. Mean SDS target height was -0.45±1.16. Median HbA1c was 8.70% at pubertal onset and 9.10% at puberty end, with no significant correlation between height gain or diabetes duration. Acute complications were experienced by 70.5% of patients and chronic complications by 34,1% at Lipodystrophy (61.4%), and hypertension (34%) were the commonest. Most presented ketoacidosis (50%) and ketosis without acidosis (42.2%) at debut. Mean diabetes duration was 7.84±2.92 years. No significant differences in HbA1c were found between patients with and without complications. Associated conditions (hypothyroidism 31.8%, celiac disease 13.6%) were found in 54.5% of patients. No significant differences in growth compared to patients without these conditions.
Conclusions
This cohort of children with T1D presented adequate growth during puberty, reaching their target height, despite suboptimal HbA1c levels. Acute complications and the presence of associated conditions did not affect the final growth outcomes.
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EP509

JOINT3050
Type 2 diabetes mellitus in teenagers – a growing concern for armenia
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Introduction
Type 2 diabetes mellitus (T2DM), once considered a disease primarily affecting adults, is now increasingly diagnosed in children and adolescents. This shift is largely attributed to rising rates of obesity, poor dietary habits, and reduced physical activity among younger populations. In the United States and other developed countries the prevalence of T2DM in teenagers has risen sharply in recent years, prompting a need for greater awareness and early intervention. An increase in T2DM cases is also observed in Armenia, not only among adolescents in late but also in early puberty.
Case Description
This case report describes a 12-year-old boy who presented with excessive thirst, frequent urination, fatigue, and a 5 kg weight loss over the past month. His home blood glucose levels were consistently elevated, with one reading as high as 29 mmol/l. On clinical examination, he was found to have obesity (BMI: 36.9 kg/m^2), height = 176.5sm, height SDS= +1.42, acanthosis nigricans, and breasts enlargement, all indicative of insulin resistance Tanner 3 stage Family history was positive for T2DM, which further supported the diagnosis. Laboratory findings confirmed the diagnosis of T2DM: Fasting glucose: 28.7 mmol/l HbA1C: 11.0% C-peptide: 2.6 ng/mL Ketones: 3+ (indicating ketosis) Autoantibodies: Anti-GAD, IgG – 46.6 (>N) Anti-IA-2- 180.59 (>N) Anti-insulin, IgG – 10.13 (N)

The patient's treatment regimen included diet therapy (25 kcal/kg/day), insulin therapy (NovoRapid and Levemir), Metformin, and blood glucose monitoring 5-7 times per day. In addition, physical activity was strongly encouraged to enhance metabolic control.

Conclusions

This case underscores the rising incidence of T2DM in adolescents, a trend that calls for heightened awareness among healthcare providers and families. Early diagnosis and intervention, including lifestyle changes and pharmacological treatment, are essential to managing T2DM in teenagers and preventing long-term complications. Given the increasing prevalence of the condition in this age group, it is critical to recognize the early signs and implement appropriate strategies to address this growing public health issue.

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EP510

JOINT1503

It is not always insulinoma

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M.A, 8 years, presented by frequent attacks of hypoglycemia during sleep, sweating, rigors and drowsiness Family history of T2DM grandmother on glibenclamide Sought medical consultation in which RBG was 28 mg/dl at presentation Critical sample was obtained, and the result were non ketotic, insulin was 21.74 mIU/ml (high), C-peptide 5 ng/ml (high), normal cortisol, ACTH, GH, pyruvate and lactate, FFAs HBA1C 4.9 Triphasic CT abdomen and pelvis was done and normal PET SCAN also normal No more attacks of hypoglycemia with admission in hospital Sulphonylurea drug screen was positive So he diagnosed as exogenous sulphonylurea consumption by mother (MUNCHAUSEN SYNDROME) in which the clinical picture may mimic an insulinoma with high levels of both insulin and c-peptide

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EP511

JOINT4012 Successful treatment of a foot ulcer in a female patient with newly diagnosed T1DM (LADA)

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Diabetic foot is a term used to describe the foot of a patient suffering from diabetes who is at potential risk of several pathological consequences, including infection, ulceration, and/or destruction of deep tissues associated with neurological abnormalities, varying degrees of peripheral vascular disease, and/or metabolic complications of diabetes in the lower extremity. A diabetic ulcer is a critical and central event of the cascade of diabetic foot. A 42-year-old female patient was admitted as an emergency in November 2020 with ketoacidosis (pH 6.9) with impaired consciousness, glucose on admission 38.3 mmol/l, HbA1c 14.01%, CRP 429.98 mg/l, negative for COVID. Anamnestic data indicate that over the past 2 years, she has gradually started to lose more than 12 kg of body weight, especially during the last 5-6 months, when she noticed the blisters on her heels that began to spread. Also, she has experienced the absence of menstrual cycles for 7-8 months. She denies previous illnesses and is a non-smoker. On physical examination, body weight was 56 kg, height 1.78 m, and BMI 17.7 kg/m2, ulcer on the right heel and a deep, ulcerative change on the left heel and exposed region in the area of the left Achilles tendon, and hypotrophy of the muscles of both the upper and lower extremities. Hormonal analyses showed the values of thyroid hormones, cortisol, and PTH within the reference range, FSH 0.66 mIU/l, LH 0.18 mIU/l, estradiol 54 pmol/l, progesterone <0.3 mmol/l. Immunological analyses showed IA At 2.5 IU/ml within the reference range, highly positive GAD-65At 749.3 IU/ml, and antiTPO positive at 10.35 IU/ml. The echo-Doppler of the lower extremity blood vessels was normal, as was the X-ray of the bones of the feet. The neurological examination showed bilateral sensorimotor polyneuropathy, and the ophthalmological examination showed non-proliferative diabetic retinopathy, and the cataract in the right eye. Upon admission, intensified insulin therapy with human insulin analogues was introduced and excellent glycoregulation was achieved. A multidisciplinary approach was applied in the treatment of diabetic foot, with ulcer treatment by a surgeon, neurological therapy, and regular follow-up and hyperbaric oxygen therapy for 6 months. The ulcerative changes were completely healed after 5 months with no recurrence during the previous 4 years of follow-up.. Studies have shown that early recognition of LADA and strict glycaemic control is the key to improving the prognosis for LADA and reducing the risk of developing complications.

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EP512

JOINT347

Diabetic foot ulcer. peripheral artery disease and treatment with angioplasty

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Introduction and Objectives

Diabetes mellitus-related foot disease is one of the most serious complications of DM with loss of quality of life and high economic cost. Peripheral arterial disease is present in $>$ 50% of patients and infection affects 60% ulcers (main cause of amputation). The risk of death in 5 years for a patient with an ulcer is 2-5 times higher.

Material and Method

We performed a descriptive of the patients treated in our diabetic foot clinic during one year (September 2023-2024), including patient profile, risk factors, complications, history of amputation, pathophysiology, treatment and evolution to propose improvement options.

Results

97 new patients. From Primary Care, Emergency, Infectious Diseases, Internal Medicine, CCV or Endocrinology. Complex cases presented to the committee (endocrinology, infectious diseases, rehabilitation, trauma, CCV, radiology). Our patient profile: mean age 66.7 years, male (74%), diabetes 2 88% (8 patients type 1), long history (mean 19 years) and poor metabolic control (mean HbA1c 7.8%), hypertensive (76%), dyslipidemia (89%) and smokers (59%). Complications: retinopathy (58%), nephropathy (42%), stroke (15%) and heart disease (19%). Polyneuropathy 76% and arteriopathy 76% patients. Most combine both. History of previous ulcer (63%) and previous amputation (37%). Patients with isglt2 (54%): (empagliflozin 30%, dapagliflozin 23%, canagliflozin 0%). 55.6% of the total (54 patients) had active ulcer. 43 high-risk patients who no longer had ulcers. Type of ulcer: ischemic 35.2%/neuropathic 14.8%/neuroischemic 50%. 2 classifications indicating ulcer severity and longer healing time, SINBAD and PEDIS. SINBAD score $>$ or equal to 3 (32 patients), PEDIS 3 (17 patients) and PEDIS 4 (2 patients). Infection (23 patients). 24 patients required admission, Infectious Diseases or Traumatology, due to complicated ulcer or scheduled admission CCV (preferential angioplasty). All cases require education or care by specialized nursing. Most require angioplasty:

- Dressing and antibiotic therapy: 8 patients
- Antibiotic therapy, debridement and angioplasty: 16 patients
- Debridement and angioplasty: 16 patients At the time of cutting, 32% closed ulcer, healing time (2-32 weeks). Amputation was required due to poor evolution; 7 minor amputations and 4 major ones. One patient died due to a cause unrelated to diabetic foot. In the subgroup with iSGLT2, some amputations were not under treatment, so there is no clear association. We should use them whenever they are indicated due to "high CV risk".

Conclusion

It is important to have a multidisciplinary team and preferential care consultations, in order to reduce mortality.

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EP513

JOINT420

Exploring the role of type 2 diabetes mellitus factors in the progression to advanced fibrosis in MASLD

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Background

Metabolic-associated steatotic liver disease (MASLD) is increasingly recognized as a severe comorbidity in patients with Type 2 diabetes Mellitus (T2DM). Despite the known overlap between these conditions, the specific diabetes-related

factors that drive the progression to advanced liver fibrosis in MASLD remain poorly understood. This study aims to investigate the associations between T2DM factors and the risk of advanced fibrosis in T2DM patients with MASLD.
Methods
This was a retrospective, descriptive and analytical study of T2DM patients with MASLD, followed at the Endocrinology-Diabetology Department of Hedi Chaker University Hospital in Sfax, Tunisia. We used the fibrosis-4 index (FIB-4) and the NAFLD fibrosis score (NFS) to evaluate the risk of advanced fibrosis among the patients. High risk of advanced fibrosis is indicated by a FIB-4 score >2.67 and an NFS score >0.675. The patients were categorized then into two groups : a high-risk group for advanced fibrosis and an intermediate and low-risk group.
Results
This study included 101 T2DM patients with MASLD. Neither the age at diagnosis of T2DM nor its duration were significantly associated with advanced fibrosis ($P>0.05$), regardless of the score used. However, blood glucose levels (12.0 mmol/l [7.2-14.6], 8.0 mmol/l [6.0-12.0], $P = 0.024$) and HbA1c levels (9.7% [6.9-12.0], 7.2% [6.6-9.8], $P = 0.038$) were significantly lower in the high-risk fibrosis group, according to NFS score. The use of anti-diabetic medications did not seem to be associated with the progression to advanced fibrosis when predicted by the FIB-4 score. However, when the NFS score was used, insulin therapy was more frequently associated with the high-risk fibrosis group ($P = 0.007$), while sulfonylureas were more prescribed in the low- and intermediate-risk group ($P = 0.004$). Renal function was significantly more impaired in the high-risk fibrosis group according to both NFS ($P = 0.001$) FIB-4 ($P = 0.044$) scores, and erectile dysfunction was significantly associated with the progression to fibrosis when predicted by NFS score ($P = 0.039$). When NFS score was used, individuals at high risk of fibrosis exhibited significantly higher rates of microangiopathies ($P = 0.046$) and ischemic heart disease ($P = 0.037$) compared to those with low or intermediate risk. These significant differences disappeared when subgroups were based on the FIB-4 score.
Conclusion
Understanding how these diabetes-related factors interact with MASLD to accelerate fibrosis progression is crucial for improving patient outcomes.

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EP514

JOINT1631

Perceived stress levels in women with gestational diabetes and associated factors

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Introduction and objective
Gestational diabetes is a common pregnancy complication that poses unique health challenges, often leading to increased stress for affected women. High stress levels can affect both maternal well-being and pregnancy outcomes. This study aims to examine perceived stress levels and identify factors linked to elevated stress in this population.
Materials and methods
A cross-sectional study was conducted in Department C of the National Institute of Nutrition in Tunis over 7 months. Stress levels were measured using the Perceived Stress Scale (PSS-10), with scores above 27 indicating high stress.
Results
A total of 163 women were included with a mean age of 33.21 ± 4.82 years. The median gestational age was 28.5 weeks $\pm$ [21.9; 33.3]. Insulin therapy was prescribed for 27.6%of the patients and glycemic control was achieved in 60.1% of them. Macrosomia was the most common complication, affecting 14.1% of fetuses. About one-third of women(32.5%) reported not desiring their pregnancies. The average PSS score was 17.11 ± 6.78. Moderate stress was noted in 58.3% of participants, while 9.8% reported high stress levels. High perceived stress was more prevalent among women with unwanted pregnancies (17% vs. 6.4%; $P = 0.03$), those undergoing insulin therapy (17.8% vs. 6.8%; $P = 0.04$), and those at risk of preterm delivery (12.5% vs. 1.4%; $P = 0.04$). Multivariate analysis identified insulin therapy as a significant risk factor for high stress levels (OR = 6.4; 95% CI [1.5, 27.19]).
Conclusion
These findings underscore the importance of targeted psychological support and stress management strategies for pregnant women with gestational diabetes, especially those receiving insulin therapy.

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EP515

JOINT3335

Mauriac syndrome and autoimmune hepatitis: a rare combination in a patient with type 1 diabetes

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Background
Mauriac syndrome, a rare and severe complication of poorly controlled type 1 diabetes mellitus, is characterized by growth retardation, delayed puberty, and hepatomegaly. We report the case of a patient with Mauriac syndrome and autoimmune hepatitis.
Observation
A 16-year-old patient diagnosed with type 1 diabetes for 4 years was admitted to the endocrinology department of Charles Nicolle Hospital in Tunis for further evaluation of hepatomegaly. The patient's diabetes management history revealed poorly controlled diabetes, resulting in frequent hospital admissions due to ketoacidosis decompensations. On physical examination, the patient presented with severe underweight and growth retardation, with a height of 144cm (-3.5 SD) and a weight of 20kg (-3.2 SD) as well as a delayed puberty (Stage I according to Tanner classification). The liver span was 14cm and the liver enzyme levels were three times the upper limit of normal: the level of glutamic-oxaloacetic transaminase (SGOT) was at 102 UI/l [5-34 UI/l], and the level of serum glutamic-pyruvic transaminase (SGPT) at 147 UI/l [10-49 UI/l]. The investigation has excluded drug-induced hepatitis, and the hepatitis C and B virus serology was negative. The immunological work-up revealed negative anti-nuclear and anti-mitochondria antibodies while testing positive for anti-smooth muscle and anti-LKM1 antibodies. The liver biopsy identified an inflammatory infiltrate indicative of chronic hepatitis with mild interface hepatitis and also revealed an accumulation of glycogen in the hepatocytes, suggestive of Mauriac syndrome. Nevertheless, the possibility of autoimmune hepatitis remains under consideration due to the individual's personal history of autoimmunity, as well as the positive antibody findings.
Conclusion
Mauriac syndrome, a rare complication of chronic hyperglycemia and hyperinsulinism, presents a diagnostic challenge, especially when hepatic autoimmunity indicators are present. optimizing diabetic control can help confirm the diagnosis over time.

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EP516

JOINT3623

Vitamin D and microvascular complications in type 1 diabetes

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Background
Type 1 diabetes (T1D) is a chronic condition that predisposes individuals to a range of long-term complications, including microvascular complications. Vitamin D deficiency has been associated with various adverse health outcomes, and emerging evidence indicates that it may influence vascular health and microvascular damage in diabetes.
Objective
This study aimed to explore the relationship between 25-hydroxy vitamin D (25(OH)D) levels and microvascular complications in patients with type 1 diabetes.
Methods
We conducted a cross-sectional study, including 50 type 1 diabetic patients. All patients underwent measurement of 25(OH)D levels, and a clinical evaluation for microvascular complications, including a detailed medical history, a thorough physical examination, assessment of the albuminuria-to-creatininuria ratio and a fundus examination.
Results
The median age of the participants was 26 years [21.00 - 31.75], with a sex ratio (F/M) of 1.4. The median duration of diabetes was 13.00 years [9.25 - 17.75]. The average level of 25(OH)D was 11.14 ± 6.49, and 92% of patients had vitamin D deficiency (≤ 20 ng/ml). Diabetic nephropathy was observed in 24% of patients, while diabetic neuropathy was present in 12% of patients. Diabetic retinopathy was noted in 24% of cases. It was classified as non-proliferative mild, moderate, severe, and proliferative in 33%, 9%, 25% and 33% of patients, respectively. The median 25(OH)D level was lower in patients with diabetic nephropathy compared to those without, although the difference was not statistically significant (8.3

ng/ml [6.87–10.78] versus 9.02 ng/ml [7.78–14.39]; $P = 0.42$). Similarly, the 25(OH)D level was lower in patients with diabetic neuropathy ($n = 6$) compared to those without, but the difference was not statistically significant (8.44 ng/ml [4.68–13.52] versus 9.16 ng/ml [7.57–14.34]; $P = 0.29$). The median 25(OH)D level in patients with mild, moderate, severe, and proliferative retinopathy was 12.07 ng/ml [9.67 – 15.95], 14.31 ng/ml [14.31 – 14.31], 4.51 ng/ml [2.40 – 4.81], and 6.38ng/ml [2.71 – 15.51], respectively. Severe retinopathy and proliferative retinopathy were significantly associated with lower 25(OH)D levels ($P = 0.05$).
Conclusion
Our findings suggest a potential link between vitamin D deficiency and the progression of diabetic retinopathy, though further research is necessary to establish causality and the benefit of vitamin D supplementation in preventing or managing microvascular complications in type 1 diabetes.

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EP517

JOINT3945

Specificities by gender of macroangiopathic complications in type 2 diabetic patients

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Introduction
Although the mechanisms and risk factors for macroangiopathies in type 2 diabetic (T2D) patients are similar between genders, clinical and epidemiological differences may influence their prevalence and management. This study aimed to investigate the association between macroangiopathic complications and gender.
Materials and Methods
A study was conducted on 70 T2D patients, divided into two groups : Group 1 (G1) with 35 women and Group 2 (G2) with 35 men, matched by age, diabetes duration, and HbA1c levels. Clinical and biological data were collected from medical records.
Results
The average age was 56.7 $\pm$ 7.5 years. The mean diabetes duration was 11.7 $\pm$ 5.1 years, with an average HbA1c of 10.2 $\pm$ 1.1%. A total of 82.9% of women and 62.9% of men had no macroangiopathic complications. Single macroangiopathy was observed in 11.4% of women and 5.7% of men (P = NS). Two macroangiopathies were present in 31.4% of women and 5.7% of men (P = NS). No patients had more than two macroangiopathies. The prevalence of coronary artery disease (CAD) was identical in both groups (11.4%). Stroke and peripheral artery disease (PAD) were more frequent in men, with a prevalence of 11.4% and 17.1%, compared to 5.7% and 2.9% in women, respectively (P = NS). A significant association was found between CAD and hypertension in men ($P = 0.041$) but not in women ($P = 0.326$).
Conclusion
The simultaneous presence of multiple macroangiopathies, PAD, and stroke was more frequent in men. Additionally, hypertension could be a predictive factor for CAD in the male population. That's why more frequent screening in this group seems to be necessary.

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EP518

JOINT4003

Gender differences in prevalence, clinical features, and treatment of hypertension in type 2 diabetes

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Introduction
Hypertension(HTN) and type2 diabetes(T2D) are often associated and have a bidirectional relationship. On one hand, T2D increases the risk of HTN due to vascular damage caused by glucotoxicity. On the other hand, HTN exacerbates diabetic complications. This study aimed to determine the prevalence of HTN in T2D patients and its characteristics based on gender.
Methods
A study was conducted on 70 T2D patients, divided into two groups : Group1(G1) with 35 women and Group2(G2) with 35 men, matched by age, diabetes duration, and HbA1c levels. HTN was defined as persistently elevated blood pressure(BP) measured in a medical office, with systolicBP (SBP) $\geq$ 140 mmHg and/or diastolic BP(DBP) $\geq$ 90 mmHg.
Results
The average patient age was 56.7 $\pm$ 7.5 years. The average diabetes duration was 11.7 $\pm$ 5.1 years, and the mean HbA1c was 10.2 $\pm$ 1.1%. The mean body mass index(BMI) was 30.26 $\pm$ 6.4 kg/m^2 in women and 26.24 $\pm$ 5.68 kg/m^2 in men. Average SBP and DBP in women were 137.7 $\pm$ 14.3 mmHg and 78 $\pm$ 9 mmHg, higher than in men(130 $\pm$ 14.9 mmHg and 76.8 $\pm$ 8.6 mmHg, respectively). HTN prevalence was 51.4% in G1, while in G2, 45.7%. The most prescribed antihypertensive drugs in G1 were ACE inhibitors (34.3%), calcium channel blockers(CCBs) (17.1%), angiotensin II receptor blockers(ARBs) (14.3%), thiazide diuretics(8.6%), beta-blockers(5.7%), and centrally acting antihypertensives(CAD) (5.7%). In G2, ARBs were the most prescribed (22.9%), followed by CCBs(20%), ACE inhibitors(14.3%), thiazide diuretics(11.4%), beta-blockers(8.6%), and CAD(2.9%). Monotherapy was the most common prescription(G1: 25.7%; G2: 17.1%), followed by dual therapy (22.9%) and triple therapy(2.9%) in women, whereas in men, triple therapy(8.6%) was the second most frequent, followed by dual therapy(14.3%). In G2, but not in G1, HTN was significantly associated with coronary artery disease($P = 0.02$), nephropathy($P = 0.00$), peripheral neuropathy($P = 0.017$), and microalbuminuria($P = 0.00$). In both groups : no significant association was found between HTN and autonomic neuropathy($P = 0.19$), stroke($P = 0.526$), or peripheral artery disease($P = 0.785$), however, HTN was correlated with BMI($P = 0.00$) and retinopathy($P = 0.022$).
Conclusion
In hypertensive T2D patients, monotherapy was the most common treatment. ACE inhibitors, ARBs, and calcium channel blockers were the most frequently prescribed drug classes. HTN appears to be a stronger risk factor for coronary artery disease, nephropathy, and peripheral neuropathy in men, while retinopathy was a shared risk factor in both genders among T2D patients.

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EP519

JOINT1156

Unconventional use of continuous glucose monitoring: case report

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Background and aim
Continuous glucose monitoring (CGM) is an essential part of diabetes management. It allows to assess blood glucose level in real time and avoid hyper- and hypoglycemia. But in this case report we describe a patient without diabetes but frequent hypoglycemic events. With the help of CGM he was diagnosed with insulinoma and treated properly.
Clinical case
A 59-year man presented with palpitation, dizziness, tremor, and general weakness that occur during fasting. History revealed that he experienced these symptoms nearly 6 months. Preliminary diagnosis was hypoglycemic syndrome. At outpatient's clinic fasting glycemia was in reference range. Laboratory tests demonstrated: fasting glycemia 5.1 mmol/l; HbA1c level 5.2%; C-peptide test 4.9 ng/ml (1.1-4.4); insulin level 27 mIU/mL (3-25); plasma cortisol and plasma ACTH levels were in reference ranges. Family history is negative for diabetes. On examination: dry skin, BMI 25,9 kg/m2. Patient did not take any pharmacological agents, including sulfonylurea and insulin. He was proposed to use CGM to find out a cause of his symptoms. CGM report revealed that he experienced unexplained hypoglycemic states at night and early morning. After detailed questioning patient reported that at those exact times he felt hunger, was sweaty, and agitated. Our next step was to perform CT-scan of abdomen to look for a tumor. CT-scan revealed a 2 cm tumor in the head of pancreas. After successful surgery we still follow-up the patient.
Conclusion
Our clinical case describes an unconventional use of CGM. It can be used not only to manage diabetic patients, but also to monitor glucose levels in all patients with disordered glucose metabolism.

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EP520

JOINT647

Vitamin D status and features of carbohydrate metabolism in fertile women with diabetes mellitus

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Introduction.
Vitamin D deficiency is prevalent among individuals with latent autoimmune diabetes in adults (LADA) and has been linked to various metabolic disturbances. In fertile women with LADA, maintaining adequate vitamin D levels is crucial, not only for metabolic health but also for reproductive health. Vitamin D deficiency has been linked to various reproductive issues, including menstrual irregularities and complications during pregnancy.
The aim of the study.
To evaluate the vitamin D status and features of carbohydrate metabolism in fertile women with latent autoimmune diabetes in adults and classical type 1 diabetes (T1DM).
Material and methods.
15 patients with LADA as well as 16 patients with classical T1DM and 25 practically healthy individuals were examined. In addition to general clinical research methods cholecalciferol status was evaluated as well as indicators of carbohydrate metabolism (fasting glycemia, glycated hemoglobin (HbA1c)), and C-peptide level.
Results.
Cholecalciferol level was registered 45.1% lower in LADA group compared to control (20.48 [18.41;25.71] ng/ml vs 33.00 [27.00;60.00] ng/ml) ($P = 0.000$) and by 37.9% in T1DM (20.48 [18.41;25.71] ng/ml vs 33.00 [27.00;60.00] ng/ml) ($P<0.001$). In LADA patients the level of cholecalciferol was lower by 11.5% ($p<0.05$) compared to T1DM. The fasting plasma glucose level was 10.91 [10.00;12.30] in LADA and 10.67 [7.04;12.51] in T1DM group and probably differed between LADA/control and T1DM/control – control level 4.78 [4.40;5.05] (decrease by 2.3 times and 2.2 times, respectively ($P = 0.000$)). The level of HbA1c was the highest in LADA group (9.90 [7.6;10.20]%: by 46% compared with control (5.35 [5.30;5.52]%) ($P = 0.000$) and did not significantly differ with T1DM group where the level was 8.85 [7.90;9.55]%. The C-peptide level was significantly higher in control group (3.20 [2.10;4.00] ng/ml) by 6.4 times compared with the LADA group (0.50 [0.20;0.65] ng/ml) ($P<0.05$) and 32 times compared with T1DM (0.1 [0.10;0.15] ng/ml); the difference between LADA and T1DM showed that C-peptide level was higher by 5 times in patients with LADA compared to T1DM group ($P = 0.000$). In patients with LADA negative correlations of average strength were recorded between vitamin D level and BMI ($r= 0.442$; $P<0.05$), fasting glycemia ($r= 0.348$; $P<0.05$), HbA_{1c} ($r= 0.414$; $P<0.05$), HOMA-IR ($r= 0.671$; $P<0.05$).
Conclusions.
Vitamin D deficiency in fertile women with LADA is associated with reduced beta-cell function and poorer glycemic control. Ensuring sufficient vitamin D levels remains a vital component of managing overall health in this population.

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EP521

JOINT3936

Elevated risk of life-threatening metabolic acidosis with combined metformin and SGLT2 inhibitor therapy in the elderly

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Background
[1]Metformin use in patients with type 2 diabetes (T2D) is associated with lactic acidosis, although exceedingly rare. [2]However, the risk of lactic acidosis is high in patients with underlying CKD. SGLT2 inhibitors have been increasingly used in patients with CKD in recent years due to their benefit in preventing the progression of diabetic nephropathy. In this case, we present the case of a 79-year-old elderly patient with T2D using both Metformin and an SGLT2 inhibitor who was admitted for life-threatening lactic acidosis.
Clinical Case
A 79-year-old female with T2D and co-morbidities including CKD 3b, HTN HLD, and dementia, presented with altered mental status. Her home medications included Dapagliflozin 5 mg (started 6 months ago), Metformin XR 500 mg BID (started 8 years ago), Amlodipine, Atenolol, Hydrochlorothiazide, Olmesartan, and Rosuvastatin. Upon admission, she exhibited severe hypotension (BP: 74/35 mmHg), bradycardia (HR: 54 bpm), and hypothermia (Temp: 34.4°C), while maintaining normal oxygen saturation. Laboratory results showed glucose at 94 mg/dL, potassium at 6.8 mEq/l, BUN at 45 mg/dL, creatinine at 8.86 mg/dL (baseline: 1.3 mg/dL), anion gap at 37.4, pH at 6.8, HCO3 at 2.6 mmol/l, PCO2 at 15 mmHg, lactate at 19.9 mmol/l (reference range < 2), and urine positive for ketones. Despite intensive care with intravenous hydration, a bicarbonate drip, and three vasopressors, her hypotension persisted, and lactate levels rose to 24 mmol/l. Emergent continuous renal replacement therapy (CRRT) was initiated, which improved her hemodynamics and lactic acidosis—all potential causes of lactic acidosis, including infection work-up such as blood cultures, were negative.
Conclusion
Although it is often challenging to identify the exact cause of lactic acidosis, her clinical picture raised suspicion of metformin-induced lactic acidosis due to the initial failure to respond to fluid resuscitation and pressors, followed by improvement after CRRT, and a negative work-up for infection and other causes. [3]There is a similar case presenting severe euglycemic ketoacidosis and lactic acidosis in a diabetic patient on chronic Dapagliflozin and Metformin therapy, which was triggered by poor oral intake and dehydration, ultimately requiring dialysis. Our case underscores the caution needed when using a combination of metformin and SGLT-2 inhibitors, especially in elderly T2D patients with decreased GFR.

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EP522

JOINT1289

Hepatic glycogenosis in poorly controlled type 1 diabetes mellitus

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Background
Hepatic glycogenosis is the liver response to poor glycemic control in type 1 diabetes mellitus The rarity of the glycogenic hepatopathy in children leads to misdiagnosis. In this case report, we highlighted the identification of key clinical symptoms, of HG, in order to prevent HG from continuing to be misdiagnosed, and to ensure prompt management.
Case presentation
A twelve years old boy who was diagnosed one year earlier to his presentation to ED with abdominal pain. His Growth percentiles were below 3rd centile for the weight and on the 20th centile for the height. His **abdominal examination**showed tenderness in the right lower quadrant of the abdomen with hepatomegaly of 8 cm below the costal margin. The **laboratory investigations**revealed a very high HbA1C of 15.0 %, elevated liver enzymes and negative CMV and EBV serology, and other infectious causes of hepatomegaly. **Ultrasound abdomen**reported an Enlarged liver, measuring 17.9 cm with coarse parenchyma, but no sizeable focal mass lesion.
Conclusion
Although rare complication, of poorly glycemic control of type 1 Diabetes mellitus in children, hepatic glycogenosis, a temporary finding these patient which improves with glycemic control of children with T1DM. We report this case to raise attention of physicians to such complication, as it should not be misdiagnosed and for the prompt and early management of these patients.

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EP523

JOINT1298

Challenge in the follow-up of a type 1 diabetic patient with short stature - how craniopharyngioma can disturb the hormone status

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A 14 year old boy with delayed puberty and short stature has been diagnosed with Type 1 (insulin-dependent) diabetes mellitus (T1DM). During the first six month of his diabetes treatment, in his honeymoon period, he did not required insulin substitution, but his short stature did not change, there was no growth velocity. Because of these symptoms, insulin tolerance- and glucagon stimulation test was performed after androgen priming. Growth hormone (GH) peak was not detectable in any stimulation test, the hormone concentrations were below the measurable limit. Brain MRI scan revealed a cystic intrasellar craniopharyngioma with moderate suprasellar extension. Chronic diseases like T1DM can cause short stature, but other organic failures could be also considered. Strict patient follow up can help to make the correct, complex diagnosis. After neurosurgical intervention hypoglycemic episodes can be life-threatening especially together

with insulin replacement in T1DM, since counter regulatory hormones are missing.

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EP524

JOINT918

Genetic diagnosis of MODY: a case highlighting the role of 17q12 deletion

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Maturity onset diabetes of the young (MODY) is a non-insulin dependent variant of diabetes mellitus characterized by autosomal dominant pattern of inheritance. It is commonly seen amongst the younger population with typical features of early onset diabetes, strong family history of diabetes in multiple generations and mild fasting hyperglycemia or fluctuating glucose levels without severe complications (e.g., acidosis). Many are mistakenly treated as type 1 or type 2 diabetes for years. Of the 14 types, MODY 5 is a lesser common variant caused by HNF1β mutation and is associated with organ anomalies. We describe here a 13-year old asymptomatic patient presented similarly with elevated blood sugars at a primary clinic. Her father and 3 siblings were diabetic and mother had hypothyroidism suggesting a strong history. She was treated as prediabetes (HbA1c 6.4%) with lifestyle modifications. Months later the patient continued to have elevated blood sugar levels (HbA1c 8%) and type I diabetic mellitus was suspected. The patient was started on Degludec to 16 Units and Lispro to 6 Units with 3 meals and advised to test for autoantibodies like Glutamic Acid Decarboxylase Antibodies (GAD) & Islet cell Antibodies (ICA) which resulted negative. MODY was suspected and genetic testing revealed HNF1β mutation. All other investigations were unremarkable. All her family members, Father and two sisters with type one diabetes and brother with type two diabetes, had negative genetic screening. Currently the patient is maintaining normal sugar levels on degludec and semaglutide with HbA1c 6.6% and latest time in Target/Time in Range is 88% with 11% Time in High in Orange Color. Patients with typical features of MODY like strong family history of diabetes and hyperglycemia without acidosis should be genetically screened to avoid delay in diagnosis and management like organ anomalies. Early disease intervention can improve outcomes for affected individuals.

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EP525

JOINT2457

Severe hypercalcemia in a teenager with inaugural diabetic ketoacidosis

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Introduction
Ketoacidosis is the presenting condition in a third of cases of type 1 diabetes, mainly affecting children or young subjects. Many associated electrolyte abnormalities have been described, such as dysnatremia and dyskalemia. However, severe hypercalcemia in diabetic ketoacidosis remains rare, with very few publications in the literature. We report the case of a patient with major hypercalcemia discovered during diabetic ketoacidosis (DKA).
Case report
A 16-year-old patient was admitted to the intensive care unit for management of status epilepticus, where an inaugural DKA was diagnosed. After conditioning and first-line treatment, a laboratory work-up revealed major hypercalcemia corrected to 152 mg/l. After rehydration and intravenous insulin therapy, the ketoacidosis was brought under control and the calcemia recontrolled at 83 mg/l (86-103). The rest of the work-up showed mild hypophosphatemia at 22 mg/l (27-45), 25 OH vitamin D deficiency at 14.20 ng/ml and a low parathormon level at 4 ng/l (9-80).
Discussion
Calcium is the most abundant cation in the human body and plays an essential role in nerve transmission, enzyme activity, myocardial function, coagulation and other functions... Phosphocalcic metabolism is tightly regulated by 3 main hormones : parathyroid hormone (PTH), vitamin D and calcitonin. The etiologies of hypercalcemia can be divided into 2 major categories: PTH-mediated (primary and tertiary hyperparathyroidism and familial hypocalciuric hypercalcemia) and non-PTH-mediated (neoplasia, drugs, hyperthyroidism, immobilization, etc.). Hypercalcemia in diabetic ketoacidosis may be explained by several mechanisms. Metabolic acidosis induces calcium efflux from the bones through increased osteoclastic bone resorption and reduced osteoblastic bone formation. Acidosis also directly reduces tubular reabsorption of calcium and increases its ionization. Dehydration, secondary to hyperglycemia, osmotic diuresis and insufficient oral intake, also causes hypercalcemia. Rhabdomyolysis, which is sometimes observed in patients with ACD, can lead to hypercalcemia.
Conclusion
Electrolyte disorders are common in diabetic ketoacidosis. However, severe hypercalcemia remains a rare complication, and its treatment essentially consists in correcting acidosis and dehydration with sufficient and appropriate fluid intake.

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EP526

JOINT3523

Quality of life in patients with diabetes mellitus

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Introduction
The prevalence of diabetes mellitus (DM) is reaching epidemic proportions in many parts of the world. People with DM have a worse quality of life (QoL) than those without chronic disease. DM is associated with a high risk of serious complications that affect the QoL.
Aim
To determine whether there is a difference in the quality of life in patients with DM2 receiving SGLT-2 inhibitor therapy compared to ones receiving insulin analogues.
Methods
Cross-sectional, case control study with 30 DM2 patients (mean age 59.7 ± 2.9) and 15 healthy controls, matched for age, sex and educational level, were included. DM2 patients were divided into 2 groups, 15 patients receiving SGLT2-inhibitors and 15 patients receiving insulin analogues. Measurement of glucose, HbA1c, urea, and creatinine was done. Evaluation of QoL was evaluated by QoL questionnaire - SF36. Fisher's ANOVA analysis was used to compare means between (sub)groups.
Results
Both DM2 groups had higher levels of glucose (SGLT2inh vs insulin) vs control group (7.37 ± 0.87 vs 8.21 ± 1.42 vs 5.15 ± 0.6 mmol/l, $P = 0.000$) as well as HbA1c (6.86 ± 0.31 vs 7.32 ± 0.62 vs 5.23 ± 0.29%, $P = 0.000$). Patients in both SGLT2inh and insulin groups vs control group reported worse quality of life in all scales measured by SF36. Physical health – Dimension A (48.91 ± 5.49 vs 35.73 ± 7.16 vs 53.28 ± 5.29 $P = 0.000$) and mental health – Dimension B (39.77 ± 8.15 vs 25.06 ± 10.11 vs 47.28 ± 6.30, $P = 0.000$).
Conclusion
Use of SGLT-2 inhibitors represents a significant step forward in the treatment of patients with DM2. These drugs not only improve the control of blood glucose levels, but also significantly contribute to improving the quality of life of patients, reducing complications and facilitating daily life. Assessment of the quality of life should become part of the routine control of patients with DM2, to determine the priority for each patient at the beginning of treatment and accordingly adjust therapeutic modalities in accordance with the latest medical recommendations.

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EP527

JOINT418

Unveiling the cardio-metabolic factors driving advanced fibrosis in type 2 diabetic patients with MASLD

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Background
The progression of advanced fibrosis in type 2 diabetes mellitus (T2DM) patients with metabolic associated steatotic liver disease (MASLD) is shaped by a

complex interplay of cardio-metabolic risk factors, many of which remain poorly understood. Identifying the specific cardio-metabolic factors driving this progression could unlock new opportunities for early intervention and personalized treatment strategies. This study aims to uncover the key cardio-metabolic risk factors that promote advanced fibrosis in diabetic patients with MASLD.
Methods
This retrospective and comparative study included T2DM patients with confirmed MASLD, followed from 2012 to 2024 at the Endocrinology-Diabetology Department of Hedi Chaker University Hospital in Sfax, Tunisia. We used the fibrosis-4 index (FIB-4) and the NAFLD fibrosis score (NFS) to evaluate the risk of advanced fibrosis among the patients. High risk of advanced fibrosis is indicated by a FIB-4 score exceeding 2.67 and an NFS score exceeding 0.675. The patients were categorized then into two groups : a high-risk group for advanced fibrosis and an intermediate and low-risk group.
Results
This study included 101 T2DM patients with MASLD. Neither the presence of metabolic syndrome nor its individual components (waist circumference, dyslipidemia, systolic blood pressure, diastolic blood pressure) were significantly associated with the risk of fibrosis in our cohort (FIB-4: $P = 0{,}068$; NFS: $P = 0{,}232$). The most notable association was with hypertension, which was significantly linked to fibrotic liver lesions based on the NFS score ($P = 0{,}033$). Regardless of the fibrosis score used, spironolactone prescriptions were significantly more frequent in patients at high risk of advanced fibrosis (FIB-4 : $P = 0.031$; NFS : $P = 0.006$). Other antihypertensive treatments (renin-angiotensin system blockers, calcium channel blockers, thiazide diuretics, and beta-blockers), as well as their adherence, had no significant impact on the progression to advanced fibrosis. Additionally, no substantial effect on advanced fibrosis was observed from any dyslipidemia parameters or lipid fractions in the included patients.
Conclusion
This study aims to shed light on key cardio metabolic risk factors contributing to fibrosis progression, ultimately informing targeted interventions.

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EP528

JOINT422

Prevalence of metabolic dysfunction-associated steatotic liver disease in patients with type 2 diabetes mellitus: a tunisian study

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Background
Metabolic Associated Steatotic Liver Disease (MASLD) is a growing global health concern. The coexistence of MASLD and Type 2 Diabetes Mellitus (T2DM) poses a significant clinical challenge, as both conditions are intertwined through common pathophysiological mechanisms. Understanding the prevalence of MASLD in T2DM patients is crucial for developing effective screening, prevention, and treatment strategies. This study aims to investigate the prevalence of MASLD in T2DM patients.
Methods
This was a retrospective study that included patients followed for T2DM from 2012 to 2024 at the Endocrinology and Diabetology Department of the Hedi Chaker University Hospital in Sfax, Tunisia. The diagnosis of MASLD within T2DM patients was based on the 2024 EASL-EASD-EASO guidelines on the Management of MASLD.
Results
A total of 734 patients with T2DM was recruted and underwent abdominal imaging. 609 patients (83%) had normal imaging results, while 125 patients (17.03%) were diagnosed with hepatic steatosis. Thus, the prevalence of MASLD in our cohort of T2DM patients was found to be 17.03%. The mean age of the diabetic patients with MASLD was 53.7 ($\pm$15.2) years, with a female predominance of 62.4%.
Conclusion
Our study provides valuable insights into the burden of this dual diagnosis emphasizing its clinical significance. These findings highlight the critical need for early detection and effective management of MASLD in diabetic patients.

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EP529

JOINT471

Dietary impact on the risk of progression to hepatic fibrosis in patients with type 2 diabetes

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Background
Metabolic Associated Steatotic Liver Disease (MASLD) is an emerging condition among individuals with Type 2 Diabetes Mellitus (T2DM). Diet plays a critical role in metabolic health, yet its precise effect on the risk of progression to fibrosis in MASLD remains underexplored understanding the dietary factors contributing to its progression toward fibrosis is becoming crucial. This study aims to evaluate the dietary impac on the risk of progression from MASLD to fibrosis in case of T2DM.
Methods
This analytical study included type 2 diabetic patients with confirmed MASLD, followed at the Endocrinology-Diabetology Department in Sfax university in Tunisia. The fibrosis-4 index (FIB-4) and the NAFLD fibrosis score (NFS) were used to evaluate the risk of advanced fibrosis among the patients. For each patient, we assessed macronutrient intake, including daily caloric intake in Kcal, as well as the percentage of daily intake from lipids, proteins, and carbohydrates. We also evaluated the intake of saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids along with micronutrient intake, including fiber (g/day), iron (mg/day), calcium (mg/day), and cholesterol (mg/day).
Results
Our study was conducted on 202 T2DM patients with confirmed MASLD. Total energy intake was not associated with the progression MASLD to fibrosis, as assessed by the FIB-4 and NFS scores ($P = 0.223$ and $P = 0.163$, respectively). Similarly, macronutrient intake did not correlate with fibrosis progression based on the NFS score. However, when the FIB-4 score was applied, significant associations were observed, specifically in carbohydrate intake ($P = 0.003$), lipid intake ($P = 0.041$), and polyunsaturated fatty acids intake ($P = 0.008$). No significant differences were found in protein intake or consumption of saturated and monounsaturated fatty acids, regardless of the score used. Additionally, we found that individuals with advanced fibrotic risk for MASLD, according to the NFS score, had higher dietary iron intake ($P = 0.048$). In contrast, no significant differences were observed in the intake of calcium, fiber, or cholesterol.
Conclusion
Our study aims to provide insights into the role of diet in the progression of MASLD to fibrosis in T2DM patients, offering potential avenues for targeted nutritional strategies to prevent or slow this progression.

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EP530

JOINT987

Influence of degenerative complications of diabetes on the occurrence of infections

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Background
Infections in diabetic patients represent a significant clinical challenge, particularly in those with degenerative complications of diabetes. The potential role of these complications in increasing infection risk warrants further investigation. This study seeks to examine the association between degenerative complications and the occurrence of infections.
Methods
A retrospective study was conducted involving diabetic patients hospitalized in the Endocrinology Department over one year who had undergone an evaluation of diabetes-related complications within the previous six months.
Results
The study included 195 patients, comprising 91 men and 104 women, with 29% having type 1 diabetes and 71% having type 2 diabetes. A significant difference was observed between the two groups in the prevalence of infectious complications (37% in type 2 diabetes versus 15% in type 1 diabetes ; $P < 0.05$). The most common bacterial infections in this population were urinary tract infections ($n = 21$), which were more frequent in women ($P < 0.05$), soft tissue

infections ($n = 21$), with 40% involving the foot, and bronchopulmonary infections ($n = 12$). The frequency of urinary tract infections, septicemia, and bronchopulmonary infections was not influenced by the presence of degenerative complications. However, foot infections were more frequent in patients with lower limb arteriosclerosis obliterans and those with sensorimotor polyneuropathy.
Conclusion
We highlight that among the most common bacterial infections in hospitalized diabetic patients, only foot infections are more frequent in the presence of peripheral artery disease or sensorimotor neuropathy. This underscores the importance of hygiene precautions and proper foot care.

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EP531

JOINT3627

Cardiovascular risk in relation to Body Mass Index in patients with type 2 diabetes mellitus

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Introduction
Epidemiological and clinical studies in the general population have demonstrated that overweight and obesity increase the risk of developing chronic conditions and are associated with all-cause and cardiovascular (CV) morbidity and mortality, independently of gender, age, and ethnicity. The aim of this study was to demonstrate this correlation.
Methods
Descriptive cross-sectional study conducted over 4 months in department A of The National Institute of Nutrition of Tunis which included patients with type 2 diabetes mellitus.
Results
Sixty patients were included amongst whom 36 were women and 24 men. The characteristics of the patients were respectively: age: 56 ± 13 years, Body Mass Index: 28 ± 6 Kg/m^2. There was no statistically significant correlation between the Body mass index and coronary artery disease ($P = 0.6$), stroke nor transient ischemic attack ($P = 0.4$). However, obesity was a predictive factor for the development of lower extremity artery disease ($P = 0.001$).
Conclusions
The degree of obesity is an important factor that can aggravate the metabolic patients' profile, but its effect on cardiovascular risk is rather correlated to its association with the other risk factors.

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EP532

JOINT3753

Can we predict the onset or worsening of microangiopathies in pregnant women with diabetes mellitus during pregnancy?

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Introduction
Pregnancy is a major factor in the imbalance of diabetes, irrespective of its type. It favours the onset and/or worsening of microvascular complications such as diabetic retinopathy and nephropathy. Our study aims to highlight potential predisposing factors to these microangiopathies in diabetic pregnant women.
Methods
We conducted a descriptive retrospective study involving 100 known diabetic pregnant women in ward C of the National Institute of Nutrition.
Results
The mean age was 32.87 ± 5.3 years, with a predominance of multigestational women (54%) and nulliparous women (37%). Type 2 diabetes was present in 52% of parturients. The average duration of diabetes for all types was 7.57 ± 6.66 years. A minority (29%) had well-controlled diabetes on treatment, with an HbA1C < 7%. Non-proliferative diabetic retinopathy and diabetic nephropathy associated with at least one microalbuminuria complicated 6.1% and 4.8% of diabetics, respectively. No new onset or worsening of diabetic retinopathy was detected throughout the pregnancy. The same applies to the worsening of diabetic nephropathy and creatinine clearance. The only patient with macroalbuminuria decreased her proteinuria during pregnancy.
Conclusions
Glycaemic and blood pressure control are protective factors against microangiopathies during pregnancy, even in cases of previously complicated diabetes. Hence, the importance of pregnancy planning and monitoring during the gestational period.

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EP533

JOINT1340

Case of complete remission of diabetes mellitus type 1

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A 27-year-old female was referred to the outpatient clinic due to symptoms of insulinopenia, unintentional weight loss, polyuria, and polydipsia. The patient was obese with an ITM of 31 kg/m^2 and had prior GDM during her first pregnancy three years ago with a burdened family history (her father has DM2). Fasting blood glucose was 9.3 mmol/l with HbA1c 10.9% and mild ketonuria but no DKA. Due to anamnestic data, pancreatic islet cell antibodies and C-peptide were measured. Treatment with lifestyle modification—diet to reduce weight, with basal insulin detemir and metformin—was recommended. After one week, C-peptide came around the low reference range limit (0.30 nmol/l), and IA-2, ICA, and GADA antibodies all came back positive. Three weeks later, the patient came for a check-up after she found out she was pregnant. Since pregnancy, insulin treatment was continued with a basal bolus insulin regime and strict control of glycemia was targeted. The patient refused the insulin pump and continued to use the CGM Dexcom One Plus. Detemir two times daily with aspart insulin before meals were given, and the patient had satisfactory levels of blood glucose with a fasting glucose level usually below 6 mmol/l and PPG < 8 mmol/l. Nine months later, the patient gave birth naturally to a healthy baby girl weighing 3 kilograms. Shortly after delivery, the patient had hypoglycemia, so insulin therapy was discontinued completely. Since she continued to use the Dexcom One Plus glucose sensor and glycemic values were continuously within limits, she discontinued any medication and came for a diabetologist check-up one month after delivery. Since this situation seemed to be a complete remission of type 1 diabetes, C-peptide and pancreatic islet cell antibodies were measured again. Now C-peptide arrived within normal values (1.12 nmol/l) with still positive anti-insulin antibodies in repeated measurements. The patient was advised to preserve lifestyle and diet measures and to take metformin since she was obese and did not breastfeed. The patient will continue to be under diabetologist care since her diagnosis of diabetes mellitus type 1 is established, and insulin treatment is expected to be necessary again once the honeymoon period passes. We present this case since it is not usual for obese adult women with prior GDM and a family history of type 2 diabetes mellitus to develop type 1 DM and even less often to develop complete remission shortly after delivery and pregnancy.

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EP534

JOINT2374

Diabetic ketoacidosis secondary to immunotherapy-induced diabetes mellitus

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Introduction
Immune checkpoint inhibitors have changed the landscape of cancer therapy by targeting proteins that regulate immune checkpoints. However, their use is accompanied by adverse events, including endocrinopathies and diabetes mellitus (DM), which can be initially presented with diabetic ketoacidosis (DKA). We present here two cases of DKA in patients on immunotherapy for cancer.
Cases: 1
A 57-year-old man with not known DM and with non-small cell lung cancer, developed after 7 months on PD-1 checkpoint inhibitor (nivolumab), altered consciousness, tachypnea and vomiting. The laboratory findings, pH: 7.15, HCO3-: 11.8 mEq/l, blood glucose: 367 mg/dl and blood ketones > 8 mmol/l, confirmed the diagnosis of DKA. He was managed with intravenous fluids and

insulin with resolution of acidosis. Additional tests results included HbA1c:7.3%, negative anti-GAD, anti-islet and anti-insulin autoantibodies and a C-peptide:0.47 ng/mL. The patient was put on a 4 injection regimen and his blood glucose is well controlled. 2. A 52-year-old male, with no history of diabetes and bladder carcinoma, developed one month after starting PD-L1 checkpoint inhibitor (durvalumab), DKA with abdominal pain, polyuria and weight loss, pH: 7.09, HCO3-: 7.3 mEq/l, blood glucose: 436 mg/dL and HbA1c:9%. After hydration and insulin therapy, acidosis was restored within 24 hours. Anti-GAD, anti-islet and anti-insulin autoantibodies were negative and c-peptide:0,41 ng/ml. The patient was discharged on an intensified insulin regimen.

Discussion

DM is a rare but it can be a life-threatening complication of immunotherapy. Real world data show an incidence of 2% and a mean age of onset at 60 years. Initial presentation varies but in 70% of the cases, DKA is the presentation at diagnosis, due to rapid destruction of beta cells by the immune system. Due to the almost complete pancreatic beta cells' destruction, ICI-DM is insulin-dependent. Doctors in charge of patients undergoing immunotherapy, should be on high alert, in order to recognize and treat on time this sudden and potentially life-threatening condition, optimising prognosis and minimizing disease complications.

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EP535

JOINT834

Impact of gestational diabetes and maternal obesity on fetal growth: reduced length and cephalic circumference

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Introduction

Maternal obesity is a global public health concern, and gestational diabetes mellitus (GDM) stands as the most common pregnancy complication. Both conditions are linked to adverse outcomes in offspring, including increased birth weight and an elevated risk of developing obesity and chronic diseases later in life.

Objective

To evaluate the association of maternal obesity and GDM with fetal growth indicators at birth and placental weight.

Methods

This cross-sectional analysis is based on data from mother-child dyads attending the Gynecology Service at Hospital General de México. The inclusion criteria were: 1) singleton pregnancy, 2) maternal age $\geq$18 years, and 3) either gestational diabetes mellitus (GDM) or an uncomplicated pregnancy. Women with systemic diseases or preeclampsia were excluded. Maternal and newborn data were obtained from clinical records. Fetal growth indicators included birth weight, birth length, abdominal circumference, and cephalic circumference. Descriptive analyses were conducted to characterize the study sample, and multiple linear regression models were used to evaluate the association of GDM and maternal obesity with fetal growth indicators. The models were adjusted for maternal age, newborn sex, gestational age at birth, and gestational weight gain. An interaction between GDM and pre-gestational BMI category were tested to evaluate if having both conditions affected the association with growth indicators. All analyses were performed in STATA 15. This research receive funding from the Secretaría de Educación, Ciencia, Tecnología e Innovación (SECTEI/1492023).

Results

A total of 74 mother-child dyads were included in the study. Among them, 39.2% (n= 29) had GDM, while 60.8% (n= 45) had normoevolutive pregnancies. The mean maternal age was 25.9 (6.2) years. Newborns of mothers with GDM were shorter (β=-1.08, P = 0.045) compared to those of mothers without GDM. Regarding cephalic circumference, newborns of mothers with obesity had larger values (β=1.6, P = 0.027). However, the interaction term with GDM was significant (β=-1.9, P = 0.078), indicating that when both conditions were present in mothers, the cephalic circumference was reduced compared to newborns of mothers without obesity and GDM. Neither GDM nor maternal obesity were associated with birth weight, abdominal circumference, or placental weight.

Conclusions

GDM was associated with a reduction in birth length, while maternal obesity was linked to an increased cephalic circumference. However, when both GDM and obesity were present in mothers, newborns had a significantly smaller cephalic circumference. These findings suggest that GDM may negatively impact fetal growth.

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EP536

JOINT283

Solving a hypoglycaemia mystery

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A previously well 22-year-old female with no medical history presented obtunded to the emergency department. Capillary blood glucose returned "LO" with corresponding venous glucose at 2.1mmol/l. Prompt reversal of severe hypoglycaemia led to full resolution of symptoms. She continued to have multiple episodes of hypoglycaemia daily during her inpatient stay. Biochemistry revealed the cause of hypoglycaemia to be endogenous hyperinsulinaemia, accompanied with a clean toxicology screen and negative insulin antibody assessment. Interestingly, she was also hyperthyroid and concomitantly diagnosed with Graves' Disease at the same encounter. Further history suggested that she may have had the hypoglycaemia disorder since early childhood for which she had been compensating for with lifestyle interventions. Genetic testing for congenital hyperinsulinaemia was inconclusive. Medical therapy with Diazoxide was initiated with good effect, with dose adjustments aided by continuous glucose monitoring. Etiology of hyperinsulinaemia was rigorously assessed, first with anatomical imaging of the pancreas (computed tomography and magnetic resonance imaging), followed by endoscopic ultrasound, all of which returned no positive result. Eventually, functional imaging with Exendin-4 PET/CT suggested a more diffuse process consistent with pancreatic islet cell hyperplasia.

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EP537

JOINT222

Mucormycosis infections in a child with type 1 diabetes mellitus

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Background

A relatively uncommon infection, mucormycosis, in diabetes, stood out as the main underlying medical comorbidity for the infected patients. It was determined to be an independent risk factor for severe infection depending on which organ was affected. Mucormycosis detects several host-dependent clinical manifestations. Factors that impede host immune function can also play a role in the aggressiveness of mucormycosis infection. Mucormycosis have also been well studied with regard to the effects of hyperglycemia, and acidosis on their pathogenesis. The purpose of this paper is to present a case successfully management of type 1 diabetes mellitus (DMT1) with mucormycosis.

Case

S, a 10-year-old girl, was admitted to Soetomo Hospital, East Java, Indonesia, with complaints of fever accompanied by abdominal pain and a subsequent loss of consciousness. The patient was diagnosed with diabetic ketoacidosis (DKA) and type 1 diabetes mellitus (HbA1c 9.9%, blood glucose 478 mg/dL). Further examination revealed the presence of a white plaque on the soft palate (palatum molle) along with a perforation in the area. Additionally, the patient exhibited facial paralysis on one side. Laboratory findings and investigations conducted revealed the following: a pathological anatomy biopsy indicated chronic suppurative inflammation consistent with a nonspecific abscess; the C-peptide level was 0.193 ng/mL; ASTO was 315.27 IU/mL (normal range: $<$ 200 IU/mL); the anti-dsDNA antibody test was negative; blood culture was sterile, and urine

culture revealed the presence of *Candida glabrata*. A palatal swab culture identified *Candida dubliniensis* and mucormycosis. Additionally, *Acinetobacter baumannii* was detected in the palatal swab. The patient only received a 3-day treatment due to difficulties in obtaining amphotericin-B. However, she underwent surgical debridement performed by the surgery department to aid in wound healing. Despite the limited treatment duration, the patient successfully recovered, and the wound healed completely. After a few months of recovery and rehabilitation, patients can walk and eat well and go to school again.

Conclusion

Early diagnosis for mucormycosis is a key to rapid and appropriate treatment and better outcomes. Underlying risk factors influence the clinical presentation. The cornerstone for management of invasive mucormycosis involves surgical debridement and antifungal therapies.

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EP538

JOINT1435

Renal complications in diabetic subjects

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Today, diabetes mellitus is a major public health problem. Type 2 diabetes is the most common form, accounting for around 90% of all forms of diabetes. The ever-increasing frequency of this condition may be explained by lifestyle changes, particularly sedentary lifestyles, high-fat diets, obesity and an ageing population. The seriousness of this condition is linked to the occurrence of metabolic, infectious and degenerative complications, including renal manifestations. The aim of our work was to determine the distribution of diabetes according to sex, age and renal complications, and to study certain biochemical parameters of the glycemic and renal balance of people with diabetes and/or diabetic nephropathy ($n = 65$). We found that the risk of diabetic nephropathy was higher in women than in men, and that 11% developed renal complications. 86% had above-normal fasting blood glucose levels, and blood glucose levels were higher in those with ND (2.52 ± 0.95 g/l) than in patients without ND (1.92 ± 0.72 g/l). 85% of patients had HBA1c values above threshold, and mean HBA1c was higher in those with ND ($9.2 \pm 2.24\%$) than in those without ND ($8.28 \pm 1.60\%$). In addition, 47% had hypercreatininemia, of whom 11% had ND and 7% had hypocreatinemia. Hyper-uremia was present in 56% of patients, of whom 15% had ND, and 45% of patients had hyper-uricemia, of whom 10% had ND. It also appeared from our results that renal workup is effective in estimating function as well as the degree of renal complication.

Key words

Diabetes, nephropathy, glycemia, HBA1c, creatinemia, uremia, uricemia.

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EP539

JOINT203

Effects of weight loss after bariatric surgery on pregnancy outcome

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Background and aims

Overweight and obese women have an increased risk of spontaneous miscarriage as Type 2 (T2DM) diabetes mellitus is associated with increased rates of adverse maternal and neonatal outcomes. Adverse outcomes are more common in women with pregestational diabetes compared to GDM. Obesity, with its associated metabolic and endocrine aberrations, can directly influence the reproductive health of women. Bariatric surgery, which is primarily designed to induce significant weight loss, has been shown to have a positive impact on fertility outcomes

Methods

The patient was diagnosed with type 2 diabetes at the age of 29. At the age of 33, she gave birth to a dead fetus in the 7th month of pregnancy with fetal hydrocephalus. At that time BMI -50kg/m2. The second pregnancy at the age of 38 ended with spontaneous abortion at 7 weeks. BMI -52.1 kg/m2. Insulin therapy was used during both pregnancies. Diabetes mellitus was controlled before and after pregnancy. Bariatric surgery was performed at the age of 40. BMI -53.3 kg/m2. After 4 years BMI -33.3kg/m2. Secondary infertility was established. Pregnancy with twin fetuses occurred through *in vitro* fertilization. Diabetes was managed with insulin. 2 healthy newborns were born by cesarean section at 34 weeks of pregnancy

Results

Significant weight loss in obese T2DM patients after bariatric surgery was associated with a substantial reduction in BMI from 53.3.5 kg/m^2 to - 33.3 kg/m2. Gradual weight loss has been shown to improve fertility and outcomes of fertility treatments and reduce cardiovascular and diabetes-associated morbidity and mortality

Conclusion

Women should be advised pre-pregnancy about the impact of being obese and risk of early pregnancy complications. Epidemiological evidence suggests an increased risk of both spontaneous and recurrent pregnancy loss with obesity. The ESHRE guidance recommends that couples with obesity and previous repeated pregnancy loss achieve a normal range BMI (20–25 kg/m2 for White individuals) before conceiving. A normal BMI can be associated with multiple health benefits for both mother and baby.

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EP540

JOINT1925

Kyrle's disease: a rare complication of diabetes (case report)

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Introduction

Kyrle's disease (MK) belongs to the group of acquired perforating dermatoses. It is a rare pathology characterized by transepidermal removal of keratotic material. We report the case of a diabetic patient with MK.

Observation

This is a 47-year-old patient, diabetic for 15 years on insulin at the degenerative complication stage: hypertensive for 3 years and chronic renal disease for 2 years on treatment, amputation of the right big toe 6 years ago. Consulted for multiple ulcerated nodules of the lower limbs for several months, with loss of substance in the pulp of the big toe. The whole evolving in a context of feverish sensations and conservation of the general state. clinical suspicion of the diagnosis was confirmed by histological examination of a skin biopsy. This revealed a crater-shaped lesion filled with keratotic material, showing an image of incipient epidermal elimination on one cut level. The epidermis was acanthosic with significant compact parakeratotic hyperkeratosis and a slightly inflammatory dermis. The diagnosis of MK was therefore accepted. The patient was put on emollient and antihistamines.

Discussion

Acquired perforating dermatoses are rare pathologies characterized by transepidermal elimination of certain dermal constituents. Acquired MK is characterized by an invagination of the epidermis with keratotic content. MK is often associated with diabetes mellitus (50%) and chronic end-stage renal disease (70%). Diabetes is in the insulinocarrying stage. The pathophysiology of MK is still unknown, but hypotheses have suggested the role of cutaneous trauma and diabetic vasculopathy. Treatment is mainly symptomatic, based on emollients and keratolytics. Other options include topical or systemic retinoids, surgery or CO2 laser and phototherapy.

Conclusion

MK is a rare papulokeratotic dermatosis. It should be particularly sought after in diabetics. Diagnosis is confirmed by histology.

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EP541

JOINT3911

Stress perception among patients with type 1 diabetes

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Introduction

Stress is often a part of every individual's life. Living with a chronic illness such as type 1 diabetes adds an additional layer of stress and negative burden.

Objective
To assess the level of stress in a population of patients with type 1 diabetes.
Materials and methods
A cross-sectional descriptive study using the Perceived Stress Scale (PSS) questionnaire, which evaluates the level of stress based on feelings and thoughts over the past month. The PSS comprises 10 items, with a total score calculated out of 40.
Results
Our study included 71 patients with an average age of 25.42 ± 8 years and a sex ratio of 1.09. The average duration of diabetes was 8.59 ± 6.8 years, and the mean HbA1c level was 11.07 ± 4%. In our population, 60% of the participants were considered to have a high level of stress, while 40% were deemed to have a moderately high level of stress. None of the patients were categorized as having a low level of stress. The average stress level in the population was 24, identified as a moderate overall level. Among the patients, 50% reported feeling irritated quite often due to events beyond their control, and 38% felt upset by an unexpected event. Only 4 patients expressed confidence in their ability to manage personal problems, and only 6 believed that things were going their way.
Conclusion
Thus, more than half of the studied population suffers from high stress levels, representing an additional burden with implications for both disease management and the overall health of individuals.

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EP542

JOINT307

Tracing the causes: why hypoglycemia strikes in type 1 diabetes mellitus

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Background
Hypoglycemia is one of the most challenging and potentially dangerous complications faced by individuals with Type 1 Diabetes Mellitus (T1DM). Episodes of low blood glucose not only jeopardize immediate health but also complicate long-term diabetes control. Patients living with this condition may experience a loss of autonomy, anxiety, and fear of the next hypoglycemic event, which impacts their daily lives. Understanding why hypoglycemia occurs is critical for improving treatment strategies and overall patient outcomes.
Methods
This retrospective, descriptive study included patients with T1DM experiencing recurrent hypoglycemia who were hospitalized in the Endocrinology Department of Taher Sfar University Hospital in Mahdia, Tunisia, over a seven-year period.
Results
This study included 42 patients, with a mean age of 42 ± 25 years, the majority of whom were female (71%). The average glycated hemoglobin level was 10.7%. Notably, 26.7% of the patients were receiving insulin analogs. At the time of hospitalization, the mean insulin dose was 0.77 IU/kg/day, which decreased to 0.61 IU/kg/day upon discharge. Hypoglycemia was observed as moderate in 35% of cases and severe in 29%, occurring at a frequency of two episodes per week. The causes of hypoglycemia were multifactorial, with adrenal insufficiency being the most common, affecting 84% of the patients, as reflected in a mean early morning cortisol level of 82 µg/l. Additionally, 6.25% of patients had profound hypothyroidism, while no cases of hepatocellular insufficiency were found. Renal insufficiency was noted in 12.5% of patients, and 3 patients had malabsorption due to celiac disease. Insulin doses exceeding 1.5 IU/kg/day were noted in 21.9% of the cases, and 22.7% exhibited lipodystrophic regions. Moreover, 3 patients experienced hypoglycemia due to toxic factors, particularly alcohol abuse, and 2 patients (6.3%) presented with factitious hypoglycemia.
Conclusion
Hypoglycemia in T1DM poses significant challenges to patient management and quality of life. Understanding its multifactorial causes is crucial for developing targeted strategies to prevent and better manage this complication.

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EP543

JOINT424

Antidiabetic treatment patterns in type 2 diabetic patients with metabolic associated steatotic liver disease

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Background
Metabolic Associated Steatotic Liver Disease (MASLD) is increasingly recognized as a common comorbidity in patients with type 2 diabetes mellitus (T2DM), complicating their management. The presence of MASLD may influence choice and effectiveness of antidiabetic pharmacotherapy, as certain treatments may have varying impacts on both liver function and glucose control. This study aims to explore the pharmacotherapeutic profile of T2DM patients with MASLD.
Methods
A retrospective, descriptive, and analytical study was conducted on 202 T2DM patients followed at the Endocrinology Department of Hedi Chaker Hospital in Sfax, Tunisia. The patients were equally divided into two groups based on the presence or absence of MASLD.
Results
Hygienic and dietary measures without pharmacotherapy were recommended for 14.9% of patients. Nearly half of the patients (48.5%) received exclusive oral pharmacotherapy, while 21.8% were treated with insulin therapy, either as monotherapy (12.9%) or in combination with oral antidiabetic agents (8.9%). Metformin was the most frequently prescribed medication, used in 57.4% of cases, followed by sulfonylureas, prescribed in 27.7% of cases—glimepiride in 15.8%, glibenclamide in 7.9%, and gliclazide in 4%. The use of newer antidiabetic drugs was limited, with only two patients receiving SGLT2 inhibitors, specifically dapagliflozin, and no patients on empagliflozin. Incretin mimetics (DPP-4 inhibitors and GLP-1 agonists) were not prescribed. Acarbose was used in 2% of cases, and glinides in 5%. Among insulin treatments, human insulin was more commonly prescribed (17.8%) compared to insulin analogs (4%). The most frequent therapeutic combinations in this population were metformin with sulfonylureas (25.7%) and insulin with metformin (10.9%). Antidiabetic treatments were not associated with the development of MASLD for oral medications (metformin: $P = 0.131$, sulfonylureas: $P = 0.557$). However, insulin therapy was significantly associated with the absence of MASLD lesions in diabetic patients ($P = 0.027$).
Conclusion
Understanding the nuances of antidiabetic treatment of diabetic patients with MASLD is crucial for optimizing patient care and improving therapeutic strategies.

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EP544

JOINT464

Type 2 diabetes-related features in patients with metabolic associated steatotic liver disease

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Background
Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder commonly associated with various comorbidities, including Metabolic Associated Steatotic Liver Disease (MASLD). The overlap between these conditions presents significant challenges in both diagnosis and management. Understanding the specific diabetes-related characteristics in patients with T2D and MASLD is essential for improving clinical outcomes. This study explores the clinical features of T2DM patients with MASLD.
Methods
This retrospective study was conducted on T2DM patients with confirmed MASLD, who were followed at the Endocrinology-Diabetology Department of Hedi Chaker University Hospital in Sfax, Tunisia, over a 12-year period.
Results
This study was conducted on 101 diabetic patients. The mean age of diabetic patients with MASLD was 53.7 (±15.2) years, with a female predominance of 62.4%. T2DM was diagnosed at a mean age of 48 [40-57] years. They had a median HbA1c of 9% [6.8-11.3] and a median blood glucose level of 10.3 mmol/l [4.5-16.1]. After a median duration of 3 [0.7-10] years, 54.5% of these patients developed microvascular complications, while 31.7% had macrovascular complications. The most common microvascular complications were diabetic nephropathy (40.9%) and neuropathy (35.4%), followed by diabetic retinopathy (25.7%) and erectile dysfunction (23.1%). Positive albuminuria was detected in 35.6%, and impaired glomerular filtration rate (GFR) was observed in 27.7%,

predominantly at stages CKD-G3 (10.9%) and CKD-G4 (15.8%). Regarding macrovascular complications, ischemic heart disease (26.7%) and peripheral arterial disease (13.9%) were most frequently noted. Nearly half of the patients (48.5%) were treated with oral medications alone. In 21.8% of cases, insulin therapy was initiated, either as monotherapy (12.9%) or in combination with oral antidiabetic drugs (8.9%).
Conclusion
Our study provides insights into how the features of diabetes may contribute to the development and progression of MASLD.

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EP545

JOINT466
Chronic kidney disease in type 2 diabetes patients with metabolic associated steatotic liver disease
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Background
Chronic kidney disease (CKD) is a common complication in type 2 diabetes mellitus (T2DM) patients, and its clinical profile may be altered by the presence of Metabolic Associated Steatotic Liver Disease (MASLD). While the association between these two conditions is increasingly recognized, their combined impact on renal function requires further investigation. This study aims to describe the CKD profile in T2DM patients with MASLD.
Methods
This retrospective descriptive study included T2DM patients with confirmed MASLD, followed from 2012 to 2024 at the Endocrinology-Diabetology Department of Hedi Chaker University Hospital in Sfax, Tunisia. The study focused on CKD, analyzing its stages based on glomerular filtration rate (GFR) and levels of albuminuria. Albuminuria was classified as mild (<30 mg/g of urinary creatinine), microalbuminuria (30–300 mg/g of urinary creatinine), and macroalbuminuria (proteinuria) defined as values exceeding these thresholds.
Results
We included 101 patients in this study. The mean age of patients was 53.7 ($\pm$ 15.2) years, with a female predominance of 62.4%. CKD-G1, defined by a GFR of $\geq$90 ml/min/1.73m^2, was observed in 43.6% of patients. In comparison, CKD-G2, characterized by a GFR ranging from 60 to 89 ml/min/1.73m^2, was found in 28.7% of the cases. Furthermore, CKD-G3, with a GFR between 30 and 59 ml/min/1.73m^2, was present in 10.9%, while CKD-G4, where the GFR ranged from 15 to 29 ml/min/1.73m^2, was identified in 15.8% of patients. Notably, CKD-G5, indicating a severe reduction in renal function with a GFR <15 ml/min/1.73m^2, was seen in only 1%. Regarding albuminuria, a normal to mildly elevated level was detected in 56.4% of patients, whereas microalbuminuria was observed in 35.6%, and proteinuria was found in 7.9%.
Conclusion
These findings collectively highlight the diverse renal involvement in this population, underscoring the need for vigilant monitoring and early therapeutic interventions.

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EP546

JOINT2530
Mycosis fungoides and diabetes mellitus: is there a link?
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Background
Mycosis fungoides (MF) is the most common type of primary cutaneous T-cell lymphoma, often presenting with chronic nonspecific skin lesions that can mimic inflammatory dermatoses. Diabetes mellitus (DM) is a metabolic disorder frequently diagnosed incidentally during routine evaluations. The coexistence of MF and DM is rare, and their potential pathophysiological link remains unclear.
Case Presentation
A 63-year-old woman with a family history of hypertension and type 2 diabetes mellitus, and a personal history of dyslipidemia, treated with atorvastatin, presented with progressive, pruritic, erythematous plaques with fine scaling, well-demarcated pigmentation, and atrophic hypopigmented areas. Some lesions exhibited a wrinkled skin appearance. These lesions had been evolving over the past nine months with diffuse involvement of the trunk and extremities. A skin biopsy was performed at the Department of Dermatology and histopathological analysis with immunohistochemistry confirmed the diagnosis of mycosis fungoides. The patient was started on topical corticosteroids and retinoids. During the diagnostic workup, routine laboratory investigations revealed newly diagnosed diabetes mellitus. The patient was subsequently initiated on oral antidiabetic therapy. Under treatment, her glycemic control improved, and her cutaneous lesions stabilized.
Discussion
MF is characterized by dysregulated T-cell activation, leading to increased levels of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-17. These cytokines are also implicated in insulin resistance and β-cell dysfunction in DM. Chronic immune stimulation in MF could contribute to metabolic disturbances, potentially increasing the risk of DM.
Conclusion
This case highlights the importance of metabolic screening in patients presenting with unexplained dermatological symptoms. Further research is needed to explore potential links between mycosis fungoides and diabetes mellitus.

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EP547

JOINT3579
Diabetic retinopathy in normoalbuminuric patients with type 2 diabetes mellitus: any predictive factors?
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Introduction
As far as known today, microalbuminuria is an independent risk factor for the prevalence of diabetic retinopathy (DR) in patients with type 2 diabetes mellitus (DM). For this reason, the clinical significance of DR in normoalbuminuric type 2 DM patients may be overlooked. The aim of this study was to investigate the prevalence of DR and predictors for DR in normoalbuminuric patients with type 2 DM.
Methods
Descriptive cross-sectional study conducted over 3 months in department A of The National Institute of Nutrition of Tunis which included patients with type 2 diabetes mellitus.
Results
Sixty-two patients were included amongst whom 36 were women and 26 men. The characteristics of the patients were respectively: age: 58 ± 11 years, Body Mass Index: 28 ± 6.1 Kg/m^2. Twenty-seven patients had a DR as a complication of diabetes. The onset of diabetic retinopathy was correlated with age, with a statistically significant correlation ($P = 0.017$). There was no statistically significant correlation between DR and gender ($P = 0.54$), smoking status ($P = 0.7$), Body mass index ($P = 0.48$), duration of diabetes progression ($P = 0.12$), HbA1c ($P = 0.2$).
Conclusions
Our findings suggest that patients with normoalbuminuric type 2 DM also require close monitoring for the early detection of DR, for all patients especially in case of increasing age. There is no specific glycaemic or metabolic profile to prompt screening for DR.

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EP548

JOINT3658
Vitamin D status in type 1 diabetic tunisian patients: a case-control study
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Background
Vitamin D, a fat-soluble vitamin, is essential for calcium homeostasis and bone health, but emerging research highlights its broader role in immune function, inflammation, and metabolic regulation. Several studies have reported a high prevalence of vitamin D deficiency in individuals with type 1 diabetes (T1D).

Objective
The aim of this study was to assess 25-hydroxy vitamin D (25(OH)D) levels in Tunisian T1D patients, comparing them with those of healthy control subjects.
Methods
We conducted a case-control study including 50 patients with T1D and 50 healthy controls matched for age, sex and body mass index, recruited from the general population. All participants underwent measurement of serum (25(OH)D) levels.
Results
The median age was 26 years [21.00 – 31.75] for the diabetic group and 25 years [22.00 – 30.75] for the control group ($P = 0.95$). A slight female predominance was observed, with 56% ($n = 28$) of participants being female in both groups. The mean 25(OH)D level was 11.14 ± 6.49 ng/ml in the diabetic group and 11.67 ± 6.11 ng/ml in the control group, with no statistically significant difference between the two groups ($P = 0.67$). Vitamin D insufficiency, defined by 25(OH)D levels <30 ng/ml, was identified in 98% of diabetic patients and in all control subjects. A confirmed deficiency, characterized by 25(OH)D levels <20ng/ml, was observed in 92% of diabetics and 94% of controls. Severe deficiency, with 25(OH)D levels ≤ 10 ng/ml, was present in 56% of the diabetic group and 42% of the control group with no statistically significant difference between the two groups ($P = 0.32$).
Conclusion
The prevalence of vitamin D deficiency was particularly high in both groups, highlighting the need for preventive measures such as public awareness campaigns and the promotion of vitamin D fortification of foods.

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EP549

JOINT3670

Acute pancreatitis in type 1 diabetic patients: etiological and evolutionary profile

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Objective
This study aimed to describe the etiological and evolutionary profile of acute pancreatitis (AP) in type 1 diabetic (T1D) patients.
Patients and Methods
A retrospective descriptive study including 10 T1D patients who experienced at least one episode of AP during follow-up.
Results
The average age at T1D diagnosis was 19.7 ± 9.3 years, with a female predominance (60%). T1D was frequently first diagnosed through classic cardinal symptoms (50%) or spontaneous DKA (20%). In 10% of cases, T1D was diagnosed during an AP episode. AP occurred at an average age of 26.9 ± 14.9 years. AP was classified as stage E in 57.1% of cases, while stages A, B, or C were less frequently reported (14.3% each). Identified etiologies of AP included autoimmune causes (20%) and severe hypertriglyceridemia (10%). In 70% of cases, the underlying mechanism remained undetermined. Despite a favorable outcome after the first episode, AP recurrence was common in T1D patients, with a recurrence rate of 16.7%.
Discussion
The pathophysiological mechanism of AP in T1D patients remains poorly understood. The impact of AP on pancreatic tissue, already weakened by autoimmune destruction in T1D, may be more pronounced compared to non-diabetic individuals. Our study highlights an increased incidence of stage E AP and a higher recurrence rate in this population. Further studies with larger sample sizes are needed to provide more precise explanations.

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EP550

JOINT3747

Microbiota and type 2 diabetes: current status and future perspectives

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Introduction
Growing evidence underscores the pivotal role of gut microbiota (GM) in metabolic regulation, systemic inflammation, and insulin resistance, key factors in the development of type 2 diabetes (T2D). This systematic review aims to examine the causal relationship between GM composition and T2D, elucidate the underlying mechanisms, and explore potential microbiota-targeted therapeutic strategies for T2D management.
Materials and Methods
We performed a comprehensive literature review across PubMed, ScienceDirect, and Google Scholar to identify the most relevant studies. After removing duplicates, ten articles were included.
Results
Under normal conditions, the microbiota, particularly the GM, maintains a balanced state, ensuring a harmonious coexistence of its diverse microbial populations. Disruption of this balance leads to dysbiosis. In individuals with type 2 diabetes, GM composition is characterized by dysbiosis, which significantly impacts metabolic health and inflammation. Compared to healthy individuals, T2D patients exhibit notable alterations in their GM profile, including a reduction in beneficial butyrate-producing bacteria such as Faecalibacterium, Clostridium, and Akkermansia, along with an increase in opportunistic species like Escherichia coli and Bacteroides fragilis. The gut microbiota influences the progression of type 2 diabetes by increasing intestinal permeability, allowing harmful molecules such as lipopolysaccharides (LPS) to enter the bloodstream. This triggers systemic inflammation and disrupts insulin signaling. Additionally, GM alterations lead to changes in metabolite production, including an overproduction of branched-chain amino acids, imidazole propionate, and LPS, alongside a reduction in short-chain fatty acid (SCFA) synthesis. Given its critical role, GM modulation is considered a promising therapeutic target. Potential interventions include probiotics, prebiotics, synbiotics, and fecal microbiota transplantation.
Conclusion
In conclusion, gut microbiota plays a crucial role in the progression of type 2 diabetes (T2D) through various mechanisms. Future research should prioritize refining microbiota-targeted interventions, such as prebiotics, synbiotics, and fecal microbiota transplantation, to enhance T2D management and metabolic health.

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EP551

JOINT4013

Assessment of nutritional status in elderly diabetics in hospital

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Introduction
The assessment of the nutritional status of elderly diabetics is essential; it makes it possible to detect undernutrition which could increase morbidity and mortality and prolong the duration of hospitalization. The objective of this study was to evaluate the nutritional status of elderly diabetics.
Methods
This is a descriptive study carried out on 50 hospitalized elderly type 2 diabetics. The assessment of nutritional status was based on the Mini Nutritional Assessment (MNA) questionnaire.
Results
The average age of patients was 69.36 years with a female predominance (74%). The average BMI was 26.7 kg/m2. The average duration of diabetes progression was 15 years with an average HBA1c of 10.2%. Half of the patients aged between 65 and 80 years presented a risk of malnutrition (score: 17 to 23.5), while all subjects aged over 80 presented this risk. However, we did not find a correlation between age and nutritional status ($P = 0.44$). Nearly two thirds of women (60%) were at risk of malnutrition. This risk is twice as high as in men ($P = 0.04$). We did not find a correlation between the duration of diabetes and nutritional status.
Conclusion
Undernutrition in elderly diabetics is associated with increased morbidity and mortality and impaired quality of life. This observation justifies the imperative of an early assessment of nutritional status using the MNA questionnaire which must be part of the gerontological examination.

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EP551

JOINT4013

Assessment of nutritional status in elderly diabetics in hospital

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Introduction
The assessment of the nutritional status of elderly diabetics is essential; it makes it possible to detect undernutrition which could increase morbidity and mortality and prolong the duration of hospitalization. The objective of this study was to evaluate the nutritional status of elderly diabetics.
Methods
This is a descriptive study carried out on 50 hospitalized elderly type 2 diabetics. The assessment of nutritional status was based on the Mini Nutritional Assessment (MNA) questionnaire.
Results
The average age of patients was 69.36 years with a female predominance (74%). The average BMI was 26.7 kg/m2. The average duration of diabetes progression was 15 years with an average HBA1c of 10.2%. Half of the patients aged between 65 and 80 years presented a risk of malnutrition (score: 17 to 23.5), while all subjects aged over 80 presented this risk. However, we did not find a correlation between age and nutritional status ($P = 0.44$). Nearly two thirds of women (60%) were at risk of malnutrition. This risk is twice as high as in men ($P = 0.04$). We did not find a correlation between the duration of diabetes and nutritional status.
Conclusion
Undernutrition in elderly diabetics is associated with increased morbidity and mortality and impaired quality of life. This observation justifies the imperative of an early assessment of nutritional status using the MNA questionnaire which must be part of the gerontological examination.

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EP552

JOINT102

Type 2 diabetes diagnosed after 10 years of insulin therapy

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Background
Diabetes is a major global health problem, Until recently, immune-mediated type 1 diabetes mellitus was the only type of diabetes considered prevalent among children, now type 2 diabetes accounts for about 15% to 45% of all newly diagnosed cases of diabetes in children and teenagers (1). This could be due to the pandemic of obesity in childhood (2).
Case Report
29 years old male patient diabetic 10 years ago presented with uncontrolled diabetes HbA1c 8.4 % on multiple daily injections. BMI 32 kg/m^2 and had acanthosis nigricans on the neck. We introduce metformin 2gm/day and decrease dose of insulin. He came on the next week with decreased attacks of hypoglycemia. We ordered C peptide and it was found normal hence we gave dulaglutide 1.5 weekly with metformin and decreased insulin gradually based on blood glucose. Three months later we stopped insulin and patient BMI 26 kg/m^{2}and HbA1c 5.8 % on metformin and dulaglutide.
Discussion
Type 2 diabetes mellitus had always been considered a disease of older adults, while type 1 diabetes mellitus, was considered a disease of children (3). That is why our patient was misdiagnosed and managed as a case of type 1 diabetes. There has been an increase in the incidence of T2DM in children and adolescents. This is due to a rise in prevalence of obesity in adolescents (4). Presence of obesity, acanthosis nigricans and normal C peptide level confirmed our diagnosis(5)
Conclusion
We should raise awareness among clinicians that type 2 can occur in young adult and children to avoid mismanagement of diabetes.
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EP553

JOINT2185

Impact of vitamin d and vitamin d receptor activator in diabetic nephropathy

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Vitamin D is a hormone which is involved in many physiological processes in addition to bone metabolism and the muscular system. Based on several animal and human studies, it has been established that vitamin D plays an important role in the development of diabetic nephropathy (DN). DN is a frequent and severe chronic microvascular complication of diabetes mellitus (DM). As such, DN and cardiovascular complications are considered the main risk factors for the death of patients with DM. Recent studies have shown the renoprotective effect of vitamin D and its receptor (VDR) based on its effect on endothelial function, preservation of podocytes, anti-inflammatory effect, and direct influence on the renin-angiotensin aldosterone system. The renoprotective effect of Vitamin D has been shown to potentially delay the onset of DN, which is the main cause of end stage renal diseases (ESRD). The impact of vitamin D on the recovery of already existing kidney damage is debatable and doubtful. Increasing evidence has shown that the VD/VDR interaction possesses a series of renoprotective effects in DN patients based on the anti-proteinuric, anti-fibrotic, and anti-inflammatory effect, as well as the preventive effect of podocyte damage. Based on this important renoprotective effect, important data for therapeutic and effective methods for DN have also been presented. It was performed a structured search of published research literature for several databases regarding the impact of vitamin D on the pathophysiology of diabetic nephropathy as well as its therapeutic implications in terms of renoprotection of VD and VDRA in animal research and human clinical research as RCT, reviews and meta-analyses over the last decade.
Keywords
diabetic nephropathy, Vitamin D, Vitamin D receptors, Vitamin D receptor activator, renoprotection

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EP554

JOINT1508

Targeted, rapid glycaemic control and its potential adverse outcomes

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Introduction
Following delivery, insulin sensitivity doubles, and breastfeeding further lowers insulin needs, increasing the risk of severe maternal hypoglycaemia [1], particularly with prior hypoglycaemia unawareness [2]. This case describes a 28-year-old woman with uncontrolled type 1 diabetes (T1D) in early pregnancy, where tight glycaemic control during gestation led to fatal postpartum hypoglycaemia.
Case Presentation
The patient's pre-pregnancy HbA1c level was >10%, decreasing to 7.1% by 13 weeks of gestation and further to 5.7% at 31 weeks. Treatment with daily subcutaneous injections of insulin degludec and ultra-fast-acting insulin aspart was continued at the woman's request. At 31 weeks of gestation, the woman's continuous glucose monitor (CGM) indicated normoglycaemia 81% of the time, hyperglycaemia 20%, and hypoglycaemia 9%. Delivery at 37 weeks of gestation was uneventful, a healthy preterm infant weighing 2355 grams was born. The patient began breastfeeding promptly after delivery. Within 24 hours after delivery, the woman was found unconscious and without vital signs. CGM recorded hypoglycaemia at 2.2 mmol/l and later as low as 0.1 mmol/l. Prolonged hypoglycaemia likely contributed to altered consciousness, acute respiratory failure, and subsequent cardiac arrest.

Discussion
Guidelines from the American Diabetes Association and the National Institute for Health and Care Excellence recommend achieving a HbA1c level $<6.5\%$ before conception [3]. Poor glycaemic control and altered insulin sensitivities during pregnancy increase the risk of hypoglycaemia unawareness. Additionally, sudden changes in diabetes control can significantly impact pregnancy outcomes, increasing the risk of maternal and neonatal complications [4].
Conclusion
This case highlights the importance of pregnancy planning for women with T1D and hypoglycaemia unawareness, particularly after delivery when insulin sensitivity undergoes dramatic changes.
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JOINT2478

Unbalanced diabetes leads to orbital myositis with oculomotor nerve palsy (ONP)

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Introduction
Orbital myositis remains a rare condition that typically presents in an idiopathic acute form in young adult females. However, atypical forms related to specific autoimmune and inflammatory conditions are increasingly recognized. We report the case of a female patient with poorly controlled diabetes who developed acute orbital myositis with oculomotor nerve palsy.
Observation
A 50-year-old woman with 10 years of poorly controlled diabetes mellitus was referred to the Endocrinology department of IBN SINA university hospital in RABAT for further treatment of severe acidosis decompensation due to a medication discrepancy. During hospitalization, the patient developed sudden-onset ptosis associated by pain in the left orbit. Ophthalmological examination of the left eye revealed oculomotor paralysis, including divergent strabismus, diplopia, and mydriasis. An emergency cranio-orbital CT scan was performed and found to be normal. Magnetic resonance imaging (MRI) of the orbit showed homogeneous thickening of the right medial oculomotor and the levator palpebrae superioris muscles of the left eye, with no other associated abnormalities, suggesting myositis of probably inflammatory origin. Biological tests revealed a moderate inflammatory syndrome. Etiological work-up, including thyroid, immunological, and infectious tests, was negative. The diagnosis of orbital myositis in a patient with unbalanced diabetes was therefore established. The patient was started on oral corticosteroids (1 mg/kg/day) and referred to the ophthalmology department for further management.
Discussion and Conclusion
Diabetic oculomotor nerve palsy (ONP) is a complication of diabetes mellitus with distinct clinical sequelae that can affect a patient's quality of life. Recent studies have confirmed that microvascular factors are responsible for nerve damage, leading to a loss of nerve function. Hyperglycemia causes microvascular alterations that reduce nerve perfusion and induce endoneurial hypoxia. Therefore, vasa nervorum dysfunction contributes to nerve ischemic injury during the development of diabetic neuropathy. Orbital myositis is a condition that most often occurs in middle-aged women. Its etiopathogenesis remains incompletely understood. The association with certain autoimmune diseases and small-vessel vasculitis suggests an immunological origin. Corticosteroid therapy remains the first-line treatment, with a good response, and an immunosuppressant can be added if necessary.
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EP556

JOINT292

Barriers to achieving glycemic control in type 2 diabetes mellitus: focus on therapeutic adherence

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Background
Diabetes management is a multifaceted challenge influenced by treatment patterns, adherence to therapy, and patient-specific factors. Achieving optimal glycemic control is essential to reducing the risk of microvascular and macrovascular complications, yet many patients fail to meet recommended targets. Understanding the interplay between treatment patterns, adherence barriers, and their impact on glycemic control can provide valuable insights into improving diabetes care and outcomes.
Methods
This was a descriptive cross-sectional study conducted on 80 patients with type 2 diabetes mellitus (T2DM) patients who had been followed at the endocrinology outpatient clinic of Fattouma Bourguiba University Hospital in Monastir, Tunisia, for over six months.
Results
Among the 80 patients studied, 65% were female, with a mean age of 57.9 years. The average duration of diabetes was 12.83 years. Diabetes was complicated in 63.8% of cases, and 51.3% of patients were not meeting therapeutic glycemic targets. The mean HbA1c was $8.91\% \pm 2.08$. Microvascular complications were present in 57% of patients, and 23% were at secondary prevention. Adherence to antidiabetic treatment was influenced by several factors affecting glycemic control. These factors included hypoglycemia (10%), therapeutic inertia (2.5%), negligence (3.8%), and financial issues (3.8%). Additionally, digestive intolerance (12.5%), visual impairment (2.7%), and treatment unavailability (2.3%) further hindered patients' ability to follow their prescribed regimen. Moreover, forgetfulness (15%) and medication errors (1.5%) were also significant barriers.
Conclusion
Achieving glycemic control in patients with T2DM remains a significant challenge. Future strategies should focus on enhancing patient education, providing better access to medications, and addressing factors that hinder adherence.

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EP557

JOINT659

Peri-esophageal infections due to foreign body in the esophagus: a serious complication in diabetic patients

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Introduction
Peri-esophageal infection is the most concerning complication of traumatic esophageal perforations. These perforations occur in 1-4% of cases involving esophageal foreign bodies, either spontaneously or during rigid endoscopic extraction. They can lead to severe infections such as cervical cellulitis and mediastinitis, posing life-threatening risks.
Objective
This study aims to analyze the specifity of peri-esophageal Infections clinical, paraclinical characteristics and their therapeutic management in diabetic patients.
Methods and Observations
A retrospective analysis of four cases with an age varying between 4 and 60 years, all 4 patients were diabetics and admitted for accidental ingestion of sharp foreign bodies. Patients presented with persistent solid dysphagia and subfebrile states.

Thoracic xray confirmed foreign bodies in three cases and suspected complications in one case. Endoscopic extraction identified esophageal perforations, while CT scans revealed cervical cellulitis (2 cases), prevertebral abscess (1 case), peri-esophageal abscess (1 case), and mediastinitis (1 case). Management included broad-spectrum antibiotics, absolute diet, surgical repair, drainage, or tracheotomy, depending on the case. All patients recovered fully over a three-year follow-up.
Conclusion
Clinicians must always consider esophageal perforation in cases of foreign body ingestion. Early imaging and appropriate therapeutic strategies are essential to prevent severe outcomes

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EP558

JOINT3369
Benefits of SGLT2 inhibitors on cardiovascular and renal health in clinical practice

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Background
SGLT2-inhibitors have revolutionized the management of type 2 diabetes mellitus by promoting urinary glucose excretion, thereby reducing blood glucose levels. Beyond their role in diabetes management, these agents have shown promise in mitigating cardiovascular and renal complications. This study aimed to evaluate the effects of SGLT2-inhibitors on glycemic control, renal function, and metabolic parameters in patients with diabetes.
Methods
A descriptive retrospective study was conducted at the Endocrinology Department of Farhat-Hached University Hospital in Sousse, Tunisia. The study included diabetic patients evaluated over two periods: P1 from January to March 2024 and P2 from March to June 2024. They were divided into two groups: those receiving SGLT2-inhibitor treatment in P2 (G1) and a control group (G2). All patients underwent fasting blood glucose (FBG), glycated hemoglobin (A1c), lipid profile, renal assessment, and microalbuminuria testing.
Results
A total of 72 patients were evaluated. G1 included 36 patients, and G2 also consisted of 36 patients. The mean age of participants was 64 ± 9.26 years in G1 and 62 ± 8.64 years in G2, with no significant difference ($P = 0.36$). Both groups had a female predominance (55.5%). Chronic imbalance of diabetes under insulin was the most common reason for admission (52.8%). During P1, no significant differences were observed in A1c, FBG, creatinine, or microalbuminuria between the groups. However, during P2, G1 demonstrated significantly lower A1c ($9.07\% \pm 1.82\%$ vs. $10.16\% \pm 1.40\%$, $P = 0.007$) and FBG levels (1.51 ± 0.57 g/l vs. 2.36 ± 0.80 g/l, $P < 10^{-3}$) compared to G2. Microalbuminuria was also significantly reduced in G1 (65 ± 111.18 mg/24h vs. 492 ± 1137.80 mg/24h, $P = 0.032$). No significant differences were noted in lipid profiles or creatinine levels between the groups.
Conclusion
SGLT2-inhibitors significantly improved glycemic control and reduced micro-albuminuria in diabetic patients, highlighting their potential to slow the progression of chronic kidney disease (CKD). Their efficacy and safety across CKD stages 1 to 4 position them as a promising therapeutic option for managing diabetes and its renal complications.

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EP559

JOINT40
Cardiometabolic profile in type 2 diabetics with vitamin D deficiency

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Objectives
The diabetic patients are subjects at high cardiovascular risk. Vitamin D plays a significant role in minimizing chronic metabolic syndromes such as type 2 DM and cardiovascular diseases. Vitamin D deficiency increased CVD risk in poor glycemic control in diabetics. The objective of our study is to describe metabolic profile in type 2 diabetics with vitamin D deficiency and its associations with CVD.
Methods
Included a total of 64 type 2 diabetics in whom a vitamin D dosage was carried out. The presence of CVD was determined based on medical records. Control of diabetes was assessed based on HbA1C levels.
Results
The average age of our patients was 57.04 years ± 11.05. 45 patients had poor glycemic control and the other had good glycemic control. Patients with poor control had a significantly higher level of total cholesterol (TC), triglyceride (TG), and non-high-density lipoprotein lipase cholesterol (non-HDL-C), compared to patients with good glycemic control. Was observed significant negative correlation of vitamin D with lipid markers. Hyperuricemia was present in 20 patients. 65% of patients had high blood pressure under medication, 21 patients were on ACE- inhibitor or ARB, 9 on calcium channel blockers, 5 on thiazide diuretics and 7 on beta blockers.
Conclusions
Patients with T2DM who are at risk for diabetic complications under poor glycemic control should be advised for vitamin D measurement, and vitamin D supplementation may reduce the risk of CVD.

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EP560

JOINT1181
Hypoglycemia and autoimmune diabetes; a cause not to be

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Introduction
Hypoglycemia is a metabolic emergency that can increase micro and macrovascular complications through glycemic variability. The diagnostic approach differs according to the type of Through this observation, we report a racist cause of hypoglycemia in a type 2 diabetic subject.
Observation
This is a 34-year-old patient with type 1 diabetes since childhood, treated with basal bolus analogues with U100 glargine in the evening and insulin aspart before each meal, who presented in consultation for exploration of refractory hypoglycemia. The patient presented with hypoglycemia at 0.3 g/l, generally in the morning and not felt because of associated dysautonomia. This prompted a blood glucose holter test, which revealed hypoglycemia at dawn and late postprandially. The 1st-line workup for organic damage or autoimmunity was strictly normal, except for antiinsulin AC positivity. This positive assay incriminates first and foremost the type of insulin with an immunogenic effect in type 1 diabetics, a high-risk area. Our attitude was to switch to the least immunogenic and most stable insulin, i.e. degludec, with the result that hypoglycemic episodes disappeared completely.
Discussion and conclusion
Insulin is an immunogenic protein, and this same protein is the main autoantigen responsible for the onset of type 1 diabetes. When administered exogenously, i.e. in insulin-requiring subjects of any type of diabetes, the latter can lead to a pathogenic reaction that is all the more exaggerated when it occurs on a background of autoimmunity. Since the introduction of the latest-generation insulin analogues, the frequency of these reactions has fallen sharply. The use of these insulins should be considered when the etiological search for hypoglycemia is undetermined.

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EP561

JOINT2216
Pancreatic diabetes: diagnostic, therapeutic, and evolutionary particularities

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Introduction
Pancreatic diabetes, or type 3c diabetes, is a specific form of diabetes caused by pancreatic dysfunction due to diseases affecting its insulin production capacity. It remains underdiagnosed, often leading to a delayed diagnosis. The aim of this study is to analyze the diagnostic, therapeutic, and evolutionary particularities of this form of diabetes.
Materials and Methods
This is a retrospective descriptive study including 12 patients followed for pancreatic diabetes at the endocrinology department of Charles Nicolle Hospital in Tunis between 2019 and 2024.

Results
The median age was 60 ± 11.6 years, with a male-to-female ratio of 11.5. The median duration of diabetes was 5 ± 6.7 years. Two patients had pancreatic cancer, while ten had pancreatitis, including four with acute pancreatitis and six with chronic pancreatitis. Additionally, four patients had a history of pancreatic surgery. Half of the patients were treated with basal human insulin and basal insulin analogs, and a quarter required rapid insulin. All patients had poorly controlled diabetes, with a fasting blood glucose level of 2.46 ± 1.56 g/l and an HbA1c of 10.2 ± 2.17%. Four patients exhibited unstable diabetes, with hypoglycemia occurring in approximately 30% of cases. Macrovascular and microvascular complications were present in half and one-third of the patients, respectively.
Conclusion
Pancreatic diabetes remains a rare form of diabetes that requires early diagnosis. Its management is challenging due to its instability, the very high risk of hypoglycemia, and its association with serious conditions, such as chronic pancreatitis or pancreatic tumors.

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EP562

JOINT1184

Successful treatment of 138000 patients with multimodal drug approach

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Background and Aim
Guidelines of diabetes societies for type II DM in terms of dose and drug escalation are misleading. Fear of hypoglycemia has prevented early elaboration of multiple effective drugs. Clever, circadian based combination of drugs with low hypoglycemia risk added to slow release Glyclazide, suppressing Gut microbia, targeting Glut-4 expression, adding appetite suppressors have shown new horizons in DM treatment with complete normalization of HbA1C irrespective of baseline HbA1C, possibility of treatment cessation.
Methods
Auditory Insulin tolerance test explained before was used to predict effectiveness. In eight years of study, hundred and thirty eight thousands patients received Sitagliptin 100mg at noon, Glucophage 500mg and Empagliflozin 12.5mg BID, slow release Gliclazide 60mg TID. In small pilot studies of 30 patient groups superiority of Sitagliptin at noon, morning and afternoon for Empagliflozin and Metformin, TID slow release Gliclazide were shown based on circadian rhythm. Two weeks later addition of Metronidazole, Bismuth and Doxycycline for ten days suppressed the gut diabetogenic flora. A1C below 6, 5.5 and 5 were reacted by omitting 1, 2 or 3 gliclazide after each 3 months cycle.
Results
Ninety-four and 87% attained HBA1C under 6.5 and 6 within 3 to six months. These values remained for a mean of 24 months (range 6-78). At least 23% i.e. 14490 patients could discontinue their medication with a relapse rate of 32%. Less than 0.2% needed additional insulin. Four to eight percent did not respond enough and were regarded as special refractory subgroups due to MODY, Glut mutations or downstream genes. Neither response nor side effects were correlated with duration of disease, previous drug exposure, A1C at begin, inter current disease, age, sex… Thousands of patients were lost from follow up above 36 months but results remain reliable for the rest.
Discussion
We have shown that type II diabetes is a potentially curable disease with an acceptable percentage. This treatment may become the gold standard of type II diabetes at any stage as it is easy with good compliance, abolishes additional insulin, very cost effective, very low need for surveillance and uniformly effective. It covers all theoretical and empirical sorts of resistance. All patients maintain on 2 tablets every 8h. Gliclazide 60 1 1 1 (Empagliflozin + Metformin) 500/12.5 1 1 Sitapliptin 100 1

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EP563

JOINT287

Diabetes and self-harm: a struggle beyond the surface

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Background
The psychological burden of diabetes remains largely underestimated. Often perceived as an intimate tragedy, it can manifest outwardly through self-destructive behaviors such as self-harm. Diabetic patients are consequently at a heightened risk of mortality associated with severe psychiatric disorders, including suicide. Early and tailored intervention is essential to mitigate these adverse outcomes.
Case Reports
Case 1: A 50-year-old woman with a long-standing history of type 1 diabetes since childhood, managed with insulin therapy, experienced multiple hospitalizations due to poorly controlled diabetes. Her medical history included a lacunar ischemic stroke and hypertension. During her hospital stays, she presented with polymorphic skin lesions, including excoriations, linear scratches, and occasionally lichenified ulcers, predominantly on her arms and legs. These lesions were attributed to intense pruritus. A skin biopsy excluded cutaneous leishmaniasis. The lesions were suspected to be exacerbated during episodes of metabolic decompensation. Following the exclusion of systemic causes, a diagnosis of psychogenic pruritus was established. Case 2: A 48-year-old woman with a two-year history of type 2 diabetes and hypertension presented with a four-month history of skin lesions localized to her legs, characterized by ulcers and linear scratch marks. A skin biopsy revealed no abnormalities. The patient reported experiencing severe itching episodes, particularly during acute metabolic decompensations.
Conclusion
Psychiatric disorders are significantly more prevalent among diabetic patients compared to the general population. Routine screening for anxiety and depressive symptoms is imperative in this vulnerable group to ensure timely and effective management, thereby reducing their psychological and physical burden.

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Endocrine Related Cancer

EP564

JOINT540

Incidence and survival of neuroendocrine neoplasia in the maltese islands – a population-based study

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Introduction
The global incidence of neuroendocrine neoplasms (NENs) is increasing worldwide, however most studies are based on cancer-registry data, with different data collection methods, making it difficult for cross-country comparisons. Our study aims to analyze the incidence and survival of NENs in a well-defined population of the Maltese islands based on histological and radiological data.
Methods
A retrospective analysis of patients diagnosed histologically or radiologically with NEN at Mater Dei Hospital, the only central national service hospital in Malta, between 1st January 2015 and 31st December 2020, was performed. Detailed clinical, histopathological and radiological data was obtained. Patients were followed up till 31st December 2024 or death, whichever came first. Age- and sex-adjusted standardized incidence rates (SIRs), prevalence and mortality rates were calculated.
Results
A total of 435 patients were identified, of which 237 (54.48%) were males. The median age at diagnosis was 68 years (IQR 59-74). The overall age-adjusted SIR was 8.78/100,000/year, with a male-to-female ratio of 1.2:1. The age-adjusted SIR of bronchopulmonary NEN (BP-NEN) was 2.77/100,000/year whilst that of gastro-enteropancreatic NEN (GEP-NEN) was 4.02/100,000/year. The 6-year limited duration prevalence rate was 43.7/100,000. The most frequent location of GEP-NEN was the pancreas (11.26%) followed by the appendix (7.13%) and rectum (5.98%) whilst the duodenum (2.76%) and the oesophagus were the less frequent (0.69%). Well-differentiated Grade 1 GEP-NEN prevailed at 63.74%, followed by Grade 2 at 8.24% and Grade 3 at 7.69%. Poorly differentiated neuroendocrine carcinoma was found in 7.14% of the patients. Most tumours were localized (57.59%) with 28.02% having disseminated disease at presentation. Distant metastasis were most commonly observed in NEN of the jejunum and ileum (27.45%) and the rectum (21.57%). Two hundred and forty-five patients (56.32%) passed away during the study period. The standard mortality ratio (SMR) of all NEN was 4.59 (95% CI 4.02-5.17). A higher mortality was observed in BP-NEN, which had an SMR of 6.52 (95% CI 5.35-7.68), compared to GEP-NEN, which had an SMR of 3.68 (95% CI 2.3-4.56). Univariate analysis revealed a statistically significant association between mortality and male gender (p 0.001), age at diagnosis ($P < 0.001$), primary site ($P < 0.001$), grade ($P < 0.001$), stage ($P < 0.001$) and Ki67 ($P < 0.001$).

Conclusion
This is the first study reporting the incidence, prevalence and survival rates of NEN in the Maltese Islands. Our findings suggest that GEP-NEN and BP-NEN incidence and survival in the Maltese Islands is comparable to that observed in other countries.

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EP565

JOINT1569

V804M RET mutation screening and familial medullary thyroid carcinoma in the Maltese Islands

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Introduction
Multiple Endocrine Neoplasia Type 2 is linked with activated germline mutations of the RET proto-oncogene, one of which, Val804Met (V804M) mutation has been classified as moderate risk to develop medullary thyroid carcinoma (MTC) according to the American Thyroid Association. Our study aims to investigate a cohort of Maltese patients carriers for V804M mutation and compare their clinical, biochemical and histopathological characteristics.
Methods
Genetic screening of relatives of the index case, who was diagnosed with homozygous V804M mutation in the RET gene in 2022, was done in Malta, between November 2022 and December 2024. Detailed clinical, radiological and histopathological data was obtained for each patient who had the mutation.
Results
A total of 57 patients were screened, of which 31 (54.4%) were positive for V804M mutation. Eighteen patients (58.1%) were males and only 1 patient (index's case brother) was homozygous for this mutation. The median age at diagnosis was 44 years (IQR 26.0-52.5). Five (16.1%) were 1st degree relatives to the index case, 11 (35.5%) were 2nd degree, 12 (38.7%) were 3rd degree and 2 (6.5%) were 4th degree. The index case had a co-existing somatotropinoma. No patients had phaeochromocytoma, hyperparathyroidism, Hirschsprung disease or cutaneous lichen amyloidosis throughout the study period. The median initial calcitonin was 5pg/ml (IQR 3.7-17.0). The highest initial calcitonin was observed in the index case and her brother, (4300pg/ml and 403pg/ml, respectively). Thirteen (42.0%) patients underwent surgery. Eleven (84.6%) had MTC present on histological analysis, whilst one had only C-cell hyperplasia and another had neither MTC nor C-cell hyperplasia. One of the patients with MTC had an undetectable pre-operative calcitonin level. The median size of the largest focus of MTC was 7mm (IQR 2.5-12.5). Two patients (15.4%) had concurrent papillary thyroid carcinoma. Distant metastasis was only observed in the index case, whilst lymph node metastasis was present in 2 patients (30.8%). Post-operative calcitonin remained elevated in 3 cases at 525pg/ml, 150pg/ml and 10ng/ml, respectively. None received adjuvant radiotherapy or chemotherapy. No patient died during the study period.
Conclusion
This is the first study evaluating carriers of V804M RET mutation in the Maltese Islands. Despite most studies recommend total thyroidectomy based on elevated calcitonin level in carriers, our study suggests that MTC can be present even at undetectable calcitonin levels. However, further screening of the relatives of the index case is still undergoing, which can enhance our understanding of the natural history of this condition.

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EP566

JOINT2144

Usefulness of the braf gene study in the evaluation of the thyroid nodule

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Introduction
Fine needle aspiration puncture (FNA) is the method of choice for the study of the thyroid nodule. However, its diagnostic yield decreases in case of indeterminate cytological results. Our aim was to evaluate the usefulness of molecular study of the BRAF gene in thyroid nodule aspirate samples in deciding the therapeutic attitude.
Material and Methods
Retrospective observational study of 51 patients evaluated at the Thyroid Nodule consultation of the Hospital Universitario Clínico San Cecilio who underwent FNA and BRAF gene sequencing on thyroid nodule between October 2019 and February 2024.
Results
Thirty-five females and 16 males were studied. The mean age of the sample was 52.8 $\pm$ 12.5 years. The cytological results of FNA of the thyroid nodule according to the Bethesda system were: 66.7% BIII, 11.8% BV, 9.8% BIV and 3.9% BII, 7.9% BI. BRAF V600E mutation was present in 17.6% of the sample. 29 patients had undergone surgery and 18 of them had papillary thyroid carcinoma on pathology. In the intervened patients, total thyroidectomy was more frequent than haemithyroidectomy in those patients with mutated BRAF gene ($P = 0.001$) and pathological anatomy of malignancy more frequent in those with BRAF gene mutation ($P = 0.026$). In patients with Bethesda III and BRAF gene mutation, the decision to perform total thyroidectomy compared to haemithyroidectomy was more frequent ($P = 0.006$) as well as an anatomopathological diagnosis of papillary thyroid carcinoma of the surgical specimen compared to benignity ($P = 0.055$).
Conclusions
The study of mutations in the BRAF gene is useful for the therapeutic decision of thyroid nodules with indeterminate cytological results, as well as to determine the extent of thyroid surgery.

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EP567

JOINT2330

Diffuse large B-cell lymphoma leading to polyendocrine involvement (pituitary, adrenal, and thyroid)

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Introduction
Diffuse large cell B lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin's lymphoma (30%). Its clinical presentation is highly heterogeneous and endocrine involvement is a rare manifestation. Non-Hodgkin's lymphomas account for 3% of intracranial tumours. DLBCL is an even rarer cause of metastatic pituitary infiltration (<0.5%).
Observation
We report the case of a 54-year-old patient hospitalized for altered general condition and B symptoms. The initial work-up revealed low TSH and low T4, prompting further assessment of the other pituitary hormones, confirming the presence of thyrotropic, corticotropic and somatotropic insufficiencies, disconnection hyperprolactinaemia, and diabetes insipidus. Pituitary MRI was consistent with hypophysitis. The infectious and autoimmune work-up was unremarkable. PET-18FDG revealed pathological hypermetabolism of the left adrenal gland, pituitary gland, thyroid, subdiaphragmatic lymph nodes and subcutaneous nodules. The adrenal lesion was suspicious on contrast-enhanced CT, with plasma metanephrine levels normal. Thyroid ultrasound suggested thyroiditis with weakly positive anti-TPO antibodies. High LDH levels (936 IU/l, normal < 225), rapidly worsening pancytopenia and splenomegaly on ultrasound raised suspicion of haemopathy. A biopsy of the subcutaneous nodules finally led to the diagnosis of DLBCL. Corticotropic, thyrotropic insufficiencies and diabetes insipidus were managed with appropriate hormonal replacement therapy, and R-CHOP chemotherapy was rapidly initiated. After four treatment cycles, follow-up pituitary MRI and FDG-PET scan showed a complete morphometabolic regression of adrenal, pituitary, subcutaneous, radicular, lymph node, and bone involvement. The loss of hypersignal of the posterior pituitary gland persisted on MRI. Hormone replacement therapy remained necessary.
Conclusion
A haemopathy should be sought in cases of suspected secondary hypophysitis. The literature reports very few cases of DLBCL with synchronous involvement of several endocrine glands, and their prevalence is yet to be determined. A multidisciplinary collaboration between endocrinologists, haematologists and oncologists is essential to optimise patient management.

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EP568

JOINT2029

Bone metastases revealing a follicular carcinoma of the thyroid

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Introduction
Follicular thyroid carcinoma represents 5 to 8% of malignant thyroid tumors and 10 to 20% of differentiated thyroid cancers. It is characterized by the frequency of visceral metastases, particularly bone metastases.
Aim
The aim of our work is to study the clinical aspects, and the therapeutic and evolutionary modalities of metastatic vesicular carcinomas of the thyroid, through 4 observations with review of the literature.
Material and Methods
We report 4 cases of bone metastases revealing follicular thyroid carcinoma collected from a total of 30 patients treated for follicular thyroid carcinoma treated in the ENT and CCF department of over a period of 24 years.
Results
The average age was 51 years (35–72 years) with a female predominance (three women and one man). The reason for consultation was bone pain in 3 cases, a pathological fracture in one case. The ENT examination showed anterior cervical base swelling in 3 cases and was normal in one case. The cervical ultrasound showed thyroid nodules in all cases with malignancy criteria in 2 cases. Bone metastases were lumbar in three cases and femoral in one case, all confirmed by bone biopsy. The diagnosis of associated pulmonary metastasis was made by bronchial biopsy in one case. Treatment was based on total thyroidectomy associated with central lymph node dissection. The anatomopathological examination confirmed the diagnosis of follicular carcinoma in all cases. All patients underwent IRA therapy and were put on hormone-restricting therapy. Radiochemotherapy was indicated in the patient with bone and pulmonary metastases. The outcome was favorable in two cases; one patient was lost to follow-up and one patient died.
Conclusion
The presence of metastases in association with follicular thyroid cancer worsens the prognosis. Bone localization is the majority. Its management is multidisciplinary. Treatment consists of total thyroidectomy with excision of the metastatic lesion, if possible. Depending on the functional impact of the metastases, treatment will be supplemented by the administration of radioactive iodine and/or external radiotherapy. Hormonal inhibitory treatment is systematic in all cases.

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EP569

JOINT1614

Autoimmune endocrinopathies associated with the use of immune checkpoint inhibitors: a clinical case of a combination of primary hypothyroidism due to destructive thyroiditis and diabetes mellitus

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Introduction
Immune checkpoint inhibitors (ICIs) have transformed cancer treatment by enhancing the immune system's ability to recognize and destroy cancer cells. These drugs target regulatory pathways in T-cells, particularly programmed cell death protein 1 (PD-1) and its ligand PD-L1, which can allow cancer cells to evade immune detection. While ICIs have demonstrated significant success in improving survival rates across various cancers, their use is often associated with autoimmune adverse events (AIAEs). Among these, endocrinopathies are particularly common, as the heightened immune response can sometimes attack healthy endocrine organs, leading to conditions such as thyroiditis and diabetes mellitus.
Materials and Methods
In 2018, at the age of 33, Patient T. underwent surgical excision of melanoma in the right subclavian region. Disease progression led to further surgeries in May 2021, including right-sided axillary-subscapular-subclavian lymphadenectomy, left kidney resection, and liver biopsy. In December 2022, the patient was prescribed prolgolimab, a human monoclonal antibody that binds specifically to PD-1, inhibiting its interaction with PD-L1 and PD-L2 to prevent tumor cells from evading the immune system. In January 2023, while undergoing oncoimmunotherapy, the patient reported symptoms of severe thirst, frequent urination, and hyperglycemia, with initial blood glucose levels reaching 40.9mmol/l. He was promptly hospitalized in intensive care, where a diagnosis of mixed-genesis ketoacidosis with cerebral edema was made. Basal-bolus insulin therapy was initiated to manage blood glucose levels. Further evaluation at the National Medical Research Center of Endocrinology in June 2023 revealed significant endocrine findings: C-peptide levels at 7.0pmol/l (reference range: 100–1100), insulin autoantibodies at 3.4IU/mL (0–10), GAD autoantibodies at 0.1U/mL (0–10), and pancreatic beta cell autoantibodies at 0.35 (0–1). Insulin therapy was adjusted to optimize glycemic control, and the patient's glucose levels were stabilized within individually targeted ranges. Approximately one year after the diabetes mellitus diagnosis, and following three courses of immune checkpoint therapy (nivolumab + ipilimumab), the patient developed destructive thyroiditis in its hypothyroid phase. Laboratory values indicated TSH at 56.9mU/l (0.27–4.2), free T4 at 2.71pmol/l (12–22), and free T3 at 1.65pmol/l (3.1–6.8). Levothyroxine sodium was initiated at 75mg/day, with gradual titration to 112.5mg/day to achieve targeted hypothyroidism compensation.
Results
This case highlights the complex immune response triggered by ICIs, as evidenced by the sequential onset of two significant autoimmune endocrinopathies-diabetes mellitus and thyroiditis. The varied timing of these events underscores the need for diligent monitoring for endocrine disorders throughout different phases of ICI therapy.

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EP570

JOINT526

Hyperprolactinemia and cancer risk: a swedish population-based cohort study

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Background
Concerns about the potential link between hyperprolactinemia (HPL) and cancer primarily arise from prolactin's (PRL) role in promoting cell proliferation and the increased expression of PRL receptors in various cancer types. However, only a few studies have examined cancer risk in patients with HPL.
Purpose
To investigate cancer risk in a nation-wide cohort of patients with a diagnosis of HPL, with special emphasis on breast cancer.
Methods
In a Swedish population-based cohort study, we used nationwide registries to identify 3837 patients with HPL treated with dopamine agonists (DA) diagnosed between 2006 and 2019, along with 38370 controls matched by age, sex and county of residence. Cancer outcomes (overall and specific types) as registered in the Swedish Cancer Registry, were analyzed using Cox regression, internally stratified by the matching variables and additionally adjusted for diabetes mellitus, obesity, smoking, alcohol overconsumption, hormone replacement therapy and educational level to estimate adjusted hazard ratios (aHRs).
Results
During a median follow-up time of 6.1 years (interquartile range [IQR] 3.4-9.6), 168 (4.6%) new cases of cancer were identified in patients with HPL and 1608 (4.4%) in the control group (aHR 1.05 [95% CI: 0.89-1.23]). Twenty-eight (0.7%) patients (all women) in the HPL group and 267 (0.7%) in the control group developed breast cancer, (aHR 1.02 [95% CI: 0.68-1.51]). Similarly, there was no increased risk of any other site-specific cancer.
Conclusions
In this nation-wide cohort study of patients with DA-treated HPL, no increased risk of overall cancer, breast cancer or other site-specific malignancies was observed.

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EP571

JOINT2618

Cowden syndrome: a case report

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Cowden syndrome, also known as multiple hamartoma syndrome, is a rare condition with an autosomal dominant inheritance pattern, characterized by cutaneous and mucosal lesions associated with various neoplasms.
Case Presentation
This is the case of a 47-year-old woman who was admitted to our Endocrinology department in February 2024 for the management of profound hypothyroidism (FT4 = 0, TSH > 51) associated with hypocalcemia (1.6 mmol/l) resulting from the discontinuation of her replacement therapy. In her personal medical history, the patient underwent a total thyroidectomy for minimally invasive carcinoma in 2008, complicated by permanent hypoparathyroidism, and has a history of fibrocystic breast disease. On examination, macrocephaly was noted, along with cutaneous and mucosal lesions: about ten acral palmoplantar keratosis lesions and gingival papules. Cowden syndrome was therefore suspected, and further evaluation revealed a suspicious nodule in the right breast, colonic polyposis, nodular gastritis, duodenal polyposis, and endometrial thickening.
Discussion
The association of cutaneous and mucosal lesions with benign breast disease and/or thyroid, breast, and uterine neoplasms should lead clinicians to suspect Cowden syndrome, which requires a careful examination and comprehensive lesion evaluation. Diagnosis is based on the presence of major and minor pathognomonic criteria. Management is multidisciplinary, and lifelong surveillance is necessary.
Conclusion
Early diagnosis of Cowden syndrome is crucial. Genetic counseling and family investigation are mandatory as part of the management process.

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EP572

JOINT985

Neuroendocrine tumors in association with other primary neoplasms

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Background
Neuroendocrine tumors (NETs) mostly affect the gastro-entero-pancreatic system and then the lungs. One significant clinical phenomenon observed in patients with NETs is the increased prevalence of synchronous or metachronous secondary primary neoplasms (SPMs), mainly gastrointestinal, raising questions about whether these occurrences are coincidental or reflect underlying genetic factors.
Materials and Methods
A retrospective observational study was conducted on a cohort of 93 patients diagnosed with neuroendocrine neoplasms in our department between January 2018 and January 2025. Data including demographics, histopathological and immunohistochemical profiles, imaging findings, and treatment details were collected from medical records.
Results
Twelve patients were diagnosed with SPMs and there were 14 distinct types of neoplasms identified. Among these, 50% of SPMs were diagnosed prior to the detection of NETs. There were 7 males (58.3%), 5 females (41.7%) and the mean age was 58.8 years. The most frequent SPM sites included the biliary (3 cases) and genitourinary (3 cases) tracts. There were three patients with multiple endocrine neoplasia type 1 (MEN1) syndrome, genetically confirmed. A unique case of MEN1 syndrome was identified, involving multiple malignancies: papillary thyroid carcinoma, tonsillar squamous cell carcinoma, a pancreatic grade 1 NET, an atypical thymic carcinoid and a lung adenocarcinoma. This case highlighted a large heterozygous deletion in the MEN1 gene (exons 3–8), suggesting a possible pathogenic variant contributing to the disease's course. The impact of a second neoplasm on the disease progression was less significant compared to the influence of NETs.
Conclusions
Patients with NETs exhibit an incresed risk of developing SPM, with potential genetic syndromes like MEN1 playing a pivotal role in predisposing individuals to multiple neoplasms. Furthermore, the diagnosis of SPMs both prior to and following NET detection emphasizes the importance of vigilant, ongoing surveillance in this patient population. The progression of NETs rather than SPMs was the dominant determinant of patient outcomes, suggesting a unique dynamic that warrants further investigation.

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EP573

JOINT1987

Case series: ^{131}I-MIBG treatment in pheochromocytoma and paraganglioma – insights from our experience

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Introduction
Pheochromocytomas (PCC) and paragangliomas (PGL) are neuroendocrine tumors arising from chromaffin cells, often presenting with catecholamine hypersecretion. For metastatic or unresectable cases, ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) therapy offers a targeted radiopharmaceutical approach, delivering beta radiation. This case series explores the therapeutic role of ^{131}I-MIBG in different clinical settings from the experience of our department.
Methods
A retrospective analysis was conducted on five patients diagnosed with PCC or PGL and treated with ^{131}I-MIBG at our institution. The study includes cases where ^{131}I-MIBG was utilized as primary therapy, neoadjuvant treatment, or for metastatic disease. Clinical, biochemical, imaging, and treatment outcome data were analyzed.
Case Summaries
- **Case 1:** A 29-year-old female with metastatic pelvic PGL received four cycles of ^{131}I-MIBG (28 GBq), leading to tumor shrinkage and enabling surgical resection. No complications were noted.
- **Case 2:** A 41-year-old female with bilateral PCC and pelvic metastasis underwent surgery but had residual disease. Two cycles of ^{131}I-MIBG (11.1 GBq) achieved complete biochemical and morphological response.
- **Case 3:** A 55-year-old female with recurrent para-aortic PGL received one adjuvant ^{131}I-MIBG cycle (5.5 GBq) following multiple surgeries. A three-year follow-up showed normal urinary normetanephrines with no reported side effects.
- **Case 4:** A 50-year-old female with inoperable mediastinal and retroperitoneal PGL underwent two cycles of ^{131}I-MIBG (14.8 GBq), achieving biochemical improvement and stable disease. A third cycle was planned. Side effects were mild (nausea, fatigue).
- **Case 5:** A 48-year-old male with metastatic PCC (liver and bone) received one cycle of ^{131}I-MIBG (7.4 GBq) post-radiotherapy. He developed pancytopenia five weeks later but recovered.

Results
- **Tumor Response:** ^{131}I-MIBG therapy reduced tumor size in some cases, aiding surgical resection, and stabilized disease in others.
- **Biochemical Outcomes:** Significant decreases in urinary catecholamines and metanephrines were observed, with normalization in select cases.
- **Symptom Control & Safety:** Symptoms improved, with manageable side effects (nausea, fatigue, myelosuppression). No hypertensive crises occurred.

Discussion
This case series illustrates the versatility of ^{131}I-MIBG therapy, demonstrating its role in neoadjuvant, primary, and palliative settings. Tumor downstaging, biochemical response, and symptom control were achieved. A multidisciplinary approach is important in optimizing treatment strategies. Further research is could refine protocols and improve patient selection.
Conclusion
^{131}I-MIBG therapy remains an effective treatment for PCC and PGL, offering tumor control, biochemical improvement, and symptomatic relief. This series highlights its use beyond metastatic disease, particularly in neoadjuvant and primary treatment settings.

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EP574

JOINT2890

A case of a 5.5-years-old girl with clitoromegaly, café-au-lait spots and a pathogenic variant in NF1 gene inherited from the mother

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Background
Clitoromegaly in infant girls is usually related with conditions from the Disorders of sexual development (DSD) spectrum but can also be an unusual manifestation of other diseases such as Neurofibromatosis type 1 (NF1). NF1 is a rare

autosomal-dominant disorder caused by heterozygous mutations in *NF1* gene; 50% of the cases are de novo. Phenotype includes café-au-lait spots, axillary and/or inguinal freckling, increased susceptibility for development of benign/-malignant tumors in peripheral nerves, etc., but in sporadic cases a clitoromegaly was also reported.
Case presentation
The index patient is a 5.5-years-old girl referred for genetic testing due to a progressive enlargement of the clitoris during the last year. The child was assigned as a female with no other signs of virilization but with growth delay and few café-au-lait spots from the birth. Retrospectively, a positive family history for hyperpigmented café-au-lait spots and short stature was announced in mother and maternal grandfather with no other severe presentations of Neurofibromatosis. The laboratory tests in proband revealed normal thyroid function, normal levels of androgens and gonadotropins and 46, XX karyotype. DNA from venous blood was extracted from the patient and her parents and Whole exome sequencing (WES) was performed with targeted analysis of genes associated with DSD and NF. A heterozygous pathogenic variant NF1:c.7348C>T, p.Arg2450Ter was identified in the patient; the subsequent Sanger sequencing revealed the maternal origin of the mutation. Additionally, a prenatal diagnosis was advised in the current pregnancy in the family and a heterozygous mutation was detected in the male fetus. However, family decided to continue with the pregnancy and a boy was born at term without complications. Both children are currently on close monitoring from skilled pediatric endocrinologist in order to pursue the clinical presentation and effective treatment to be provided on time.
Conclusions
The use of advanced genetic tests might be very helpful in cases with complex presentation. Determination of correct genotype-phenotype correlations is of high importance in precise diagnosis, better follow-up and clinical management of such heterogeneous conditions as NF1 with non-typical clinical features.
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EP575

JOINT1798

A unique case of pheochromocytoma crisis leading to hypoxic cardiac arrest requiring veno-arterial-venous extracorporeal membrane oxygenation (ECMO) in a postpartum patient

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Background
Large-volume hemoptysis due to a hypertensive crisis is a rare initial presentation of pheochromocytoma. We report a case of a postpartum patient who developed severe hypoxic respiratory failure necessitating ECMO support.
Clinical Case
A 34-year-old G2P2 woman presented to the emergency department (ED) on postpartum day 1 after an uncomplicated vaginal delivery with a one-day history of nausea, vomiting, headache and chest tightness. She had experienced similar but less severe symptoms following her first delivery three years earlier, which resolved within a few months. She was asymptomatic during her second pregnancy. In the ED, her systolic blood pressure (SBP) reached 200 mmHg. A CT pulmonary angiogram, ordered to assess for pulmonary embolism, incidentally revealed a large 18 cm left adrenal mass, highly suggestive of pheochromocytoma. Upon admission to ICU, she was started on doxazosin and IV phentolamine infusion. A 24-hour urine collection for metanephrines and catecholamines was sent. Labetalol was briefly introduced for persistent tachycardia but was discontinued due to extreme blood pressure fluctuations, with SBP exceeding 200 mmHg followed by profound hypotension. She subsequently developed hemoptysis and pulmonary edema, necessitating intubation. Worsening hypoxia and hypotension led to a pulseless electrical activity (PEA) arrest. Following resuscitation and return of spontaneous circulation (ROSC), VV-ECMO was planned for respiratory failure. However, she developed a narrow-complex SVT, triggering another PEA arrest. After ROSC, she was transitioned to V-A-V ECMO due to concern for catecholamine-induced arrhythmias. Doxazosin was increased to 8 mg BID alongside continued phentolamine infusion. Verapamil was added to manage her heart rate. By day 3, her hemodynamics stabilized, allowing for extubation and ECMO decannulation. Her 24-hour urine studies revealed norepinephrine 10,670 nmol/day, epinephrine 7,216 nmol/day, normetanephrine 3,153 nmol/day, and metanephrine 4,296 nmol/day. The remainder of her hospitalization was uneventful. She was discharged on doxazosin 12 mg BID and propranolol 20 mg QID. Adrenalectomy was deferred until six weeks postpartum to allow uterine involution and vascular stabilization. She underwent an uncomplicated laparoscopic left adrenalectomy. She returned five days postoperatively with pain, nausea, and vomiting, and imaging revealed a subtotal infarction of the left kidney. Despite this, renal function remained intact, and postoperative urine catecholamines and metanephrines normalized.
Conclusion
Severe hypoxemic respiratory failure requiring ECMO due to hemoptysis and pulmonary edema is a rare presentation of pheochromocytoma. This case highlights a rare pheochromocytoma crisis in which ECMO was required for respiratory failure rather than the more frequently reported cardiogenic shock.
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EP576

JOINT2616

Higher incidence of fatigue in thyroid cancer survivors transitioning to primary care compared to other cancer survivors

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Background
Despite the high incidence of differentiated thyroid cancer (DTC), the overall mortality has remained low. Combined with a younger age at diagnosis, thyroid cancer prevalence is higher than expected necessitating a focus on survivorship issues, lifelong surveillance and transitioning low-risk DTC survivors to primary care. A recent pan-Canadian study showed that survivors of other cancers consistently report several unmet physical and psychosocial needs. However, the specific needs of DTC survivors remain unknown.
Objectives
1) To describe the self-reported physical, emotional, practical and informational needs of low-risk DTC survivors in Nova Scotia, Canada, during the transition period to primary care; and 2) To compare the physical, emotional, practical and informational needs of low-risk DTC survivors with those of melanoma, breast, colorectal, hematological and prostate cancer survivors.
Methods
A cross-sectional survey using the 83 item "Cancer Transition Survey" was conducted based on the national Experiences of Cancer Patients in Transition Study. The survey was administered to adult patients with low-risk DTC who have been discharged, or were ready for discharge, from specialist to primary care. Survey data from DTC survivors were compared with data from other cancer survivors previously surveyed as part of the national study.
Results
A total of 205 patients responded, with a response rate of 54.6%. Most respondents in the DTC sample were female (81.2%), more than half were in the 55-to 74-year-old age category. All patients had total thyroidectomy +/- I-131 therapy and were prescribed thyroid replacement therapy targeting TSH in a normal range. The most commonly reported post-treatment needs were fatigue (81.3%), anxiety/fear of recurrence (69.5%) and depression/low mood (46.3%). When compared with non-thyroid cancer survivors, DTC survivors reported higher rates of fatigue (81.3% vs. 64.3%, p-value < 0.001). Otherwise, supportive care needs of DTC survivors were similar to those of non-thyroid cancer survivors.
Conclusion
Both DTC survivors and other cancer survivors share similar supportive care needs. While fatigue is common across all cancer survivors, we found that post-treatment fatigue is significantly more prevalent in DTC survivors.
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EP577

JOINT3913

Impact of adjuvant mitotane on long-term outcomes in patients at high risk of adrenocortical carcinoma recurrence

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Introduction
Mitotane has been considered a mainstay adjuvant treatment for patients at high risk of adrenocortical carcinoma (ACC) recurrence. However, the level of evidence is graded as low to moderate, as this recommendation is based on the results of retrospective studies. The present study aimed to analyse the long-term outcomes of patients with ACC (ENSAT stage I-III, Ki-67 > 10%) based on whether they were treated with mitotane in the adjuvant setting.

Materials and Methods
This retrospective, single-center study included 34 patients diagnosed with ACC who underwent R0 surgery. Postoperatively, 26 patients received adjuvant mitotane for 24 months (IQR 20-35; M+ group). Of the 8 patients who did not receive mitotane (M- group), one stopped after one month due to liver toxicity, one refused treatment, and six underwent surgery in a non-expert center where adjuvant mitotane was not advised. The main study outcomes included recurrence-free survival (RFS), overall survival (OS) and disease specific survival (DSS).
Results
There were no significant differences between the groups in terms of age (44 years vs. 50 years; $P = 0.452$), tumor size (98 mm vs. 100 mm, $P = 0.791$) and hormonal hypersecretion (77% vs. 24%; $P = 0.067$). Patients in the M+ group had longer RFS compared to those in the M- group (133 $\pm$ 18 months vs. 52 $\pm$ 17 months; $P = 0.008$). In contrast, no differences were observed between the groups in OS (142 $\pm$ 17 months vs. 151 $\pm$ 29 months; $P = 0.941$) or DSS (180 $\pm$ 13 months vs. 167 $\pm$ 28 months; $P = 0.424$).
Conclusion
Adjuvant mitotane is associated with a significant improvement in RFS in patients at high risk of ACC recurrence. However, no significant impact was observed on OS or DSS.

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EP578

JOINT3688

Pubertal arrest, polydipsia, polyuria, headaches and diplopia in a 13 year old girl

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Introduction
Germinomas comprise 60 to 65 percent of all pediatric intracranial germ-cell tumors (GCTs). The two most frequent sites are the pineal gland and the suprasellar regions. In 5 to 15 percent of cases, patients present with tumors at both pineal and suprasellar locations, referred to as bifocal disease. Pineal tumors typically cause obstructive hydrocephalus, presenting with signs of increased intracranial pressure. Neuro-ophthalmologic abnormalities are present in half of the cases. Suprasellar GCTs most commonly present with hypothalamic/pituitary dysfunction.
Methods
Case presentation:A 13-year-old girl presented with diplopia and left eye esotropia accompanied by ptosis in the previous 20 hours. Past medical history was unremarkable until two years ago when she started suffering early morning vomiting. They reported lethargy, fatigue, polyuria, polydipsia, loss of appetite and weight loss of 7 kilograms for the previous 8 months. Additionally, her mother has noticed regression of breast tissue and pubic hair growth. The patient's family history is unremarkable.
Results
The results from her first clinical assessment are height 1.57m, weight 37kg, pulse 113/min, DBP/SBP 96/60mmHg, temperature 36^0C, GCS 15/15, meningitis signs negative, cerebellar exam normal, left eye esotropia with ptosis, anisocoria, central facial palsy. Tanner stage: Breast II, pubic hair II-III. Fundoscopy revealed bilateral optical nerve edema. An emergency CT-scan revealed hydrocephalus., while the MRI scan revealed hydrocephalus and two space-occupying lesions, one in the region of the pineal gland and one in the pituitary stalk. Laboratory investigations showed increased levels of Na: 151mmol/l, dilute urine SG:1006, TSH: 0.995μIU/ml, fT4: 0.68ng/dl, (consistent with central hypothyroidism), undetectable gonadotropins, FSH: $<$0.3 mIU/ml, LH: $<$0.3mIU/ml, increased PRL: 1240 μIU/ml, very low E2: 5.21pg/ml, very low IGF1: 31.8 ng/ml, βHCG 7.02mU/ml, βHCG CSF: 2.3ng/ml, aFP 1,4ng/ml. Hormonal levels were consistent with the diagnosis of panhypopituitarism including arginine-vasopressin deficiency. Thus, treatment with hydrocortisone, desmopressin and levothyroxine was initiated. A ventriculoperitoneal shunt was implanted According to MRI findings and the following criteria: presence of diabetes insipidus, bifocal disease, positive CSF bHCG, the diagnosis of bifocal germinoma was established and chemotherapy treatment was initiated.
Conclusions
Pubertal arrest requires immediate attention and investigation for possible intracranial pathology (germinoma, craniopharyngioma, pilocytic astrocytoma) or histiocytosis. The suspicion is heightened when it is accompanied by headaches and polyuria, polydipsia

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EP579

JOINT1048

Bilateral and malignant reninoma - case presentation

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Introduction
Reninoma, also referred to as juxtaglomerular cell tumour, is a renin-producing, typically benign lesion that originates from the juxtaglomerular cells of the afferent arterioles within the renal glomeruli. It represents a rare cause of secondary hyperaldosteronism. To date, approximately 200 cases of reninoma have been reported, with histologically confirmed metastasis described in only five patients.
Case report
This case study presents the medical history of a 26-year-old male patient with therapy-resistant hypertension and hypokalaemia, diagnosed with hyperreninemic hyperaldosteronism in 1972. Despite the extensive imagining procedures performed, the underlying cause was finally identified in 2004 when an abdominal CT scan revealed a right renal mass. The histopathological analysis of the removed tumour established the diagnosis of reninoma based on the positive immunohistochemistry results for renin and CD34 and the rhomboid-shaped renin proto-granulate crystals identified by electron microscopic examination. After 10 years of clinical remission, the patient exhibited signs of recurrent hyperreninemic hyperaldosteronism (2014). Histological investigation performed after the selective removal of a neoplastic lesion in the left kidney once again confirmed reninoma. The patient, who had developed chronic renal failure, underwent successful kidney transplantation after 2 years of regular haemodialysis (2017). Six years later, in 2023, a routine abdominal CT scan revealed solitary masses in the liver and the spleen. A biopsy of the hepatic lesion established the clinical and histological diagnosis of a bilateral, metastatic reninoma. Considering the excellent general condition of our patient at the age of 78, our multidisciplinary endocrine tumour board recommended an atypical hepatic resection and splenectomy, which was performed in 2024 (R0 resection). Following an uneventful postoperative course, based on follow-up imaging, the patient remains tumour-free. The exceptionally slow, multidecade-long progression and bilateral manifestation of the tumour suggest the etiological role of a genetic factor. Whole-exome sequencing identified a previously unreported mutation in the ARMC5 gene, whose role in the tumorigenesis remains to be clarified.
Conclusion
To our knowledge, this is the first reported case of malignant reninoma with bilateral manifestation. The bilateral presentation of our case strongly suggests the involvement of genetic factors, but the role of the identified germline **ARMC5**mutation in reninoma pathophysiology requires further investigation.

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EP580

JOINT3867

Delayed diagnosis of an optic chiasm germinoma in a child: clinical evolution and metabolic consequences

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Introduction
Germinomas are rare intracranial tumors that typically arise in the pineal or suprasellar regions, predominantly affecting adolescents and young adults, with a male predominance. When located in the suprasellar region, they may infiltrate the optic chiasm, leading to visual impairment and endocrine dysfunction. This case highlights the late diagnosis of an optic chiasm germinoma in a 9-year-old girl, emphasizing its late diagnosis and the subsequent development of hypothalamic obesity.
Case Report
A previously healthy 9-year-old girl presented with a rapid weight gain of 23 kg over eight months. Her eating habits had changed abruptly and significantly, and she developed polydipsia-polyuria syndrome (4L/day water intake), which remained unnoticed during the summer months. Upon starting school, a decline in visual acuity was observed. An optic nerve CT was performed, revealing bilateral optic nerve atrophy. Another month was lost investigating a possible neurodegenerative disease. Finally, a cerebral MRI scan revealed a tumor of the optic chiasm, initially suspected to be a craniopharyngioma. The tumor was located suprasellar, intrasellar, and retroclival, infiltrating the optic chiasm and protruding posteriorly into the third ventricle. A subtotal tumor resection was performed via a right pterional approach, and histopathological analysis confirmed the diagnosis of a germinoma, which was actually emerging from the optic chiasm. After surgery, the patient was initiated on hormone replacement therapy with hydrocortisone, levothyroxine, and desmopressin. Metabolically, she presented severe dyslipidemia (high LDL-cholesterol and triglycerides, and low HDL-cholesterol) and hepatic steatosis (as revealed by a FibroScan evaluation: CA*P* = 339 Db/m and E=3.8 kPa). She was subsequently administered chemotherapy and radiotherapy according to the SIOP CNS GCT II protocol. Her appetite remained voracious despite treatment, but her nutrition was successfully controlled with the involvement of her family. Six months after hydrocortisone substitution, the patient gradually developed a Cushingoid appearance, including truncal obesity, moon face, and extensive purple striae, but no hypertension, despite adequate weight management and controlled corticosteroid dosing. At present, the patient is in remission, with mild visual recovery, and remains under multidisciplinary follow-up involving oncology and endocrinology.
Conclusions
This case highlights the challenges in diagnosing optic chiasm germinomas, especially when visual impairment develops late. Hypothalamic obesity is a significant long-term complication following tumor resection and endocrine dysfunction. Recognizing early symptoms in pediatric patients with rapid weight gain and polydipsia can lead to timelier diagnosis and intervention, definitely improving clinical outcomes, especially visual loss.

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EP581

JOINT2561

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs): clinical profile, treatment and 10-year survival

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Introduction
GEP-NETs are rare and heterogeneous neoplasms. Its prognosis depends on the histological grade as well as the extent of the tumour.
Material and Methods
We present a retrospective descriptive study based on patients diagnosed of GEP-NET and treated in a multidisciplinary unit in the last 10 years. Demographic data, location, tumour grade, metastases, treatment and survival were collected.
Results
From january 2014 to December 2024, 134 patients were diagnosed of GEP-NET. The annual incidence was 6.47 cases per 100,000 population and the adjusted prevalence was 0.052%. The mean age at diagnosis was 58±15 years, 51% were men and 49 % women. The most common origin was the pancreas (52%), followed by the jejunum-ileum (23%). At diagnosis 24% had distant metastases, most often located in the liver (44 %), peritoneum (25%) or multiple organs (22%). Most of them were sporadic and non-functional. Only 27 tumors were functional, most common insulinomas (11) and 10 had an inherited syndrome (9 MEN1 and 1 NF1). 66 % of patients underwent surgery for the primary tumour. The histological grade was G1 73%, G2 22% and G3 5%. 47 patients had tumour persistence and received somatostatin analogues (47), liver-directed therapy (11), systemic treatments such as everolimus (20), sunitinib (5), chemotherapy (7) and lutetium (12). During the follow up 26% of patients died. 74% were alive at the time of the last visit. The mean survival after diagnosing was 6 ± 5 years (median 5 years). At last visit 44% of patients had complete remission 2.4% partial response, 30.5% stable disease and 23% progression.
Conclusions
The incidence of GEP-NETs is higher than previous reports probably related to greater diagnostic resources. GEP-NETs have a relatively long survival even in those with metastases. Early diagnosis and multimodal treatment improve survival.

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EP582

JOINT355

A rare case of chronic diarrhoea: medullary carcinoma of the thyroid

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We present an 8-year-old black African girl with no significant past medical history. The patient presented with a 7-month history of profuse watery diarrhoea after moving to the UK from Nigeria. There was no history of bloody stools, abdominal pain or vomiting. The diarrhoea had worsened to approximately 10 watery episodes per day. She was noted to have progressive neck swellings with 4kg weight loss over this time, prompting emergency department attendance. There was no history of night sweats or fever. Her weight at initial assessment was 19kg. Extensive infection screen was unremarkable, including negative stool, HIV1/2 antibody, TB gamma interferon, gastric lavage and Mantoux testing. Biochemistry results were largely unremarkable, but with a noted raised calcitonin of 117,896 ng/l (reference range: 0-6.4ng/l). Plasma and urinary metanephrine levels were normal, as were parathyroid and thyroid hormone levels. The patient had ultrasound and CT imaging of her neck, chest, abdomen and pelvis. Ultrasound imaging of the thyroid gland demonstrated suspicious inhomogeneous calcified nodules. Multiple enlarged lymph nodes were visualised in the anterior and posterior triangle of right neck and left anterior neck, containing internal calcification (the largest measuring 30x27mm). Chest imaging revealed enlarged lymph nodes and scattered lung nodules. Sclerotic lesions were identified in the sacrum, iliac bone and vertebral bodies. Infiltrative pathology was also demonstrated in the pericardial area. The imaging was suggestive of an extensive malignant process, likely arising from the thyroid. Differentials included tuberculosis, carcinomatosis and sarcoidosis. The patient underwent biopsy, revealing a diagnosis of metastatic medullary thyroid cancer (MTC), with disease in thyroid, lymph nodes, lungs and bones. MTC accounts for approximately 5% of paediatric thyroid malignancies, with an incidence of 0.27/1,000,000 cases/year. MTC originates from parafollicular C-cells; these neuroendocrine cells produce calcitonin and are not responsive to thyroid stimulating hormone. Tumour secretion of calcitonin and calcitonin-gene related peptide are known causes of diarrhoea. While 80% of MTC cases are sporadic, familial forms exist within multiple endocrine neoplasia II (MENII) syndrome. Genetic screening of this patient was consistent with MEN 2b. The MEN2 form of MTC is caused by mutations in the RET proto-oncogene. Therefore, in children with MEN2 and advanced MTC, the RET tyrosine kinase pathway is a target for treatment. The patient underwent thyroidectomy with bilateral neck dissection with a plan to start RET inhibitor therapy in the following weeks. This case highlights the importance of considering thyroid pathology in children presenting with chronic diarrhoea.

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EP583

JOINT335

A unique case of both adrenal and extra-adrenal paragangliomas in a patient with parkinson's disease

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Background
Co-existence of Paraganglioma (Phaeochromocytoma) and Parkinson's Disease (PD) in the same patient is exceptional and it is hypothesised that genetic predisposition to the two is contradictory. Only around five previous cases are recorded in the literature, all with paraganglioma found incidentally in either an adrenal or extra-adrenal location (never both). Clinically both are associated with supine hypertension and orthostatic hypotension (OH) making the management of blood pressure (BP) changes of PD in the context of paraganglioma that much more complicated.
Purpose
To highlight a) the unusual nature of this combination of illnesses and b) the difficulties of diagnosis and management when they co-exist.
Case description
A 75-year-old white British gentleman with a history of PD, hypertension, diabetes mellitus and gout was admitted to the hospital having been found on the floor at home. After further assessment for ischaemic-looking toes, a CT-angiogram revealed three incidental abdominal masses that were avidly contrast-enhancing raising the possibility of adrenal mass with further related mesenteric nodules. Biochemistry showed raised serum chromogranin A and B, urinary 24-hour normetanephrine and 3-methoxytyramine (3-MT). As 3-MT is a metabolite of dopamine it is raised in the presence of iatrogenic levodopa making interpretation confusing. Urinary 24-hour metanephrines were normal. MIBG (metaiodobenzylguanidine) scan supported a diagnosis of phaeochromocytoma with extra-adrenal secondaries. Although treatment of hypertension in paraganglioma depends on alpha and beta-blockers in our patient, who also suffered from problematic OH, such vaso-active medications were undesirable. He was discharged on pyridostigmine for OH with monitoring of hypertension and further oncology review. He was subsequently re-started on ramipril for control of symptomatic high systolic BP.
Conclusions
This case describes for the first time in literature, as far as we are aware, the presence of both adrenal and extra-adrenal paragangliomas in a patient with PD. It also highlights the complexities of diagnosis and management.
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EP584

JOINT936
Pediatric papillary thyroid carcinoma
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Introduction
Papillary thyroid cancer rarely affects children. More aggressive in form, it is often metastatic upon diagnosis; these metastases most often concern cervical adenopathies and the lung. Its prognosis remains excellent because metastases generally respond well to surgery and treatment with radioactive iodine.
Material and method
This is a retrospective study of 13 patients followed up at our facility between 2003 and 2024. A total of 13 children, sex ratio 2.25 girls, average age 14.84 years [5-18 years], one child had a history of cervical irradiation for lymphoma. All children had undergone total thyroidectomy with at least central lymph node dissection. Tumor size 21.11 mm vascular emboli, thyroid invasion and extrathyroidal invasion were noted in half of the patients. 8 patients had metastatic adenopathies, 5 of them pulmonary metastases and one patient a cranial metastasis revealing her thyroid microcarcinoma. The average iodine activity received was 300mci [30-900mci], unfortunately one patient had as a side effect the development of primary ovarian insufficiency. Currently, 9 patients are in remission, lesion stability is noted in 3 of them and one patient is lost to follow-up.
Discussion/Conclusion
The occurrence of papillary thyroid carcinoma in children is a source of anxiety for those around them and for the doctor. However, early diagnosis, as well as intensive management, most often allow stability and cure.
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EP585

JOINT2118
Gastric microbiota and antioxidants in patients with autoimmune atrophic gastritis and gastric neuroendocrine tumors
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Autoimmune atrophic gastritis (AAG) is an organ-specific autoimmune disease that is primarily asymptomatic in the early stages, and often the cause of these AAG cases is unclear. AAG exhibits vague clinical manifestations and is accompanied by the development of other autoimmune disorders and nutritional malabsorption. It has been proposed that gastric microbiota may have an essential impact on immunological processes within the gastric tissues. However, the changes in gastric microbial communities during AAG development and their potential impact on further AAG and gastric neuroendocrine tumor (GNET) development are still largely understudied.
Objectives
This study aimed to examine the gastric microbiome composition in gastric fluid samples, determine selenium, and neopterin concentrations in blood samples from patients with AAG, GNET, and healthy controls.
Materials and Methods
A total of 25 participants were included, comprising nine AAG patients, nine GNET patients, and seven control patients. Patients underwent esophagogastroduodenoscopy during which gastric fluid was collected. Bacterial DNA was extracted from gastric fluid samples using the Qiagen PowerFecal Pro Kit. Sequencing was performed on an Illumina MiSeq platform. Biochemical markers, such as selenium, and neopterin, were determined from blood samples.
Results
The study assessed microbial diversity and abundances across AAG, NET, and controls. Genera identified included *Streptococcus*, *Rothia*, *Helicobacter*, *Actinomyces*, *Veillonella*, and *Prevotella*. Significant changes were observed in four genera in AAG and six in NET, compared to controls. Compared to the control group, AAG patients showed the highest increase in *Rothia* abundance and the greatest reduction in *Haemophilus*. Similarly, in the NET group, *Rothia* also showed the highest increase, while *Gemella* exhibited the greatest reduction. The NET group was the most heterogeneous. Median plasma selenium levels were 97.17 $\pm$ 21.84 µg/l in AAG, 105.29 $\pm$ 21.15 µg/l in GNET, and 103.31 $\pm$ 29.09 µg/l in controls. Neopterin levels were 2.84 $\pm$ 0.48 ng/mL in AAG, 3.68 $\pm$ 1.58 ng/mL in GNET, and 2.95 $\pm$ 0.80 ng/mL in controls. No significant differences were observed in selenium or neopterin levels among groups.
Conclusions
Our data show that the number of identified species was similar across groups; however, significant changes were observed in the evenness metric of the identified species. Furthermore, differential abundance testing revealed that the *Rothia* genus exhibited the highest increase in both AAG and GNET groups compared to controls. No significant differences were found in biochemical markers. While this study provides initial findings, further research is essential to fully comprehend AAG and GNET. Funding:lzp-2022/1-0102.
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EP586

JOINT1105
Papillary thyroid carcinoma: a case of pulmonary metastasis
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Introduction
The papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for approximately 85% of all thyroid carcinoma cases. It is a well-differentiated cancer that is generally associated with slow tumor growth and a favorable prognosis. However, there are variants of PTC that can exhibit more aggressive behavior. Pulmonary metastasis in papillary thyroid carcinoma (PTC) is an uncommon but clinically significant manifestation of this disease.
Case Presentation
A 9-year-old female presented with an increase in volume in the anterior neck with a family history of a father with prostate cancer and a mother with a benign breast tumor. On physical examination, she exhibited bradylalia, dry skin, an asymmetrical area of alopecia on the scalp, and an anterior cervical region

enlargement of approximately 6 cm associated with three cervical lymph nodes. A thyroid profile was conducted showing TSH >100 µUI/mL, free T4 at 0.234 ng/dL, total T4 at 2.16 µg/dL, and total T3 at 64 ng/dL anti-thyroglobulin and anti-peroxidase antibodies were present with results of 706.6 UI/mL and 535.3 UI/mL, respectively. A Doppler ultrasound reported an infiltrative lesion involving the entire gland with heterogeneous echogenicity and increased vascular flow with lymph nodes losing their morphology at levels II, III, and IV on both sides. It was classified as TIRADS 5 according to ACR classification. A fine-needle aspiration biopsy of a cervical lymph node reported metastasis of papillary thyroid carcinoma. A CT scan was performed to rule out pulmonary metastasis, which was reported as negative. A total thyroidectomy and dissection of 29 metastatic lymph nodes were performed, followed by levothyroxine replacement and a 150 mCi iodine-131 ablative dose (T3 N1b M0). Follow-up iodine-131 scans revealed radioiodine uptake in para-aortic lymph nodes and multiple lung segments. A total body scan by SPECT/CT reported metastatic tissue in the mediastinum and both lung fields leading to a second dose of iodine-131 and a plan for surgery as soon as possible.

Final Comments

The case of papillary thyroid carcinoma presented underscores the importance of early diagnosis and appropriate management of this disease, despite its generally favorable prognosis. The detection of pulmonary metastasis, although uncommon, emphasizes the need for thorough follow-up and a multidisciplinary approach to treatment. It is crucial for healthcare professionals to be vigilant for signs of progression and to conduct continuous follow-up to ensure the best possible quality of life.

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EP587

JOINT1451

Oestradiol: immunoassay measurement can be inaccurate in patients taking fulvestrant

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Introduction

Fulvestrant is a selective oestrogen receptor regulator and Exemestane is a steroidal aromatase inhibitor therapy, both used in the treatment of oestrogen receptor positive breast cancer. Most manufacturers of oestradiol (E2) immunoassays state that Fulvestrant interferes in their assay, some also state that aromatase inhibitors may interfere.

Method

Sample pools ($n=3$) were prepared from off-the-clot human serum obtained from female donors: Sample A – the base serum with no added analytes, Sample B – the base pool with Fulvestrant (25 ng/mL) added, and Sample C – the base pool with Exemestane (150 pg/mL) added. The samples were distributed to all participants measuring E2 in the UK NEQAS for Steroid Hormones EQA Scheme (Distribution 523). The cross-reactivity of each method was calculated for both drugs, comparing the results obtained from the base pool with those from the spiked samples. Participants were asked to answer some web Q&A's on how requests are processed for patients on Fulvestrant and Exemestane.

Results

No significant changes in E2 concentrations were observed in samples containing 150 pg/mL Exemestane when compared to the base pool. However, in samples containing 25 ng/mL Fulvestrant a positive bias was observed for several methods. A large positive bias was observed in the Siemens ADVIA Centaur and Siemens Atellica methods. Cross-reactivity was also observed in the Abbott Alinity and Abbott Architect methods but to a lesser extent. Negligible cross-reactivity was observed in other immunoassay methods (Beckman Access/DxI, Roche Cobas, Roche Cobas Pro, QuidelOrtho) and the LC-MS/MS group. The web Q&A's received 158 responses (response rate 56%). Of the respondents, 85% analysed all E2 requests and did not vet on the basis of clinical details. 27% of respondents refer E2 requests for analysis by LC-MS/MS at the request of the clinician or after reviewing clinical details. 59% of respondents did not append comments to E2 results in regard to potential assay interference from medications including Fulvestrant.

Conclusion

Fulvestrant significantly interferes in some E2 immunoassays and may lead to over-estimation of E2 concentrations in patients receiving therapy. While most manufacturers state that Fulvestrant interferes in E2 immunoassays, many laboratories do not act on this information. This could lead to inappropriate management of patients being treated with Fulvestrant.

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EP588

JOINT1734

SPECT/CT skeletal muscle cancer in bronchial cancer, about a case

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Introduction

The most common sites of distant metastasis from bronchial cancer are lung, liver, bone, adrenal and central nervous system. While muscle metastases are rarely described in the literature. In clinical series, muscle is metastatic site in 0.03 to 0.16% of cancers while autopsy series reported a frequency up to 16%. This difference is due to the clinical aspects which are variable, This may lead to misdiagnosis.

Objective

Interest in the completion of SPECT/CT slices complementary to planar images in the presence of clinical signs of calls with a focus of hyperfixation to planar images of bone scintigraphy in the diagnosis and therapeutic guidance.

Materials and methods

We report the case of a patient referred for an extension assessment of bronchial neoplasia. A bone scan completed with SPECT/CT was performed with a GE NM/ CT DISCOVERY 670 Gamma camera.

Results

A 79-year-old patient with firm, painful swelling of the groin that was initially inconclusive on scintigraphy. Whereas, 2 years later, a control scan was performed to establish a hyperfixation focus of the metaphyseal regionproximal diaphysal of the left femur corresponding to bone lysis contiguous to an adjacent soft tissue mass extending into the spinal canal on SPECT/CT slices. The ultrasound-guided biopsy concluded an infiltration of muscle by a neoplastic malignant proliferation of epithelial nature (adenocarcinoma) with positivity to thyroid transcription factor 1 (TTF1) and CK (AE1/AE3) consistent with a pulmonary origin which confirms the loco-regional extension of muscle ass to adjacent bone. The patient was treated with chemotherapy using gemcitabine and carboplatin.

Discussion

These metastases often occur during the course of a known cancer and are rarely as revealing as in our case. SPECT/CT sections confirm the presence of muscle mass without being able to decide on its metastatic nature. They were used to guide the biopsy. In our patient, the ultrasound biopsy confirmed the diagnosis of muscle metastasis of a pulmonary adenocarcinoma due to the positivity of tumor cells at TTF1. The SPECT/CT scan of the region with signs of call during the course of a bronchial cancer allowed to correct the therapeutic conduct in the presence of skeletal muscle metastasis that escaped radiological exploration.

Conclusion

Skeletal muscle metastasis is a rare event in the course of bronchial cancer. The clinical presentation is often misleading leading to a delay in diagnosis and inappropriate therapeutic conduct. Interest in performing SPECT/CT slices in the presence of clinical signs with hyperfixation focus.

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EP589

JOINT2712

Epidemiologic profile of differentiated thyroid cancer in algeria

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Introduction

Differentiated thyroid carcinoma is the most common endocrine cancer. The aim of the study was to assess the clinical and paraclinical characteristics of differentiated thyroid carcinoma in order to determine its epidemiology in Algeria.

Patients and Methods

This is a descriptive retrospective epidemiological study of differentiated thyroid cancer, evaluating the period from January 1, 2019 to the end of 2023. We collected data from the patient files of the endocrinology department of the EPH Ibn Ziri de Bologhine in Algiers.

Results

1275 patients were included. The incidence rates of differentiated thyroid cancer during the five-year study period (2019-2020-2021- 2022-2023) were 2.78%, 4.88%, 3.36%, 6.36%, and 6.12%, respectively. The mean age of our patients was

42.79 ± 12 years. There was a clear female predominance with 84% women and 16% men, i.e. a F/M sex ratio of 5. The predominant age group was between the third and fifth decades. A family history of goiter was found in 21.18% of cases and of thyroid cancer in 7.37%, while 71.4% of patients had no history of thyroid cancer. No history of childhood thyroid irradiation was found. 43.06% of our patients consulted for thyroid nodule, 25.88% for multinodular goiter, 23.53% for cervical adenopathy and 1.96% for distant metastasis, although the finding was incidental in 5.57% of the cases. Total thyroidectomy was the initial treatment in all patients. The diagnosis of differentiated thyroid cancer was based on anatomopathologic examination of the surgical specimen, 79.14% of cases being papillary carcinoma and 20.86% being vesicular carcinoma. 20.91% of papillary carcinomas were microcarcinomas. 36.24% of the patients had tumors smaller than 1 cm, 28% between 1 and 2 cm, 18.90% between 2 and 4 cm and 16.86% larger than 4 cm. All patients received irradiation and thyroid hormone therapy. Close and regular follow-up allowed the detection of lymph node metastases in 23.22% of patients by anatomopathologic examination, while distant bone and lung metastases were observed in only 2.51% and 1.57% of patients, respectively.
Conclusions
Establishing the epidemiological profile of differentiated thyroid cancer contributes to better patient management and can help identify the risk factors and etiology of the disease. Collaboration between different departments (consultation, radiology, molecular biology and surgery) is needed to optimize patient management in Algeria.

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EP590

JOINT1943

Uncommon thyroid cancer concurrence: a case of papillary micro-carcinoma and medullary thyroid carcinoma

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Introduction
Papillary thyroid carcinoma (PTC), originating from follicular epithelial cells, accounts for over 90% of thyroid cancers. In contrast, medullary thyroid carcinoma (MTC) arises from the parafollicular cells, and is characterized by the production of calcitonin. The simultaneous occurrence of PTC and MTC is a rare phenomenon and occurs in less than 1% of thyroid tumors. Therefore, it is crucial to conduct further research on the outcomes of concurrent PTC and MTC.
Case
A 72-year-old female had been monitored for 3 years due to nodular thyroid disease and subclinical hyperthyroidism. Hashimoto's thyroiditis and Graves' disease were excluded. **Thyroid ultrasound** There are hypoechoic nodules in the upper part of the thyroid (1.7 x 1.1 cm) and in the isthmus (0.7 cm). Fine-needle aspiration biopsy (FNAB) was performed. **Thyroid scintigraphy with 99mTc** "Cold" nodule in the thyroid gland. **Cytological examination** Not possible to rule out a tumor. **Treatment** In 2018, the patient underwent thyroidectomy and neck lymphadenectomy. Levothyroxine 100 mg/day for replacement maintains stable euthyroidism. **Microscopic examination** Papillary thyroid microcarcinoma pT1a / Medullary thyroid carcinoma pT1b. No mutations were found in KRAS codons 12/13, 61, 117, 146, or in NRAS codons 12/13, 59-61, 117, 146. **Genetic consultation** No known pathogenic or potentially pathogenic mutations in the RET gene, nor mutations of unknown clinical significance or likely benign sequence alterations were detected. **Laboratory tests** Pre-surgery calcitonin level was measured at 17.1 pmol/l. The following markers were monitored for the evaluation of recurrence post-surgery: CEA, calcitonin, thyroglobulin, and anti-Tg. All values remained within the reference range. **Follow-up** The patient undergoes annual oncological surveillance for thyroid carcinoma recurrence, including neck, chest, and abdomen imaging. No metastasis or recurrence has been observed. Neck ultrasound shows no pathological changes.
Conclusions
The concurrent occurrence of PTC and MTC in a single patient is exceptionally rare. Therefore, this case provides valuable insights into the management of simultaneous thyroid malignancies, emphasizing the importance of early detection and long-term follow-up to monitor for recurrence or metastasis.

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EP591

JOINT2427

Pituitary Adenoma as the First Manifestation of MEN1: A Case Report

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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant disorder characterized by synchronous or metachronous neuroendocrine tumors. The three main clinical features of this disease are primary hyperparathyroidism (pHPT), duodenal-pancreatic neuroendocrine tumors, and anterior pituitary tumors (1,2). pHPT is the most common and often the first clinical manifestation in 90% of cases (3). We report a rare case of MEN1 in which a pituitary adenoma appeared before pHPT, emphasizing the need to consider other early manifestations of the disease.
Case Report
A 57-year-old female with a history of bilateral cystic mastopathy and LADA (Latent Autoimmune Diabetes in Adults), developed a 5 mm microprolactinoma at age 27. The adenoma was managed with transsphenoidal surgery, complicated by corticotropic insufficiency, which was corrected with hydrocortisone replacement. At age 51, 24 years after the pituitary adenoma, pHPT was diagnosed late, following the development of renal (kidney stones) and bone (recurrent fractures) complications. Histopathological examination confirmed a parathyroid adenoma. MEN1 screening did not reveal any additional components beyond the two already identified.
Discussion & Conclusion
MEN1 is an uncommon condition, with an estimated prevalence of 3 to 20 cases per 100,000 individuals (1). In this disorder, pHPT is the first clinical manifestation in 90% of cases (3). However, although less frequent, a pituitary adenoma can also present as the first expression of the disease (4). It is estimated that about 30-40% of MEN1 patients develop pituitary adenomas during the course of the disease. Among these, approximately two-thirds are classified as microadenomas, with prolactinomas predominating in 65% of cases (3). This case highlights the importance of considering pituitary adenoma as an early manifestation of MEN1, without necessarily expecting pHPT to appear first.
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EP592

JOINT3563

ENT monitoring following radioactive iodine (RAI) therapy in patients treated for papillary thyroid carcinoma

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Introduction
Radioactive iodine (RAI) therapy is an adjuvant treatment to reduce the risk of recurrence of papillary thyroid cancer (PTC).
Aim
To investigate the modalities and duration of follow up after RAI treatment.
Materials and Methods
Retrospective study of 22 patients with papillary thyroid carcinoma, treated with RAI and followed between the years 2020 and 2023.
Results
The mean age of patients was 43 years, with a female predominance (sex ratio = 0.19). The main symptom was a thyroid nodule in 19 cases, cervical adenopathy in 2 cases, and dysphagia in 1 case.Treatment consisted of Total thyroidectomy with central lymph node dissection in all patients, divided into total thyroidectomy in 10

patients and totalization after a first loboisthmectomy in 12 patients with lymph node dissection in 2 patients. The diagnosis was based on anatomopathological examination, which revealed papillary carcinoma in all patients. Treatment with RAI was carried out in 100% of cases, with a mean TG - OFF of 3.54 and mean Anti TG of 23.96. A whole-body scan was performed three days after high-dose iodine administration showing thyroid residues with no suspicious focus on the rest of the body in all patients. Biological follow up, carried out 4 months after the treatment, with an average TG of 0.1 and average anti TG of 0.2. During follow-up, every 3 to 6 months for the first 2 years, then at one year, none of the patients had a clinical, biological or radiological recurrence.
Conclusion
Surveillance in post RAI therapy in papillary thyroid cancer is crucial for early detection of recurrence and ensuring optimal patient management. Monitoring modalities, including serum thyroglobulin, cervical ultrasound, and, when necessary, functional imaging, are essential for assessing treatment response and guiding therapeutic strategies.

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EP593

JOINT339

An unusual first manifestation of pheochromocytoma leading to the discovery of a MEN2A family

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Introduction
Multiple Endocrine Neoplasia type 2A (MEN2A) is an autosomal dominant hereditary cancer syndrome caused by a germline mutation in the REarrenged during Transfection (RET) proto-oncogene. Its classic form comprises the association of medullary thyroid carcinoma (MTC), phaeochromocytoma (PHEO), and primary hyperparathyroidism. We report a case of a patient, and his first-degree relatives, diagnosed with MEN2A at the age of 23, who presented bilateral PHEO as the first manifestation.
Objective
To describe the clinical and genetic aspects of a family with MEN2A.
Methods
Review medical records and telemedicine interviews of the index case and his relatives to collect clinical information related to MEN2A.
Results
The index case was diagnosed with bilateral PHEO and MTC at the age of 22 and 26 respectively, and the allelic variant c.1900T>C;p.Cys634Arg in exon 11, rs75076352 was identified. From there, 13 family members were screened: four siblings, his only son, and eight nephews and nieces. The genetic testing found the allelic variant in eight relatives and, one of them who had not been tested manifested the disease in the follow-up. Of the ten individuals with the syndrome, eight underwent a total thyroidectomy due to MTC, one had suspicious nodules on fine needle aspiration biopsy (FNAB), and another had elevated calcitonin levels at the age of 7. Both were referred for thyroidectomy. The age at diagnosis of MTC ranged from 8 to 35 years. PHEO was diagnosed in six, all of them with bilateral involvement, and the age at diagnosis ranged from 23 to 34 years, except for one case under 20 years of age. Two patients (the index case and his brother) were diagnosed with PHEO before MTC, both had benign FNAB of thyroid nodules. Two cases presented with normocalcemic hyperparathyroidism.
Discussion
In MEN2A, PHEO is frequently diagnosed in the third and fourth decade of life and rarely prior to MTC diagnosis. In this study, we report two patients from the same family with bilateral PHEO as the first manifestation of MEN2A.
Conclusion
PHEO has a strong association with genetic syndromes when diagnosed in young patients, as well as in its bilateral form. Reporting unusual presentations of rare syndromes could help us improve the diagnosis and follow-up of these patients.

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EP594

JOINT3237

The hidden danger of small thyroid nodules: unmasking hereditary medullary thyroid carcinoma

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Background
Medullary thyroid carcinoma (MTC) is a neuroendocrine tumour originating from parafollicular C cells, with both sporadic and hereditary forms. Early detection is crucial due to its metastatic potential. Serum calcitonin is a key biomarker for MTC, often identifying cases before clinical symptoms arise. Given its autosomal dominant inheritance in hereditary cases, genetic screening plays a pivotal role in at-risk individuals.
Case Presentation
A 41-year-old woman seeking pregnancy consultation underwent thyroid ultrasound, revealing a 5×3.3 mm nodule with vague margins, hypoechoic echotexture, microcalcifications, and peripheral vascularization. Thyroid function was normal. Fine-needle aspiration returned a Bethesda V classification, suspicious for MTC. Serum calcitonin was 16 pg/mL. Family history revealed her paternal aunt and cousin had confirmed MTC, and her father had undergone a thyroidectomy two decades prior with unknown histology. A prior ultrasound a year earlier had categorized the nodules as TIRADS 1, but no family history was elicited at that time, delaying suspicion of hereditary MTC. The patient underwent total thyroidectomy. Histopathology was inconclusive, prompting immunohistochemical analysis, which confirmed MTC in the 5×3.3 mm nodule, positive for calcitonin, carcinoembryonic antigen (CEA), and thyroid transcription factor-1 (TTF-1). The final staging was pT1aN0M0R0. Postoperatively, serum calcitonin and CEA levels were undetectable. Genetic testing for RET mutations was recommended, and first-degree relatives were advised to undergo screening.
Discussion
This case underscores the critical importance of serum calcitonin measurement and family history assessment in thyroid nodule evaluation. Small nodules, often considered clinically insignificant, may harbour malignancy. The presence of microcalcifications in even tiny nodules should raise suspicion, warranting further investigation. Routine calcitonin screening facilitates early MTC detection, optimizing patient outcomes. Given hereditary MTC's autosomal dominant inheritance, timely genetic screening and family member evaluation is essential to prevent delayed diagnosis and improve prognosis.
Conclusion
Small thyroid nodules, particularly those with microcalcifications, should not be overlooked, as they may indicate hereditary MTC. Integrating calcitonin measurement, thorough family history assessment, and genetic testing into routine thyroid evaluations is crucial for early detection and timely intervention, improving patient management and familial risk assessment.

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EP595

JOINT1164

Ectopic cushing's syndrome associated with poorly differentiated nasal squamous cell carcinoma

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Introduction
Ectopic Cushing's syndrome (ECS) is hypercortisolism caused by an extra-pituitary ACTH-producing tumour, and accounts for 10-20% of all Cushing's syndrome (CS) cases. The common underline diseases of ECS are small cell lung cancer, bronchial neuroendocrine neoplasia (NENs), pancreatic NENs, thymic NENs, and pheochromocytoma. However, ECS in nasal cancer, especially nasal squamous cell carcinoma is extremely rare.
Case presentation
A 29-year-old pregnant woman presented with reduced olfactory and visual acuity. A contrast-enhanced CT revealed a tumour in the right nasal cavity. Biopsy confirmed poorly differentiated squamous cell carcinoma with neuro-endocrine differentiation. She delivered a male infant via cesarean section at 33 weeks and 4 days. Postpartum imaging, including MRI and 18-FDG-PET/CT, revealed the metastases in right pharyngeal lymph nodes and the left femoral neck, derived from inoperable nasal cavity carcinoma. Thus, chemotherapy was initiated, along with proton beam therapy to the primary lesion. Despite first-line (cisplatin and etoposide) and second-line (nivolumab) chemotherapy, the disease progressed with metastases in the liver, pleura, and breasts. Five months after the initial diagnosis, she developed hyperglycemia (plasma glucose 11.4 mmol/l, HbA1c 6.0%) and hypokalemia (K 2.4 mEq/l), prompting referral to our department. A month prior, hypokalemia had not been present. She had typical signs and symptoms of CS as follows; significant elevation of serum morning ACTH (221.0 pg/mL), cortisol (126 μg/dL), and urine free cortisol (3740 μg/day).

Lack of cortisol suppression of the high dose dexamethasone test led to the diagnosis of ECS due to nasal cavity carcinoma. She started metyrapone treatment with initial daily dose of 750 mg. Treatment with metyrapone 1000 mg and osilodrostat 2 mg successfully reduced cortisol levels (serum morning cortisol: 13.6 μg/dL, urine free cortisol: 51 μg/day) without serious side effects.
Conclusion
This case highlights the rare occurrence of ECS in nasal squamous cell carcinoma. Although the patient did not initially have the Cushing's signs, overt symptoms with ECS developed rapidly with disease progression. Further accumulation of cases is needed for better understanding of the characteristics and management of ECS due to nasal squamous cell carcinoma.

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EP596

JOINT1110

Differentiated high-grade thyroid carcinoma in pregnancy

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Introduction
Subacute thyroiditis during pregnancy is a rare condition, with an incidence of 10-20 cases per 1,000,000 pregnancies [1]. It can mimic thyroid cancer, which has an incidence of 3.6-14 cases per 100,000 pregnant women [2].
Case Presentation
A 31-year-old woman, at 6 weeks of pregnancy, presented with right-sided neck pain and difficulty swallowing. Laboratory tests revealed elevated inflammatory markers: C-reactive protein 190 mg/l, erythrocyte sedimentation rate 27 mm/h, and white blood cell count (WBC) 10.9 x 10^9/l, ANtiTPO, AntiTg – negative, euthyrosis. Ultrasound of the thyroid showed a significantly enlarged right lobe, containing a large, hypoechoic, heterogeneous, and hypervascular nodule measuring approximately 4.4 x 3.3 x 3.5 cm. The nodule exhibited multiple calcifications of varying sizes, along with avascular areas, while the left lobe appeared normal. A suspicious 0.5 cm lymph node was identified in the right side of the neck (zone IV). Based on these findings, a percutaneous fine needle aspiration biopsy was performed under ultrasound guidance, with three tissue columns collected for histopathological examination. The patient was started on ibuprofen for pain and inflammation, and over the course of her treatment, there was improvement in the inflammatory markers, and her symptoms vanished. Biopsy results revealed differentiated high-grade thyroid carcinoma (DHGTC) with areas of tumor necrosis. Immunohistochemistry showed that tumor cells were positive for TTF-1, PAX-8, CK-19, and weakly positive for thyroglobulin, but negative for BRAF. The Ki-67 proliferation index was 7%. Surgical treatment was recommended. Due to the pregnancy, surgery was planned for the second trimester. A total thyroidectomy was performed, and a lymph node in zone VI, measuring 4 mm posterior to the right thyroid lobe, was also removed. The histological examination of the excised tissue confirmed the diagnosis of DHGTC carcinoma, staged as pT3 N0a LVI1. Following surgery, the patient was started on thyroxine replacement therapy with TSH suppression. In conclusion, this case highlights the diagnostic challenge of distinguishing subacute thyroiditis from thyroid cancer during pregnancy. Despite the initial suspicion of subacute thyroiditis, further investigation revealed high-grade differentiated thyroid carcinoma. DHGTC has an intermediate prognosis, falling between well-differentiated thyroid carcinoma and anaplastic thyroid carcinoma [3]. Well-differentiated tumors do not require immediate surgical treatment but only observation during pregnancy. On the contrary, more aggressive tumors (as in our case), also undifferentiated, require surgery during pregnancy, as delay in such circumstances can significantly reduce survival [4].
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2. PMCID: PMC3272870
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EP597

JOINT255

Radiolabeled somatostatin receptor antagonist in patients with metastatic pheochromocytoma or paraganglioma; dosimetry, efficacy and safety evaluation

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Introduction
Metastatic pheochromocytomas and paragangliomas (mPPGLs) are rare neuroendocrine tumors with a variable treatment response. A new radioligand therapy (RLT), a radiolabelled somatostatin receptor antagonist (^{177}Lu-DOTA-JR11) which use has proven high efficacy in patients with NETs G1-G3, may offer increased tumor doses compared to standard RLT with 177Lu-DOTA-TOC in patients with mPPGLs which express somatostatin receptor subtype 2.
Aim
The main objective was to evaluate the tumor absorbed dose of ^{177}Lu-DOTA-JR11 and ^{177}Lu-DOTA-TOC in the same patients with progressive mPPGLs, non-responsive to conventional treatment. Secondary objectives included efficacy and safety assessment of ^{177}Lu-DOTA-JR11 in these patients.
Material and methods
We retrospectively retrieved data of 6 patientswith mPPGLs, treated with 1-2 cycles ^{177}Lu-DOTA-TOC at a standard injected activity of 7.4 GBq followed in an interval of 10-12 months by one cycle ^{177}Lu-DOTA-JR11 (2 GBq/m2 $\times$ body surface area). Tumor absorbed doses were computed using the 75 keV-window for 161Tb and the 208 keV-window for ^{177}Lu as well as the Monte-Carlo-based OSEM algorithm. Therapy efficacy was expressed as progression free survival (PFS) before and after ^{177}Lu-DOTA-JR11, symptoms control and hormonal marker response. Safety was assessed as possible adverse events associated to^{177}Lu-DOTA-JR11.
Results
Six patients (4 women; 3 PHEOs, 3 PGLs) with a median age at diagnosis of 38 (25-65), a median age when receiving first ^{177}Lu-DOTA-JR11 cycle of 57 (45-75) years and a Ki-67 between 7 and 30% were included. The median tumor absorbed dose of ^{177}Lu-DOTA-JR11 was higher compared to standard ^{177}Lu-DOTA-TOC (D=7.9 (1.1-12.1) vs. 3.7 (1.3-10.6) Gy/cycle, respectively). After one cycle of ^{177}Lu-DOTA-JR11 with a median injected activity of 3.6 GBq (2.8-4.3 GBq), patients had a higher PFS [9 (4-17) months] than before ^{177}Lu-DOTA-JR11 start [6 (2-11) months], at a median follow-up duration of 28 months. Two out of 3 patients with functional tumor were free of adrenergic symptoms after treatment. ChromograninA decreased less than baseline levels after $>$ 3 months posttreatment in 2/4 (50%) patients. The most reported adverse events were anemia grade 2 (n= 3, 50%), lymphocytopenia grade 2 and 3 (n= 3, 50%), followed by hypoalbuminemia grade 1 (n= 2, 33%). There weren't grade 4 or 5 events, thrombocytopenia or neutropenia and no kidney or liver disfunction.
Conclusion
This pilot study on mPGGLsshowed that the median tumor absorbed dose per cycle is 1.3 (0.9-3.5) times higher with ^{177}Lu-DOTA-JR11 compared to ^{177}Lu-DOTA-TOC, resulting in a longer PFS and a good clinical outcome without relevant adverse events after ^{177}Lu-DOTA-JR11 therapy.

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EP598

JOINT2538

Challenging management of paraneoplastic cushing's syndrome: a 13 year clinical journey

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Introduction
Paraneoplastic Cushing's syndrome is an uncommon cause of endogenous hypercortisolism. Only 6% of Cushing's syndrome was caused by ectopic ACTH secondary to neuroendocrine tumors [1]. These tumors may be occult and difficult to find, and imaging results are often inconclusive.
Observation
We report a case of a 21 year old patient, who presented with a Cushing's syndrome confirmed by 48-hour low-dose dexamethasone test. On physical examination, he had melanoderma, muscle atrophy, purple abdominal striae and centripetal obesity. The ACTH-dependent character was confirmed by high ACTH level. The diagnosis was complicated with diabetes, hypertension with

severe hypokalemia, cerebral and iliac thrombophlebitis and pulmonary embolism and gonadotropin deficiency. Pituitary MRI revealed a 4.5 mm pituitary microadenoma. The patient underwent total transsphenoidal hypophysectomy and the anatomopathological examination confirmed the diagnosis of pituitary adenoma with immunohistochemistry confirming ACTH-binding character. The post operative follow-up showed the persistence of clinical and biological Cushing's syndrome with high levels of ACTH. Cervical thyroid echography and thoracic-abdominal-pelvic (TAP) CT scan showed no abnormalities besides bilateral adrenal hyperplasia and bilateral pulmonary parenchymal condensation with no pathological fixation on octreotide scintigraphy. Pleural biopsy showed a cytological aspect of tuberculosis without histological signs of malignancy. The patient underwent bilateral adrenalectomy. During the 13 years follow up the ACTH levels remained high with negative anatomic and functional imaging. At the age of 34 years old, CT TAP showed thickened micronodules of the two basal pyramids, well rounded and non-specific and octreotide scintigraphy showed a 06 mm left antero-basal pulmonary nodule intensely fixating octreotide. The patient was referred to thoracic surgery.

Conclusion

This case highlights the challenges of paraneoplastic Cushing's syndrome and the importance of vigilance in identifying ectopic ACTH-secreting tumors which can remain occult for years.

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EP599

JOINT4032

A rare source of ectopic ACTH secretion causing cyclical cushing's syndrome

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We present a rare case of a 64-year-old female with no relevant past medical history, who presented in October 2023 with a 2-month history of peripheral and facial oedema, hirsutism, sleep disturbance, muscle weakness, brain fog and new onset hypertension. She also reported some initial weight loss, so a CT of the chest, abdomen and pelvis was arranged. This revealed hyperplastic adrenal glands but no other significant findings. She was found to have a raised random cortisol (1126 nmol/l) with a high adrenocorticotropic hormone (ACTH) (98ng/l, reference $\leq$ to 50ng/l) and was referred to Endocrinology with suspicion of ACTH-dependent Cushing's syndrome. Her overnight dexamethasone suppression test was markedly elevated at 621 nmol/l (reference 0-50 nmol/l), as was her 24h urinary free cortisol (886 nmol/24h, reference 0-146 nmol/24h). The rest of her anterior pituitary profile was unremarkable. An MRI of her pituitary gland revealed an incidental 3 mm Rathke's cleft cyst, but no adenoma. Inferior petrosal sinus sampling (IPSS) was arranged 3 months after her initial presentation to exclude Cushing's disease. However, the patient reported spontaneous resolution of her symptoms, with normalisation of her blood pressure and biochemistry. A diagnosis of cyclical ACTH-dependent Cushing's syndrome was made. In June 2024, the patient's symptoms recurred, with concurrent biochemical evidence of hypercortisolism, and an urgent IPSS was arranged. This did not confirm a pituitary origin and an 18-FDG PET-CT and a pituitary and thoracic 11C-Methionine PET CT were performed to identify an ectopic origin of ACTH secretion, without any focal uptake noted on either scan. A Gallium-68 DOTATATE PET CT was arranged to look for neuroendocrine tumours as an ectopic source of ACTH and revealed focal uptake in the small bowel and 2 mesenteric lymph nodes, suggestive of a small bowel neuroendocrine tumour (NET) as the source of ectopic ACTH secretion. She was commenced on block and replace therapy with metyrapone and dexamethasone, as well as apixaban for thromboprophylaxis. She underwent surgical resection with intraoperative ultrasound guidance of two tumours found in the ileum, as well as the pathological mesenteric lymph nodes identified on PET CT, with perioperative hydrocortisone and octreotide cover. Hydrocortisone was stopped 2 weeks post-operatively following a robust early morning cortisol result and post-operative ACTH levels normalised. Histopathology confirmed a grade 2 well-differentiated mid-gut NET expressing ACTH with nodal metastases. She remains under regular endocrine follow up and is awaiting a repeat Gallium-68 DOTATATE PET CT to guide further management.

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EP600

JOINT2098

Niosome-encapsulated quercetin for enhanced thyroid cancer therapy and potential minimization of thyroid surgery

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This study investigates a novel niosome-encapsulated quercetin delivery system for enhanced thyroid cancer therapy, exploring its potential to minimize thyroid surgery. Quercetin, a promising anti-cancer flavonoid, suffers from poor bioavailability. Nevertheless, some previous studies proved its efficiency in thyroid cancer treatment. Niosomes offer a potential solution by improving drug delivery. Quercetin-loaded niosomes were fabricated using thin film hydration and characterized for size, morphology, stability, and release profile. Dynamic Light Scattering (DLS) showed a uniform particle size of ~70 nm indicating the successful formation of nanosized vesicles suitable for cellular uptake. Scanning Electron Microscopy (SEM) confirmed spherical morphology and Zeta potential indicated a stable formulation. Stability studies demonstrated the niosomes' integrity over a period of time, proving their suitability for drug delivery applications. *in vitro* release profiles were evaluated at neutral and acidic pH. Sustained quercetin release was observed at neutral pH over four days. Critically, release was slower in acidic conditions, mimicking tumor microenvironments, suggesting potential for modulated drug release. These findings highlight the potential of niosome-encapsulated quercetin for thyroid cancer therapy. The nanosized vesicles, spherical morphology, pH-sensitive release, and stability suggest improved drug delivery and enhanced quercetin's anti-cancer activity. This targeted approach may potentially reduce the need for total thyroidectomy. Further *in vitro* and *in vivo* studies are warranted to evaluate efficacy and safety in preclinical thyroid cancer models, specifically investigating the potential to minimize surgical intervention. This research contributes to improved, less invasive thyroid cancer treatments.

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EP601

JOINT3495

Challenges in treatment of carotid paraganglioma: about a case report

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Introduction

Paragangliomas are rare neuroendocrine tumours that arise from the glomus cells of the embryonic neural crest and can be found from the skull base to the pelvis. Carotid paragangliomas are rare, hypervascular, slow-growing neuroendocrine tumours. A preliminary diagnosis can be made based on the patient's history, physical examination and imaging studies.Althoughresectionis a radical therapy for thistumor, completeresectionischallenging. Our objective is to report a rare case of carotid paraganglioma and describe its clinical presentation and management stategy.

Case report

A 15-year-old girl with a history of epilepsy and no family history of multiple endocrine neoplasia, Von Hippel-Lindau disease or pheochromocytoma presented with a 2-month history of laterocervical swelling with no signs of compression. On examination she had a laterocervical mass of 4 cm, firm, pulsatile, movable and indolent. She had no cervical lymphadenopathies or other palpable masses, and her nasopharyngeal endoscopy was unremarkable. Computed tomography (CT) and magnetic resonance imaging (MRI) showed a left laterocervical mass centred on the carotid bifurcation, measuring 44*28*25 mm, enveloping the distal part of the left common carotid artery and the initial part of the left internal and external carotid arteries, suggestive of a paraganglioma type 3 of the Shamblin classification.The urinarycatecholamineswerenegative. The patient was referred for vascular surgery.

Discussion/Conclusion

Cervical paragangliomas are rare tumors that can occur sporadically or be familial. Hereditary forms are associated with genetic mutations. Diagnosis relies on CT, MRI, and functional imaging. Management involves a multidisciplinary approach, combining medical and surgical strategies. Surgical excision remains the only curative treatment, but it carries a risk of significant postoperative sequelae. Therefore, cooperationwith an otolaryngologist and vascular surgeon duringsurgeryisrecommended due to frequent damage to carotidvessels by carotidparagangliomas. Detection of the tumor in the early stages improvessurgicaltreatmentoutcomes and reduces the number of complications. Regular postoperativecheck-ups are necessary due to possible occurrences of multiple tumors. Disclosure of interest: none declared

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EP602

JOINT2121

Toddler-age girl with rapidly progressing peripheral precocious puberty

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Introduction
Precocious puberty is defined as the onset of secondary sexual characteristics before the age of eight years in females and nine years in males. It is classified as Central precocious puberty (CPP), as a result of early maturation of the hypothalamic-pituitary-gonadal axis and as peripheral precocious puberty (PPP), secondary to excess secretion of sex hormones from the gonads or adrenal glands, ectopic production of bHCG from a germ-cell tumor or exogenous sources. We aim to present a preschool girl with premature menarche and adrenarche.
Methods
A 4.5-year-old girl was referred for evaluation of precocious puberty. Her mother noticed rapid breast development as well as pubic and axillary hair the previous month. She also reported vaginal bleeding. Physical examination revealed: Tanner II-III breast, axillary and pubic hair, and a palpable mass in the lower abdomen. Laboratory investigation showed elevated estradiol, suppressed gonadotrophins and elevated adrenal androgens, while tumor markers were negative (FSH: $<$0.3mIU/mL, LH: $<$0.3mIU/mL, E2:294.70pg/mL, PRL:581μIU/mL, 17- OH-Prog:5.23ng/mL, DHEA-S:0.467μg/ml, aFP:2.6ng/ml, bHCG $<$0.1UI/lt, TSH:2.13μIU/ml), suggestive of PPP. Bone age was advanced consistent with 5.5 years. Further investigation with abdominal ultrasound and magnetic resonance imaging revealed a large pelvic mass (maximum diameter $>$ 11cm), of mixed consistency possibly originating from the left ovary. Synacthen test was normal. Complete surgical excision of the tumor was performed.
Results
Histopathological examination revealed a Juvenile granulosa cell tumor (JGCT) of the left ovary, TNM/UICC stage: pT1a. Further treatment was not required, as postoperative imaging with MRI and PET-scan had no abnormal findings. Furthermore, she had complete regression of breast tissue and pubic hair while hormonal levels were prepubertal, two months post-surgery.
Conclusions
JGCT is a rare tumor in children and adolescents and most of the cases with ovarian malignancy present in advanced-stage disease. The exact etiology is unknown, while in adults, mutations in FOXL2 have been identified as the key pathogenic factor. It is treated with surgical excision and adjuvant CMT in cases of advanced disease. The prognosis is excellent in lesions confined to the ovary. The differential diagnosis of peripheral precocious puberty includes functional ovarian cysts, granulosa cell tumors, gonadoblastomas, CAH, adrenal tumors, severe hypothyroidism, McCune Albright syndrome, and exposure to estrogens or endocrine disruptors. Early diagnosis is crucial for an optimal outcome.

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EP603

JOINT1957

Adrenocortical carcinoma with co-secretion of aldosterone and cortisol: a case report

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Introduction
Adrenocortical carcinomas are epithelial malignant tumors arising in the cortical zone of the adrenal gland. They are extremely aggressive and very rare, with an incidence of 1 to 2 cases / year / million population and a prevalence of 4 to 12 cases per million population, in contrast to benign adrenal tumors, which account for 3% of the general population over the age of 50. These tumors have been divided into non-functional and functional tumors. We report a rare case of adrenocortical carcinoma with co-secretion of aldosterone and cortisol.
Case report
A 46-year-old patient referred to our department for etiological assessment of malignant hypertension for 8 years and severe hypokalemia. He presented with edema of the lower limbs and acanthosis nigricans. The aldosterone/renin ratio (ARR) was 381 pmol/mUI, indicating aldosterone excess. Dexamethasone minute braking was negative at 9.7mg/dl. Abdominal CT scan revealed a large, relatively well-limited, calcified left adrenal mass with heterogeneous enhancement, measuring approximately 63 x 86 x90 mm, with no other abdominal lesions. The patient underwent unilateral adrenalectomy, which resulted in a large, ovoid, firm, whitish-grey mass. Pathological examination with immunohistochemical complement was compatible with adrenocortical carcinoma, a Weiss score of 3. Postoperatively, the patient's blood pressure returned to normal and hypokalemia did not recur.
Discussion
Adrenocortical carcinoma is a rare malignancy. The clinical presentation is variable. Functional or secretory adrenocortical carcinomas cause an endocrine syndrome. In order of frequency, this may be isolated hypercorticism or hypercorticism associated with virilization or feminization, or primary hyperaldosteronism, as in the case of our patient. The literature confirms the rarity of exclusive aldosterone production by adrenocortical carcinoma. The diagnosis is made in the presence of signs of hormonal hypersecretion dependent on the hormone synthesis pathway developed by the tumoral endocrine tissue, or in the presence of a tumoral syndrome. Adrenal CT is the first-line examination for adrenal exploration in cases of hormonal hypersecretion syndrome. Surgery is the first-line treatment, whatever the type of secretion. In cases of recurrence where excision has been incomplete or rejected, the second-line treatment is mitotane alone or combined with chemotherapy. Adjuvant radiotherapy is not systematic, and is mainly used to treat secondary bone or brain damage.
Conclusion
This case illustrates the importance of a comprehensive hormonal evaluation of patients presenting with a picture of primary hyperaldosteronism with or without functional signs of hypercorticism, to diagnose these likely underestimated co-secretions.

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EP604

JOINT3474

When two cancers collide: a case of rectal adenocarcinoma following thyroid cancer

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Introduction
Thyroid cancer survivors, particularly those with papillary carcinoma, have an increased risk of developing a second primary cancer, including colorectal cancers. This heightened risk may be attributed to genetic, environmental factors, or prior treatments such as radioactive iodine therapy. We present the case of a patient who developed a lower rectal adenocarcinoma seven years after undergoing thyroidectomy for papillary carcinoma, highlighting the importance of vigilant surveillance in thyroid cancer survivors.
Case Report
A 43-year-old woman with no family history of cancer was diagnosed with papillary thyroid carcinoma in 2015, for which she underwent a total thyroidectomy followed by radioactive iodine therapy. In 2022, she presented with rectal symptoms, including rectal bleeding and tenesmus, leading to the diagnosis of a lower rectal adenocarcinoma. A colonoscopy confirmed the presence of a rectal tumor, and biopsy results showed a poorly differentiated, infiltrating adenocarcinoma. The patient underwent surgical resection followed by adjuvant chemotherapy and radiotherapy.

Discussion
This case highlights the increased risk of second primary cancers in survivors of thyroid cancer. Numerous studies have shown that patients with papillary thyroid carcinoma are at a higher risk for developing colorectal cancers. For instance, a meta-analysis by Berthe *et al*. reported an elevated risk of second primary cancers, including colorectal cancer, in these patients. Likewise, Rubino *et al*. observed a significant association between thyroid cancer and colorectal cancers. The underlying mechanisms could involve shared genetic mutations, hereditary syndromes, or side effects from radioactive iodine treatment.
Conclusion
Thyroid cancer survivors, particularly those with papillary carcinoma, should undergo close surveillance to detect second primary cancers, especially colorectal ones, at an early stage. Genetic evaluation and regular screening are crucial for these patients to ensure early detection and better outcomes.

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EP605

JOINT64
Reabilitation of patients who was operate from the thyroid cancer
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Rehabilitation of patients with thyroid cancer includes medical, instrumental, psychological and social support. It begins with the establishment of a preliminary diagnosis (ultrasound, cytology, laboratory tests) and continues after surgery for the rest of the patient's life. All patients need to be monitored using the necessary studies aimed at detecting relapses and metastases, as well as medical support. We analyzed 1,382 cases (1,194 women, 186 men operated on for thyroid cancer in 1996-2021). The tumor prevalence corresponded to T1 and T2 (54% and 22%, respectively), the common forms - 24%. Metastatic lesion of the neck lymph nodes was observed in 331 (23.9%) patients, including patients with T1. The main type of surgery was thyroidectomy (74%), hemithyroidectomy - in 25% of cases (with T1), thyroid resection – in 1%. The main morphological form was papillary cancer (1272 patients; 92%). 5.8% of patients had postoperative complications. In 504 people (36.5%), radioiodine therapy was included in the complex of postoperative treatment. Repeated surgical intervention was performed in 134 patients (9.7%). All patients were prescribed medication therapy. When prescribing doses of L-thyroxine, the variants of the presence of genetic mutations in patients affecting the metabolism of the drug (the SLCO1B1 Val174Ala gene) were taken into account. After 13-28 years, 734 patients (53.1%) remain under observation. During the follow-up, 415 patients died from other causes (stroke, heart attack, covid-19, and others). 33 patients (2.4%) died of thyroid cancer. Some patients refused medical examination. To assess the effectiveness of suppressive therapy, TSH and thyroglobulin levels were determined in the blood. The group of patients with a good decrease in TSH levels (less than 0.1 IU/ml and thyroglobulin less than 1 ng/ml) was large (78.4%). 11.3% of patients had impaired L-thyroxine intake. Some patients (8.5%) (after hemithyroidectomy) did not undergo medical examination and refused L-thyroxine. In 19.4% of patients who did not take suppressive doses of L-thyroxine, signs of desymination were revealed. Clinical and laboratory manifestations of hypoparathyroidism were observed in 1.4% of patients. Research by psychologists has shown that the first six months after surgery are the most "difficult", it is at this time that "positive training", "life continuation training" is needed. In the future, the level of anxiety and "immersion in the disease" tended to decrease, which ensured good professional and social adaptation for more than 10 years.

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EP606

JOINT2023
Follicular thyroid carcinomas: epidemiological, clinical, and therapeutic profiles
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Objectives
To study the epidemiological, clinical, anatomopathological, and therapeutic particularities of follicular thyroid carcinoma (FTC).
Patients and Methods
This is a retrospective study involving 20 patients treated for FTC over a period of 14 years.
Results
The average age was 49 years, with a female-to-male ratio of 5.66. The mode of discovery was a cervical mass in 17 cases, bone metastasis in 2 cases, and compression signs in 1 case. The average consultation delay was 16 months. Cervical ultrasound performed in all cases revealed thyroid nodules classified as EUTIRADS 3 (80%), EUTIRADS 4 (15%), and EUTIRADS 5 (5%). Fine needle aspiration was performed in 3 patients (15%). Surgery involved thyroid surgery in all cases, with central node dissection in 12 cases (60%) and selective lateral dissection in 1 case (5%). The frozen section examination was conducted for all patients, with benign results in 15 cases (75%) and malignant results in 5 cases (25%). Definitive histological examination confirmed the diagnosis of FTC in all cases. Staging for recurrence risk categorized the patients into 3 groups: low risk in 15 cases, intermediate risk in 1 case, and high risk in 4 cases. Ninety-five percent of patients received radioactive iodine therapy. Whole-body scanning revealed pulmonary metastases in 2 cases and bone metastasis in 2 cases. The average follow-up duration was 49.7 months.
Conclusion
FTC represents 10-15% of all thyroid carcinomas. It tends to metastasize more frequently to distant sites, particularly to the lungs and bones.

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EP608

JOINT1067
177Lu-edotreotide versus everolimus in patients with advanced neuroendocrine tumors of lung or thymic origin: progress of the LEVEL / GETNE-t2217 trial
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Background
Peptide receptor radionuclide therapy (PRRT) has shown promising activity in somatostatin receptor (SSTR)-positive lung neuroendocrine tumors (NETs) in retrospective series. This study aims to compare the efficacy, safety, and patient-reported outcomes of 177Lu-edotreotide versus the standard of care everolimus in patients with advanced lung and thymic NETs.
Methods
The LEVEL trial is a randomized, open-label, phase 3 international (France, Italy, Belgium, and Spain) trial evaluating 177Lu-edotreotide versus everolimus in patients with progressive, advanced, and well/moderately differentiated NETs of lung (typical/atypical) or thymic origin. Patients could be treatment naïve or have progressed (PD) on somatostatin analogues or up to 2 additional systemic treatments. Prior PRRT or mTOR inhibitors are not permitted. Eligible patients are randomly assigned 3:2 to 177Lu-edotreotide or everolimus. 177Lu-edotreotide is administered intravenously at a total dose of 7.5 ± 0.7 GBq per cycle for up to 6 cycles, with a 6-week interval between cycles 1 and 2 and a 8-week interval between cycles afterwards. Everolimus is administered orally 10 mg once daily until PD or unacceptable toxicity. CT or MRI scans are performed every 12 weeks until PD. Blood samples are analyzed at baseline, at 1st tumor assessment, and at PD for pharmacodynamic endpoints. Archival tumor tissue samples will be analyzed for ancillary studies. The primary endpoint is progression-free survival (PFS) according to RECIST v1.1. Secondary endpoints include overall response rate, overall survival, safety, and quality of life (EORTC QLQ-C30). The planned sample size is 120 patients using a two-sided Lan-DeMets with O'Brian-Fleming-like boundaries test to demonstrate a statistical significant reduction of PFS hazard ratio of 0.536 in favor of 177Lu-edotreotide ($\alpha = 0.05$, $\beta = 0.2$). The study includes an interim analysis after 60 PFS events are observed. The final analysis will be conducted after 87 PFS events. Recruitment started in Oct 2023. The study is active in all four countries. Currently, 57 patients have been randomized, and three more patients are in screening. Completion of recruitment is expected by the end of 2025. Clinical trial identification: EU CT: 2022-502154-13-00 / NCT05918302

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EP609

JOINT3956

Family matters! - a rare case of SDHB gene linked metastatic paraganglioma

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Background
Paraganglioma is a rare catecholamine secreting neuroendocrine tumour commonly occurring in the head and neck. They are usually slow growing and can be associated with genetic syndromes 35% of the cases. Treatment depends on the size and location of the tumour and if completely excised can have good prognosis. However, once metastasised, rapid progression and poor prognosis are observed. Here, were describe a rare case of germline pathogenic succinate dehydrogenase subunit B (SDHB) gene linked metastatic paraganglioma.
Case
A 42-year-old gentleman came into Emergency Department after he fell from a chair. MRI showed a pathological C3 collapse with tumour infiltration and enlarged jugular chain lymphadenopathy. He also had high blood pressure and upon detailed history complained of multitude of intermittent symptoms which he had ignored in the last 6 months (including chest pain, palpitations, somnolence, feeling sweaty, double vision and pins and needles in left arm). Initial biopsy after anterior C3 corpectomy showed osseous hemangioblastoma. Further biopsy of lymphadenopathy showed strong expression of inhibin and positive chromogranin and synaptophysin. MIBG and 68Ga PET scan revealed extensive metastasis from skull base into the pelvis involving cervical spine, skull base, left scapula, bilateral ribs, pelvis, bilateral para-aortic soft tissue and left liver lobe. Subsequent immunohistochemistry showed- low Ki-67 index, 1-2%. Bloods tests showed low plasma metanephrines (174.2 pmol/l (reference <510pmol/l)) and significantly raised plasma normetanephrines (30,508 pmol/l (reference <1180 pmol/l)). He was thus diagnosed with metastatic paraganglioma and treated under Endocrinology, Oncology, Neurosurgery and Ophthalmology. Genetic testing was positive for SDHB gene which was also positive in five of his other eight siblings. He was treated symptomatically with alpha-blockers and beta blockers, and received palliative surgery (e.g., for skull base/brain involvement), together with systemic treatment including treatment with CAPTEM chemotherapy, radiotherapy, and lutetium PRRT. Unfortunately, he passed away within 4 years of diagnosis.
Discussion
Metastatic paragangliomas are rare and challenging to treat due to often late presentation based on initially non-specific symptoms, often rapid spread, and limited treatment options. Patients with SDHB gene mutations have increased risk of developing metastases and hence require, long-term surveillance. Early diagnosis is crucial to ensure optimum management. Metastatic disease can be managed with options like radiotherapy, radiofrequency, chemotherapy or molecular targeted therapies like PRRT. Multidisciplinary team approach is central to treatment given its complex nature.

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EP610

JOINT1417

Molecular and functional characterisation of the somatostatin system unravels novel vulnerabilities in hepatocellular carcinoma

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Liver cancer is the sixth most incident and third most lethal cancer type worldwide. Among its subtypes, hepatocellular carcinoma (HCC) is predominant, comprising 90% of the cases. The overall 5-year survival rate of HCC patients is still extremely low (20%), partially due to a high intra- and intertumoral heterogeneity that severely complicates systemic treatment (first line: immunotherapy, second line: tyrosine kinase inhibitors). Despite its known role as a (neuro)endocrine hub, classic (neuro)endocrine tumour profiling and approaches [i.e., somatostatin (SST) system receptor expression and ligand response] have been poorly explored in HCC, with limited and inconclusive results. For this reason, this study aimed to obtain a molecular and functional description of the SST system in HCC. To achieve this, we used 2 internal retrospective cohorts [Retrospective-1 (R1): HCC vs. non-tumoral adjacent tissue (NTAT) ($n = 93$); Retrospective-2 (R2): HCC vs. NTAT ($n = 58$), cirrhotic ($n = 39$) and healthy liver tissue ($n = 5$)], 6 in silico cohorts [GSE6764 ($n = 65$), GSE14323 ($n = 107$), GSE14520 ($n = 247$), GSE164760 ($n = 141$), CPTAC-PDC000198 ($n = 165$), TCGA-LIHC ($n = 369$)] and 4 human liver cell lines [healthy hepatocytes (THLE-2), hepatoblastoma (HepG2) and HCC (Hep3B, SNU-387)]. SST receptor (SSTR1-5) and ligand (SST, CST) expression was assessed by RT-qPCR (all models) and immunohistochemistry [IHC, subset ($n = 25$) of R1]. Cell lines were also employed to evaluate the expression of key neuroendocrine markers and SST receptor (SSTR) downstream effectors, in addition to their functional response to SSTRs natural ligands, classic analogues (octreotide, lanreotide, pasireotide) and novel agonists (BIM-23926, BIM-23120) by different *in vitro* assays (proliferation, colony and hepatosphere formation). HCC patient samples were characterised by a general SST system expression downregulation, which was linked to complex patterns of tumour aggressiveness through clinical variables (e.g., survival, recurrence, microvascular invasion and portal hypertension) and complemented by IHC staining results [positiveness of infiltrating immune cells (SSTR1, SSTR2) and vascular endothelia (SSTR5)]. Cell lines mimicked this expression pattern, where the highest SSTR expression was found in low (HepG2) and intermediate (Hep3B) aggressiveness liver cancer cells. Accordingly, antitumoral effects were observed among the different *in vitro* assays for octreotide, pasireotide, BIM-23926 and BIM-23120 in HepG2; all ligands except

SST in Hep3B and SST and CST in SNU-387. These results could be explained through biased signalling by specific neuroendocrine markers and SSTR-downstream effectors profiles (e.g., CDH1 in Hep3B, AIP in SNU-387). In conclusion, our data suggests that the SST system is an intricate, yet exploitable source of informative biomarkers and individualised therapeutic options in HCC.

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EP611

JOINT2465

A case of long-standing pituitary macroadenoma leading to panhypopituitarism and visual impairment

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Introduction

Internationally, panhypopituitarism has an estimated incidence of 4.2 cases per 100,000 per year. Hypopituitarism may present as a deficiency of individual anterior or posterior pituitary hormones or as a complete deficiency of all pituitary hormones, known as panhypopituitarism. We present a case of a 67-year-old male with a long-standing macroadenoma, previously treated as a prolactinoma, complicated by anterior pituitary hormonal deficiency.

Case report

A 67-year-old male was diagnosed with a prolactinoma nine years ago and was started on cabergoline (0.5 mg, half a pill twice weekly). Upon admission to our hospital in 2024, he presented with progressively worsening blurred vision, fatigue, low energy, and hypotension. Given his deteriorating symptoms, cabergoline was discontinued, and a comprehensive endocrine evaluation, along with magnetic resonance tomography (MRT), was performed. Imaging revealed a 48 mm pituitary macroadenoma compressing the optic chiasm, explaining the patient's worsening vision. Laboratory tests confirmed secondary adrenal insufficiency and secondary hypothyroidism. The patient was started on hydrocortisone and levothyroxine to manage his endocrine deficiencies. Following stabilization, he underwent transsphenoidal pituitary macroadenoma resection in July 2024. Postoperatively, his symptoms significantly improved, except for persistent visual impairment. At a follow-up visit after surgery, the patient reported drowsiness. Laboratory tests revealed that his Free T4 levels were within the lower normal range, prompting an increase in the levothyroxine dosage. Following this adjustment, the patient experienced symptomatic improvement.

Conclusion

This case highlights the importance of regular endocrine reassessment in patients with pituitary adenomas. Early recognition and management of secondary endocrine deficiencies are essential for optimizing patient outcomes, as untreated deficiencies can lead to severe complications and even death. Although surgery successfully resolved most symptoms, persistent visual impairment underscores the need for timely intervention in pituitary macroadenomas.

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EP612

JOINT491

A case of severe hyponatremia due to SIAD likely caused by uterine sarcoma

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Case

A 78-year-old woman presented with abnormal uterine bleeding. Endometrial biopsy revealed findings suggestive of a sarcoma. Upon there were no obvious signs of dehydration or edema. Without intravenous fluids, laboratory findings were as follows: serum Na 125 mEq/l, plasma vasopressin concentration 2.4 pg/mL, plasma osmolality 257 mOsm/kg, urine osmolality 354 mOsm/kg, urinary Na 101 mEq/l, plasma renin activity 0.6 ng/mL/hr, and serum uric acid 2.7 mg/dL. Given normal renal and adrenal cortical function, a diagnosis of syndrome of inappropriate antidiuresis (SIAD) was made. Fluid restriction was implemented along with intermittent administration of hypertonic saline. On hospital day 4, treatment was switched to oral NaCl, but even with NaCl administration of 12 g/day, serum Na did not increase sufficiently. Hypertonic saline was continued until serum Na reached 130 mEq/l. By hospital day 8, serum Na improved to 137 mEq/l, and a hysterectomy with bilateral salpingo-oophorectomy was performed while maintaining serum Na levels with a continuous infusion of approximately 1.5% hypertonic saline. Pathological examination revealed undifferentiated uterine sarcoma and endometrioid carcinoma. After surgery, hypertonic saline administration became unnecessary, plasma vasopressin concentration decreased to around 1.0 pg/mL, and serum Na stabilized in the 130 mEq/l range. The patient was discharged on oral NaCl 3 g/day. AVP immunostaining was performed on the tumor tissue, revealing AVP expression in some undifferentiated areas of the uterine sarcoma. AVP was not detected in the endometrioid carcinoma.

Discussion

Based on the clinical course and immunohistochemical findings, this case was considered SIAD caused by an ectopic vasopressin-producing tumor associated with uterine sarcoma. The causes of SIAD include central nervous system disorders, pulmonary diseases, ectopic vasopressin-producing tumors, and medications. Among ectopic vasopressin-producing tumors, small cell lung cancer is the most frequently reported and is well known for secreting AVP. The association between SIAD and gynecologic malignancies is rare. A literature search for cases of uterine sarcoma or endometrioid carcinoma associated with hyponatremia or SIAD identified only case reports of SIAD occurring during cisplatin-based treatment, with no other reported cases.

Conclusion

This case suggests a potential new etiology of SIAD associated with gynecologic malignancies and highlights its clinical significance.

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EP613

JOINT630

Primary adrenal insufficiency secondary to bilateral adrenal metastasis of a prostatic adenocarcinoma: a case report

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Introduction and Background

Prostate cancer, a leading malignancy in men, predominantly metastasizes to the bone and lymph nodes. Adrenal metastases are rare, with bilateral involvement being exceptionally uncommon and signaling advanced disease.

Case Report

We report a case of a 62-year-old chronic smoker presented with progressive obstructive urinary symptoms and gross hematuria. His PSA level was 183 ng/mL, and prostate biopsy confirmed adenocarcinoma. He underwent prostatectomy and bilateral castration, revealing moderately differentiated, infiltrative adenocarcinoma (Gleason 8, ISUP grade 4) with perineural invasion. After a three-year lapse in follow-up, he returned with gastrointestinal symptoms, profound asthenia, hypotension, and generalized melanoderma. Acute adrenal insufficiency was diagnosed (cortisol 3.7 µg/dL, hyponatremia 113 mmol/l) and treated with hydrocortisone replacement and rehydration. Imaging identified bilateral adrenal masses (81 × 52 × 72 mm and 79 × 45 × 78 mm) with necrotic centers spontaneous density of 35 HU, and an absolute washout of 66%. Normal urinary metanephrines excluded pheochromocytoma. PSA had risen to 600 ng/mL, and MRI revealed recurrent prostate tumor with seminal vesicle infiltration and bone metastases. Given the advanced disease and imaging findings, adrenal biopsy was avoided, and the adrenal lesions were attributed to metastatic prostate adenocarcinoma.. Management included Docetaxel-based chemotherapy and hydrocortisone replacement (30 mg/day).

Discussion
Adrenal metastases from prostate cancer occur in 17–20% of cases in autopsy studies, with bilateral cases being particularly rare. Prostate cancer's preference for bone and lymph nodes is mediated by adhesion molecules and growth factors favoring these sites, while the adrenal gland's unique microenvironment may deter colonization. Hematogenous spread, however, can involve the adrenal glands in advanced stages. These metastases are often asymptomatic due to the adrenal glands' functional reserve, with insufficiency manifesting only after more than 90% cortical destruction. While bilateral adrenalectomy may be an option in select cases, non-surgical treatments, such as chemotherapy, are generally preferred to reduce both primary and metastatic tumors. Chemotherapy may preserve the potential for adrenal function recovery, though definitive evidence on reversibility is limited.
Conclusion
Bilateral adrenal metastases in prostate cancer highlight the complexity of metastatic behavior in advanced disease. Comprehensive imaging and biochemical evaluations are essential in symptomatic cases. Research into adrenal microenvironment interactions and steroid biosynthesis pathways in prostate cancer may improve our understanding of metastatic patterns and guide innovative therapies.

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EP614

JOINT2304

When secondary localizations reveal papillary thyroid carcinoma: a case report

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Introduction
Papillary thyroid carcinoma is the most common histological type of thyroid cancer. Its spread is essentially lymphatic. Its prognosis is generally very good, and metastases are rare. We will illustrate a case of a patient with papillary carcinoma revealed by metastatic localization.
Observation
This 86-year-old patient presented with an altered general condition and persistent cough. A cervico-thoracic CT scan was performed, revealing multiple secondary pulmonary balloon lesions and a suspicious hepatic nodule. Clinical examination revealed a fixed, hard 2 cm cervical swelling. Cervical ultrasound revealed several eutirad nodules 3 and 5 associated with a highly suspicious laterocervical adenopathy. A total thyroidectomy with lymph node dissection was performed, and pathological examination revealed an infiltrating papillary carcinoma with vascular emboli.
Discussion
Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for around 70-80% of cases. This cancer is generally well-differentiated and has a good prognosis, with high long-term survival. However, in some cases, it may be discovered atypically. Differentiated thyroid carcinomas rarely metastasize. Papillary thyroid carcinoma has a well-known tendency to spread to cervical lymph nodes, particularly in the jugular and supraclavicular areas. However, distant dissemination to other organs is less frequent. Distant localization is mainly to the lungs and bones. The standard treatment for distant metastases remains surgery, particularly if the metastases are limited and accessible. However, chemotherapy or radiotherapy may be necessary for more advanced cases or those where surgery is not possible. Treatment consists of total thyroidectomy with lymph node dissection. Adjuvant treatments, such as radioactive iodine (I-131), are also used in cases where the cancer remains differentiated and can accumulate iodine. The prognosis of patients with metastatic disease from papillary thyroid carcinoma is generally favourable, especially if the metastases are limited and accessible. However, in the most aggressive forms with diffuse metastases, the prognosis is less favourable.
Conclusions
Papillary thyroid carcinomas revealed by metastases are rare but present a major diagnostic and therapeutic challenge.

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EP615

JOINT3712

Gastrinoma and zollinger ellison syndrome: a management roadmap

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Background
The terms gastrinoma and Zollinger-Ellison syndrome (ZES) have been frequently used as synonymous. However, gastrinomas are neuroendocrine tumors that secrete gastrin, whereas ZES refers to the clinical manifestations produced by hypergastrinemia.
Material and methods
We aimed to analyze the characteristics of patients diagnosed with gastrinomas. Between 2018 and 2024, 6 patients were diagnosed with gastrinomas in our center. They were evaluated based on clinically significant symptoms, serum gastrin level, neuroendocrine markers and with the aid of imaging such as abdominal CT or MRI, EUS, Tektrotyd scintigraphy and had genetic counseling and were tested for inherited genetic syndromes. Surgery was performed according to the localization of the tumors.
Results
Six patients with a gastrinoma diagnosis were included, four out of which had ZES. The patients had a mean age of 59 years, 50% were women, with an average BMI of 30.51 kg/m2. At diagnosis, the median level of gastrin was 292 pg/ml and all of the patients had abdominal pain, 66.67% weight loss, 50% diarrhea and one had upper gastrointestinal bleed. Most common sites of lesion were gastric and duodenal (33% each) followed by pancreatic site and one patient had no evidence of primary tumor. Five patients underwent surgical treatment with histological confirmation and had controlled neuroendocrine markers and gastrin levels after surgical treatment, while the sixth had an unknown primary lesion. Two patients (33%) have metastasis: mesenteric and pancreatic and no patient has an inherited genetic syndrome. All patients were controlled with long-acting somatostatin analogues and proton pump inhibitors.
Conclusions
Gastrinoma diagnosis is quite challenging as its symptoms can frequently be nonspecific. Two thirds of the patients evaluated in our center with a diagnosis of gastrinoma had ZES. Weight loss and other gastrointestinal manifestations were almost as frequent and a third had metastasis.

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EP616

JOINT586

Anatomopathological characteristics of papillary thyroid carcinomas associated with autoimmune thyroid disease

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Introduction
The association between papillary thyroid carcinoma and thyroiditis was first reported in 1955 by Daily, in 2023 if this association is well established, it still continues to be talked about. Does cancer associated with thyroiditis have a better prognosis?
Material and Methods
We report a prospective study carried out in a hospital center in Algeria between 2020 and 2023 which included 267 papillary thyroid cancers, of which 97 (36.3%) patients had thyroiditis. 85 (87.6%) of the patients who had an association with thyroiditis were women with a sex ratio of 3.29; their mean age was 42.79 $\pm$ 1.16 years. In thyroiditis, tumor size was smaller (OR 0.51), with less vascular invasion (OR 0.39) but more multifocality (OR 1.75), with no statistically significant difference in thyroid invasion and lymph node metastases compared to patients without thyroiditis.
Discussion
The association of papillary thyroid cancer with thyroiditis has generated many studies worldwide, but it is difficult to make comparisons because of their heterogeneity; however, our study seems to be in agreement with the results obtained by a majority of studies already published.

Conclusion
The association of papillary thyroid cancer with thyroiditis seems to be a factor of better prognosis.

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EP617

JOINT728

Effective treatment of metastatic insulinoma in MEN-1 syndrom with pasireotide

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Introduction
Insulinoma is a rare endocrine tumor originating from the beta cells of the pancreas, characterized by excessive insulin secretion and resultant hypoglycemia. While most insulinomas are benign and localized, approximately 10% progress to metastatic disease. The management of insulinoma often involves a multimodal approach. Surgical resection remains the first-line treatment, however, for metastatic cases, somatostatin analogs such as lanreotide and pasireotide are increasingly employed to control insulin secretion and tumor progression
Case
We present a case of a 58-year-old woman with MEN1 syndrome, diagnosed in 1994. The patient underwent repeated parathyroidectomy for parathyroid hyperplasia. In 1994, two-thirds of the pancreas were resected, and in 2012, an adenoma in the head of pancreas was enucleated due to the discovery of an insulinoma. The prolactinoma of the pituitary gland was managed with conservative treatment. In 2020, multiple liver lesions were found, along with recurring episodes of hypoglycemia. The presumed diagnosis was insulinoma metastases, but the lesions were not detected on the Octreoscan, which seemed to contradict the presumed diagnosis. Histological analysis of a biopsy from the dominant liver lesion confirmed a neuroendocrine tumor. Receptor testing revealed positivity for SSTR5 but negativity for SSTR2, explaining the negative Octreoscan findings. In 2022, microwave ablation was performed on the largest liver lesion. After that, the treatment with somatostatin analogues was initiated. The patient was first treated with lanreotide (pasireotide was not approved by insurance company). However, it did not adequately control the insulin secretion and episodes of hypoglycemia still occurred. Subsequently, therapy was switched to pasireotide, which effectively resolved the hypoglycemia. Pasireotide, with its high affinity for SSTR5, exerts potent antisecretory and antiproliferative effects, aligning well with the tumor's receptor profile.
Conclusion
This case highlights the complexities of managing metastatic insulinoma in the context of MEN1 syndrome. It underscores the importance of individualized treatment strategies, including receptor profiling, to guide therapy selection. While lanreotide proved ineffective, the use of pasireotide successfully controlled the patient's hypoglycemia, emphasizing the value of alternative somatostatin analogs for SSTR5-positive tumors. The multidisciplinary approach, including surgical interventions, receptor testing, and tailored medical therapy, was crucial in achieving symptom control and improving the patient's quality of life.

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EP619

JOINT3869

Late endocrine disorders in surviving children with acute lymphoblastic leukemia: single center study in Egypt

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Background
Acute lymphoblastic leukemia (ALL) is the most prevalent cancer diagnosed in pediatric population. After treatment and subsequent follow- up, most children and adolescents affected by ALL are able to resume their normal routines. However, survivors of childhood cancer require careful ongoing monitoring, as the side effects of cancer therapies may emerge years following the treatment especially the endocrine disorders and its effect on growth, puberty, thyroid gland and gonadal development.
Aim
To estimate the probability of late endocrine disorders in children who received chemotherapy during their treatment for ALL at Borg El-Arab University Pediatric Oncology Hospital, Egypt & to assess the anthropometric measurements and pubertal staging and determine the risk factors for development of endocrine disorders in these children
Results
The study included 146 participants, with 73 survivors of ALL and 73 healthy controls. According to height, survivors exhibited a significantly reduced mean height (129.5 $\pm$ 18.31 cm) compared to controls (136.2 $\pm$ 22.51 cm; $t=1.974$, $P=0.050$). The majority of patients had normal TSH levels with elevated TSH observed in 7.7% of cases indicating subclinical hypothyroidism. Elevated TSH was more prevalent in the short stature group (33.3%) compared to the overweight and obese group (7.4%), 89.7% of patients had normal glucose level, while 10.3% were classified as prediabetic, who were overweight/obese group. Both groups demonstrated normal ACTH and cortisol levels Conclusion: Endocrine disorders are very common among ALL survivors and need close monitoring and prompt treatment if detected early.

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EP620

JOINT3306

Unveiling hidden hyperparathyroidism: the critical role of calcium and PTH measurement in early diagnosis

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Background
Primary hyperparathyroidism (PHPT) is an underdiagnosed condition with systemic consequences, including cardiovascular disease, nephrolithiasis, and osteoporosis. Routine calcium and parathyroid hormone (PTH) measurement is crucial for early detection. Additionally, ultrasonography plays a key role in localizing parathyroid adenomas. We present three cases highlighting the consequences of delayed diagnosis and the importance of endocrine evaluation.
Case Presentation: Case 1
A 64-year-old female presented for levothyroxine dose adjustment. Neck ultrasound revealed a suspicious adenoma, confirmed by scintigraphy. Laboratory findings showed elevated PTH (310 pg/mL), hypercalcemia, and vitamin D deficiency (18 ng/mL). She had osteoporosis and a significant cardiovascular history, including an aortocoronary bypass and cryoablation for arrhythmias eight years prior. Despite these events, hyperparathyroidism was never suspected, highlighting the potential cardiovascular impact of undiagnosed PHPT.
Case 2
A 57-year-old female with recurrent nephrocalcinosis and multiple ureteral stents due to complications over five years was diagnosed with PHPT. PTH was 160 pg/mL, calcium was elevated, and scintigraphy confirmed an adenoma. She also had osteoporosis, previously misattributed to aging. Earlier diagnosis could have prevented renal and skeletal complications.
Case 3
A female with newly diagnosed Graves' disease underwent ultrasound, which incidentally revealed a suspicious parathyroid adenoma. Biochemical workup confirmed PHPT with hypercalcemia, and scintigraphy validated the diagnosis. The coexistence of Graves' disease and PHPT highlights the need for careful endocrine assessment. All patients underwent successful parathyroidectomy, leading to normalization of PTH levels and resolution of hypercalcemia.
Discussion
These cases emphasize PHPT's systemic effects and its frequent underrecognition in patients with cardiovascular disease, nephrolithiasis, and osteoporosis. The first case underscores PHPT's potential role in cardiovascular pathology, while the first two cases highlight its impact on bone health. The third case illustrates the importance of evaluating parathyroid glands during thyroid ultrasound. Routine screening for hyperparathyroidism in high-risk patients can prevent severe complications.
Conclusion
PHPT should be considered in patients with unexplained cardiovascular disease, recurrent nephrolithiasis, and osteoporosis. Routine calcium and PTH measurement, alongside careful ultrasound evaluation, is crucial for early detection. Recognizing PHPT at an early stage can significantly improve patient outcomes.

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EP621

JOINT3327

The impact of metabolic syndrome on survival outcomes in urothelial carcinoma: a retrospective cohort study

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Urothelial carcinoma (UC) is a prevalent malignancy of the urinary system. Muscle-invasive UC is associated with significant morbidity and mortality. Metabolic syndrome (MetS), characterized by a combination of obesity, hypertension, dyslipidemia, and insulin resistance, has been implicated in various cancers, including UC. However, its impact on UC prognosis remains underexplored. This study aims to assess the association between MetS and survival outcomes in UC patients. A single-center retrospective study was conducted, analyzing 112 patients with histologically confirmed UC, diagnosed between January 2018 and February 2024. Patients were categorized based on the presence of MetS ($\geq$ 3 criteria) or its individual components. Survival outcomes, including overall survival (OS) and progression-free survival (PFS), were evaluated using Kaplan–Meier estimates and Cox proportional hazard regression models, adjusting for disease stage and other covariates. Of the 112 patients (82.1% males, with a median age at diagnosis of 71.9 years [IQR 65.8-79]), 49 (43.8%) met the criteria for MetS. In a multivariable analysis, patients with MetS exhibited significantly worse OS and PFS compared to those without MetS (HR: 2.04, 95% CI 1.13-3.68, $P = .018$; HR: 2.13, 95% CI 1.11-4.1, $P = .024$, respectively), after adjusting for disease stage and other covariates. Among individual MetS components, diabetes had the strongest association with reduced survival (HR: 3.33, 95% CI 1.59-6.98, $P = .001$ for OS). Hypertension also emerged as an independent predictor of poor OS (HR: 1.96, 95% CI 1.04-3.73, $P = .039$). MetS and its components, particularly diabetes and hypertension, are associated with poorer survival outcomes in UC patients. These findings highlight the need for integrating metabolic health management into UC treatment strategies to improve patient outcomes.

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EP622

JOINT1888

Asymptomatic insulinoma diagnosed following a motor vehicle accident: a case report

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Insulinomas are rare pancreatic neuroendocrine tumors characterized by excessive insulin production, which leads to recurrent episodes of hypoglycemia. While most patients exhibit typical symptoms such as confusion and diaphoresis, a subset may experience hypoglycemia unawareness. This condition arises when repeated episodes of low blood glucose levels impair the body's autonomic responses, hindering the patient's ability to recognize early warning signs of impending hypoglycemia. Consequently, this can lead to delayed diagnoses and heightened risk of severe complications, including seizures, coma, or accidents. We present the case of a 69-year-old male diagnosed with insulinoma following a motor vehicle accident that revealed an alarming blood glucose level of 2.8 mmol/l, despite the patient reporting no symptoms. Subsequent investigations, including a supervised 72-hour fast, demonstrated inappropriately elevated C-peptide levels (1350 pmol/l) and insulin levels (14 mU/l) with a lab glucose reading of 2.2 mmol/l. A CT scan of the pancreas identified a 1.25 cm enhancing lesion in the proximal body, consistent with insulinoma. The patient successfully underwent a Whipple procedure, and his postoperative recovery was uneventful. This case highlights the diagnostic challenges associated with insulinomas, particularly in patients who exhibit hypoglycemia unawareness. It emphasizes the importance of considering insulinoma in the differential diagnosis for patients presenting with hypoglycemia unawareness. Early recognition and intervention are crucial to prevent serious complications associated with this condition.

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EP623

JOINT3909

A lung cancer patient presenting with gynecomastia and mastodynia secondary to paraneoplastic hyperestrogenism

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Introduction
Gynecomastia is a common clinical phenomenon that can result from various etiologies. Although it is generally linked to hormonal imbalances, gynecomastia can sometimes be associated with less obvious causes, such as paraneoplastic disorders. We report the case of a patient who presented with painful gynecomastia related to paraneoplastic hyperestrogenism.
Case presentation
A 68-year-old male patient was referred to the Endocrinology Department for painful gynecomastia that had been evolving for one year. He gives a history of lung adenocarcinoma, classified as T4N0M0, and he was undergoing chemotherapy with four cycles of Navelbine and Cisplatin. Hormonal testing showed marked hyperestrogenism, with normal levels of FSH, LH, testosterone, prolactin and β-HCG. The course of the condition was marked by the persistence of painful gynecomastia and persistent hyperestrogenism despite analgesic treatment and cessation of chemotherapy.
Discussion and conclusions
This case highlights the importance of investigating all possible causes of gynecomastia, including drug-related causes such as chemotherapy agents. Our patient had received Cisplatin and Navelbine, the adverse effect of which could be painful gynecomastia, but the symptoms persisted even after stopping chemotherapy. Patients with lung cancer and gynecomastia as a paraneoplastic syndrome have a frequency of approximately 2.4%. Gynecomastia is usually caused by an increased estrogen/androgen ratio, elevated serum levels of b-HCG, or an elevated level of prolactin. Our patient had a normal b HCG, a normal prolactin level, and a very high estrogen level which argues in favor of paraneoplastic hyperestrogenism.

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EP624

JOINT3705

Humeral metastasis of papillary thyroid carcinoma: a rare localisation in a case report

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Introduction
Papillary thyroid cancer accounts for over 85% of thyroid cancers. About 3.9% of these cancers develop bone metastases. Humeral metastases are rare and exceptional.
Observation
A 57-year-old female patient underwent total thyroidectomy in 2022. Histopathological examination revealed a 9cm, poorly defined, left toto-lobar papillary carcinoma with vascular emboli and no capsular effraction. Post operative iratherapy at a dose of 100mCi was indicated, with a huge cervical residue on whole-body scan. The extension work-up revealed bone metastases at C6 and D1, with pulmonary metastases in the form of scattered pulmonary nodules, the largest of which was 19mm mediobasal on the left and 13mm posterobasal on the right. The patient underwent external radiotherapy (8Gy) for decompressive purposes, followed by sorafenib 800mg/day. Three months later, the patient presented with mechanical pain in the left humerus radiating to the left shoulder. A CT scan showed a heterogeneous hypodense mass measuring 61x56x80mm in the neck and proximal third of the humeral diaphysis, with necrotic aeras containing fluid. Bone scintigraphy confirmed metastatic lesions in the left humerus. The patient benefited from placement of a centromedullary nail with simple postoperative follow-up.
Discussion and conclusion
Bone metastases secondary to thyroid cancer are uncommon, but a rigorous clinical history and careful examination are essential for their early detection. The humerus is one of the extremely rare sites of metastatic spread. Conventional surgical approaches for humeral metastases include the use of centromedullary nails, our patient's case, plate fixation and augmentation with cement to reconstruct large bone defects.

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EP625

JOINT1908

Phenotypic diversity in patients carrying the Y791F RET proto-oncogene mutation

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The Y791F mutation of the *RET* proto-oncogene is a well-documented genetic alteration associated with familial medullary thyroid carcinoma (FMTC), multiple endocrine neoplasia type 2A (MEN2A), and familial pheochromocytoma. This mutation activates the *RET* receptor in its monomeric form. Here, we present an analysis of 15 unrelated families carrying the Y791F mutation, exhibiting diverse phenotypic expressions.

Patients and Methods

Over the past 35 years, we have evaluated 406 patients with medullary thyroid carcinoma (MTC) (age range: 2–80 years, mean age: 49 years). Genetic testing for *RET* proto-oncogene mutations was performed using direct double-strand sequencing of PCR-amplified genomic DNA.

Results

Of the 406 MTC cases, 128 (32%) were familial. Germline Y791F mutations (C791) were identified in eight patients with MTC (age at diagnosis: 33–62 years, mean: 48 years), all of whom were index cases within their families. Among these, four patients were diagnosed, surgically treated, and cured at ages 33, 42, 54, and 55, while four others presented with metastatic MTC at ages 47, 53, 54, and 62. One patient diagnosed at 53 years of age succumbed to the disease at 63. None exhibited associated disorders. The same mutation was identified in 33 family members. Prophylactic thyroidectomy was performed in five individuals, with histopathological confirmation of C-cell hyperplasia in three cases (ages 13, 16, and 29). One patient had concurrent kidney hypoplasia and primary hyperparathyroidism (PHPT), though MEN1 mutations were not detected. Two mutation carriers showed no clinical or histological evidence of thyroid disease. Additionally, six patients exhibited congenital urogenital anomalies without other associated conditions. The L769L polymorphism was detected in five individuals, including four with MTC.

Conclusion

The prevalence of inherited MTC in our cohort aligns with previous reports; however, the frequency of the Y791F mutation appears higher than in other studies. Phenotypic expression varies widely, ranging from asymptomatic carriers to overt malignancy. Notably, a more aggressive disease course was observed in patients harboring the coexistent L769L polymorphism. The presence of renal malformations suggests that despite its oncogenic potential, insufficient *RET* protein expression during embryogenesis may contribute to developmental anomalies or indicate the involvement of additional genetic factors.

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EP626

JOINT1310

Association of schmidt syndrome with papillary thyroid carcinoma

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Background

Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy. The occurrence of PTC in patients with Hashimoto's thyroiditis (HT) has been reported and a debatable explanation of the association was some common dysregulated non-immune-linked genes involved in DNA damage and repair. However, the link between PTC and autoimmune polyglandular syndromes, such as Schmidt syndrome, has been rarely described, making it an intriguing subject for further investigation.

Case report

We report the case of a 47-year-old female with a history of Addison's disease who presented with a cervical nodule that appeared suspicious on ultrasound. Fine-needle aspiration biopsy confirmed the presence of papillary thyroid carcinoma. Histopathological examination not only validated the diagnosis of differentiated thyroid carcinoma but also revealed lymphocytic thyroiditis. Laboratory investigations showed elevated anti-thyroglobulin antibodies (56 IU/mL; normal <30 IU/mL) and elevated anti-thyroid peroxidase (TPO) antibodies, with undetectable thyroglobulin levels (<0.04 ng/mL) and high TSH levels. The patient underwent total thyroidectomy, followed by radioactive iodine therapy.

Conclusion

This case highlights the rare association between Schmidt syndrome and papillary thyroid carcinoma, emphasizing the need for increased awareness of thyroid malignancies in patients with autoimmune polyglandular syndromes as underlying autoimmune conditions may influence cancer progression and therapeutic strategies.

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EP627

JOINT2038

Parathyroid carcinoma on secondary hyperpara-thyroidism: a case report

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Introduction

Parathyroid carcinoma is a rare endocrine malignant tumor accounting for less than 1% of all cases of primary hyperpara¬thyroidism. Preoperative diagnosis and management stills a real challenge. Here we report an unusual case of parathyroid carcinoma developing on secondary hyperparathyroidism and we identify diagnostic and management challenges of parathyroid carci-noma.

Observation

A 53-year-old man, with a chronic renal insufficiency on hemodialysis, operated 10 years ago of subtotal parathyroidectomy for secondary hy¬perparathyroidism with favorable outcome, was hospital¬ized for bone pain with hypocalcaemia and elevated serum Para Thyroid Hormone (PTH). Explorations showed hyper¬plasia of lower right parathyroid gland. Surgical exploration revealed polylobulated mass of 4 cm adherent firmly to the oesophagus and to recurrent nerve. Lower right para¬thyroidectomy was so performed. Histological examination concluded to parathyroid carcinoma. Patient normalized calcium and PTH levels. No recurrence was observed after 48 months of follow up.

Conclusion

Para¬thyroid carcinoma described in patients with secondary and ter¬tiary hyperparathyroidism caused by chronic renal failure, such as the case of our patient are rare. Parathyroid carcinoma is a rare malignant tumor which still presents challenges in diagnosis and treatment. Surgery with en-block resection of the tumor and involved surrounding structures is the principal modality of treatment. The prognosis is variable due to frequent recurrences.

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EP628

JOINT2289

Primary hyperparathyroidism and papillary carcinoma of the thyroid: about a case

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Introduction

Primary hyperparathyroidism (PHPT) is a frequently encountered endocrine disorder characterized by dysregulated parathyroid hormone (PTH) secretion, most commonly due to a parathyroid adenoma. The coexistence of PHPT and papillary thyroid carcinoma (PTC) is rare, with an estimated prevalence of 2.3–4.3%. This report presents a case of incidentally discovered PTC during the evaluation of PHPT.

Case Presentation

A 47-year-old female was admitted for the management of PHPT, initially detected during the investigation of persistent lumbosciatalgia. Laboratory findings revealed hypercalcemia (2.89 mmol/l) and significantly elevated PTH levels (1087 pg/mL). Morphological assessment included cervical ultrasound, which identified a 45 mm hypoechoic nodule in the retro-inferior thyroid region, highly suggestive of a parathyroid adenoma, along with bilateral thyroid nodules classified as EU-TIRADS 3. Cervical computed tomography (CT) confirmed a retrothyroidal tissue mass on the left side, with enhancement kinetics consistent with a parathyroid adenoma. SPECT-CT further supported the diagnosis by demonstrating an MIBI-avid tissue mass in the lower left pole, indicative of parathyroid origin. The patient underwent a left inferior parathyroidectomy and left thyroid lobectomy. Intraoperative frozen section analysis

confirmed parathyroid tissue and unexpectedly revealed a papillary thyroid carcinoma, necessitating completion thyroidectomy. The final histopathological examination identified an encapsulated papillary thyroid carcinoma in the left lobe measuring 1.4 cm, with lymph node involvement (1N+/N), classifying the tumor as pT1aN1aMx. Consequently, the patient was referred to the nuclear medicine department for adjuvant radioactive iodine therapy.
Discussion/Conclusion
The concurrent occurrence of PHPT and PTC remains an uncommon finding, with its underlying pathophysiology not yet fully elucidated. Several hypotheses suggest a potential link, including shared embryological origins and common genetic mutations. This dual pathology poses significant diagnostic and therapeutic challenges, particularly when thyroid cancer remains unrecognized preoperatively. A meticulous preoperative evaluation, including intraoperative frozen section analysis, is crucial to prevent the need for reoperation and to optimize patient outcomes.
Disclosure of Interest
None declared
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EP629

JOINT939
Primary thyroid lymphoma: About 2 cases
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Introduction
Primary thyroid lymphomas are rare (2-5% of thyroid cancers and less than 5% of extra-ganglionic lymphomas). The most frequent types are B-cell lymphoma and MALT lymphoma. Posing a diagnosis problem, including differential diagnosis with anaplastic cancer. We report two different cases of thyroid lymphoma.
Observation
Case 1: 44-year-old patient, with no particular history, who consulted for a rapidly increasing goiter, cervical ultrasound found a mass classified as Eutirads 4 of 83x47mm at the expense of the right lobe on thyroiditis; thoracic CT scan confirmed the tumor which was expansive, infiltrative and compressive, plunging into the mediastinum. In view of dyspnea, a tracheotomy was performed. A biopsy returned in favor of a diffuse large cell lymphoma BCD20+, BCL6- chemotherapy Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (RCHOP) was initiated. After 6 courses, the PET-SCAN found a Deauville score of 3 in complete metabolic response. Case 2: 62-year-old patient who presented 3 months previously with a pathological fracture of the right leg on an osteolytic mass, the anatomopathological study returned in favor of a large B-cell lymphoma. The extension assessment found a large goiter at the expense of the left lobe with a large left totolobar nodule Eutirads 5 with adenopathies of which the biopsy found a diffuse large B-cell lymphoma, i.e. a second location, chemotherapy (RCHOP) was initiated.
Discussion
The risk of developing thyroid lymphoma is multiplied by 67 in case of lymphocytic thyroiditis. Because of their rarity and their clinical polymorphism, thyroid lymphomas have revealed diagnostic difficulties. Therapeutic conduct is currently well codified. Their prognosis, depending on the histology and stage of the disease, was favorable with a 5-year survival rate of 70 to 80%.
Conclusion
Due to the different therapeutic management, thyroid lymphoma is a diagnosis that must be mentioned in front of any cervical mass with rapid evolution, especially if there is a history of thyroiditis
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EP630

JOINT1329
Hypercalcemia as a first manifestation of metastatic neuroendocrine tumour
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Neuroendocrine tumours are a rare, heterogeneous group of tumours arising from neuroendocrine cells, whose common feature is the production, accumulation and release of a biologically active hormone-like substance. They are dispersed in various tissues with the highest incidence in the gastrointestinal system. Most of the tumours grow slowly. They have a varied clinical symptomatology dependent on hormonal activity. Their occurrence is familial and sporadic. We present a case report of an 84-year-old biologically younger man with asymptomatic mild hypercalcaemia (3 mmol/l), which was a secondary finding on examination after a bicycle accident. CT scan of the abdomen revealed a bulky inhomogeneous lesion with a diameter of 8 cm with central disintegration in the right lobe of the liver, which was suspicious for metastasis. The patient's current personal history includes chronic heart failure with preserved left ventricular ejection fraction in atrial fibrillation, moderate aortic stenosis, arterial hypertension, and multinodular goitre with laboratory signs of hyperthyroidism. Endoscopic sonography and FNAB confirmed a neuroendocrine tumour grade 1–2. The tumour cells were immunopositive for creatine kinase, chromogranin, synaptophysin and insulinoma-associated protein 1. In particular, the proliferative activity assessed by Ki67 in hot-spots was around 5%. As a part of staging, whole-body scintigraphy was added. SPECT/low dose CT scintigraphy with ^{99m}Tc-Tektrotyd showed tumorous lesion with high somatostatin receptor expression in the caudate region of the pancreas and a disseminated lesion with marginally slightly increased somatostatin receptor expression in the right lobe of the liver. Paraneoplastic hypercalcemia (low PTH levels) was corrected with bisphosphonates. Considering the patient's age, comorbidities and asymptomatic course of the disease, the multidisciplinary team indicated palliative hormone therapy with Somatuline.
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EP631

JOINT2200
Endocrine status on glucose, thyroid and calcium metabolism after treatment for breast cancer in postmenopausal women
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Introduction
Endocrine side effects to breast cancer treatment become more prevalent as survival rates increase making it relevant to know if, when and how to treat. Previously studies described a negative effect of chemotherapy on metabolism such as weight gain and an increased incidence of the diagnosis of type 2 diabetes.
Materials and Methods
We aimed to exploratively describe selected endocrine areas in postmenopausal women with non-metastatic breast cancer focusing on glucose, thyroid and calcium metabolism. Relevant blood samples were collected at baseline immediately before chemotherapy and after completing chemotherapy. Patients were compared to healthy controls at baseline.
Results
95 patients of which 64 were fasting had higher BMI before chemotherapy, higher fasting plasma glucose, fasting C-peptide and higher HOMA-IR compared to controls. Fasting plasma glucose and fasting C-peptide were still significantly higher in patients when adjusted for BMI. After chemotherapy patients had lower ionized calcium and free T4 and higher levels of parathyroid hormone and 25-OH-Vitamin-D. No significant change was seen in blood test relevant for the glucose metabolism.
Conclusions
At baseline patients already show signs of impaired glucose metabolism compared to controls. Chemotherapy doesn't appear to change parameters of glucose metabolism. After chemotherapy changes are seen in thyroid and calcium metabolism though changes are interpreted as having no clinical significance.
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EP632

JOINT3901
Treatment of a catecholamine-secreting vagal paraganglioma with fractionated stereotactic radiotherapy
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Background
Glomus vagale tumors are rare neuroendocrine tumors belonging to the group of head and neck paragangliomas (HNPGLs). The most common symptom is a neck

mass, followed by cranial nerve palsies. In very rare instances, vagal paragangliomas (VPGLs) secrete catecholamines. The management of HNPGLs has changed dramatically in recent decades. Surgery was historically the first-line treatment for all HNPGLs and remains the primary approach for functional HNPGLs. While potentially curative, surgery carries a high risk of morbidity, including cranial nerve deficits and vascular injury. In VPGLs, a postoperative vagal deficit is almost inevitable. Fractionated stereotactic radiotherapy (FSRT) has emerged as a viable treatment option for non-secreting HNPGLs, offering excellent long-term tumor control with a low complication rate. However, data on FSRT for functional HNPGLs/VPGLs remain limited.
Case Presentation
A 65-year-old patient presented to the emergency department with syncope. A CT scan revealed a neck mass suspicious for a paraganglioma, prompting further evaluation. There was no evidence of cranial nerve palsy. His past medical history was notable for a 10-year history of hypertension, well controlled with Candesartan and Amlodipine. There were no additional signs or symptoms of catecholamine excess. Biochemical testing revealed significantly elevated plasma-free normetanephrine (6.38 nmol [0.04–1.39 nmol/l]) and methoxytyramine (0.22 nmol/l [$<$ 0.06 nmol/l]). MRI demonstrated a VPGL in loco typico, measuring 41 $\times$ 20 $\times$ 43 mm. Whole-body MRI and DOTATATE-PET/CT showed no evidence of multicentric disease, metastases, or synchronous pheochromocytoma/sympathetic PGL. Genetic testing did not detect pathogenic variants in PGL susceptibility genes. Surgical and radiotherapeutic options were discussed. The patient opted for FSRT. A total dose of 25 Gy in five fractions was administered. Prior to radiotherapy, the patient was started on phenoxybenzamine. During a 11-month follow-up, the patient developed no new symptoms of catecholamine excess. His blood pressure remained well-controlled. On MRI, the VPGL remained stable in size. Plasma metanephrine levels dropped significantly six months post-treatment (normetanephrine: 3.84 nmol/l, methoxytyramine: 0.13 nmol/l) and remained stable at 11 months (normetanephrine: 4.26 nmol/l, methoxytyramine: 0.20 nmol/l), but normalization has not yet been achieved.
Conclusion
Our case demonstrates that FSRT can reduce catecholamine secretion from functional VPGL within a short follow-up period. However, a longer follow-up is necessary to assess the further trajectory of metanephrine levels and to better evaluate the appropriateness of FSRT for managing functional VPGLs. The long-term efficacy and durability of response of FSRT may only become fully apparent over several years.

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EP633

JOINT3291

Unexpected evolution of an ACTH secreting pitnet

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Introduction
Pituitary carcinoma (PC) is a rare tumor and represents only 0,1 - 0,2% of all pituitary tumors. Early diagnosis of PC is often challenging and requires the presence of metastases.
Observation
A 59-Year-old diabetic patient was referred to our clinic. A Cushing syndrom was suspected due to hypercatabolic signs and was confirmed by elevated urinary free cortisol (UFC) = 800µg/24h [22-110]. Due to elevated ACTH levels (95pg/ml [10-50]), a pituitary MRI was performed and showed a 7mm pituitary adenoma. The patient underwent a complete transsphenoidal resection. Pathology examination showed a Corticotrop benign pitnet with a Ki67 = 1%. After surgery, diabetes and hypertension have improved, and the patient had a corticotropin deficiency. Three months after surgery, due to worsening of blood pressure and diabetes, dexamethasone suppression test was performed with cortisol levels at 1,9 µg/dL, suggesting the relapse of the Cushing disease with a normal pituitary MRI. The patient went through Radiotherapy (54 Gy) and was put on Ketoconazole 400mg per day for two years with normal UFC levels. After withdrowal of ketoconazole and increase of UFC levels, the patient underwent bilateral adrenalectomy and was under hydrocortisone and fludrocortisone replacement. After six months, she developped hyperpigmentation with ACTH levels of 1890pg/ml suggesting Nelson's syndrom, later associated with ptosis and mydriasis. A pituitrary MRI showed a 25*21*13mm macroadenoma with cavernous and optic chiasma extension. She went a second Transsphenoidal Surgery followed by gamma night radiotherapy. Pathological examination showed an atypic pitnet with Ki67 = 10% $>$ 3%, complicated by dural metastases after two years. She was treated by temozolomide for 15 months.
Conclusion
Although ACTH pitnet is a disease with frequent relapse, the Transformation of a benign pitnet to a PC is rare. A review showed that the mean time interval from initial diagnosis to diagnosis of PC was 10.7 years. This suggests to be careful and repeat MRIs if there are signs of aggressivity.

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EP634

JOINT786

Calcium as a tumour marker in PTHrP-secreting pancreatic neuroendocrine tumour: a case of multimodal management

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Introduction
Pancreatic neuroendocrine tumours (PNETs) have an annual incidence of less than 1 case per 100,000 people, with the majority being nonfunctional. PTHrP-secreting PNETs are particularly rare, with few cases reported globally. Hypercalcemia caused by PTHrPoma can be life-threatening and requires a multimodal and multidisciplinary approach for effective management. In such cases, calcium levels may serve as a reliable tumour marker, particularly when PTHrP assays are unavailable.
Case presentation
A55-year-old woman was diagnosed with an 8 cm pancreatic tumour, secreting PTHrP (2.2 pmol/l, normal range 0-1.8), with multiple liver and spleen metastases. The patient presented with cough and hypercalcemia (2.85 mmol/l) with a fully suppressed PTH. Imaging revealed a large pancreatic mass, and histology confirmed a neuroendocrine tumour (ENETS Grade 2, Ki67 7%). Initial treatment with somatostatin analogue (SSA) Sandostatin® LAR® led to excellent response and subsequent normocalcaemia. However, a side effect of extreme insomnia prompted a switch to Somatuline® Autogel®. Progression then led to treatment combination with Peptide Receptor Radionuclide Therapy (PRRT) with Lutathera®. After 4 cycles of PRRT, tumour shrinkage was observed and normalisation of calcium and PTH levels was achieved, although PTHrP assay was no longer available. The patient continued to experience insomnia with SSA, including during a trial of subcutaneous short-acting octreotide. Given her favourable response to PRRT, SSA therapy was eventually discontinued to improve her quality of life. Subsequent hypercalcaemia was poorly controlled with zoledronate and denosumab, leading to the rapid development of bilateral hip osteoarthrosis, requiring joint replacements. As the disease and hypercalcaemia progressed despite a re-trial of Somatuline® Autogel®, chemotherapy was initiated. The patient received 2 cycles of Capecitabine/Temozolomide by 8 years after her original presentation, resulting in a reduction of the primary tumour and liver metastases, along with normocalcaemia. Severe depression ensued, which was managed with citalopram and required a treatment break.
Conclusion
PTHrP-secreting PNETs are extremely rare and are associated with hypercalcaemia and increased mortality. Successful management often requires a combination of therapies, including SSAs, PRRT and chemotherapy, conferring tumour and calcium levels control and ultimately prolonging survival. This case highlights the importance of personalised management strategies for NETs, with calcium serving as a reliable tumour marker for disease monitoring and treatment assessment.

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EP635

JOINT1161

Hypoglycemia secondary to metastatic solitary fibrous tumor: doege-potter syndrome. importance of the IGF-II/IGF-I ratio

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Introduction
Doege-Potter syndrome is a rare clinical entity characterized by recurrent hypoglycemic events caused by non-pancreatic tumors secreting an incompletely

processed high-molecular-weight form of Insulin-like Growth factor-II (IGF-II). Usually caused by a solitary fibrous tumor (SFT) and mediated by the binding of IGF-II precursors to insulin receptors. They have a benign behavior in most cases and rarely produce metastasis, although up to 12% present malignant behavior. They are more frequent in men, between the sixth and eighth decade of life and predominate in the right hemithorax. The treatment of choice is surgery, but in unresectable cases, although glucocorticoids (GC) play a major role, the approach is controversial. Our aim is to present a case of Doege-Potter syndrome and the importance of the IGF-II/IGF-I ratio in individuals with hypoglycemia secondary to IGF-II-producing STF.

Case report

A 65-year-old male diagnosed with pleural SFT. He was admitted to the Emergency Department due to massive pleural effusion secondary to a large mass in the left hemithorax (> 20 cm) and extrapulmonary extension. Clinical signs of IGF-II-mediated hypoglycemia (<20 mg/dL): C-peptide 0.19 ng/mL, insulin <0.2 uU/mL, IGF-I 53.3 ng/mL (93-224), IGF-II 941 ng/mL (350-1000), IGF-II/IGF-I 17.6 (VN <10). Treatment with GC was started, requiring escalation to 1.5 mg/kg/day and glucagon to prevent hypoglycemia, so diazoxide was added to reduce the GC dose. Continuous interstitial glucose monitoring (CGM) and selective radiotherapy (SR) were started which facilitated management and subsequent surgical resection.

Discussion and conclusions

Hypoglycemia secondary to large IGF-II-producing STF is a therapeutic challenge. CGM is an aid in management, as well as a response to diazoxide and SR described in the literature to achieve tumor control and hypoglycemia that allows curative surgical treatment. However, a recurrence rate of up to 15% is estimated according to described series. These are slow-growing tumors with few initial respiratory symptoms and in which hypoglycemia may be the initial symptom, so emphasis should be placed on the evaluation of thoracic imaging studies in the event of persistent hypoglycemia. The plasma IGF-II/IGF-I ratio better indicates the Doege-Potter syndrome's metabolic impairment than isolated measurements of circulating IGF-II or IGF-I levels.

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EP636

JOINT3388

An unusual evolution of a malignant metastatic pheochromocytoma: A case report

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Introduction

Malignant metastatic pheochromocytoma is a rare neuroendocrine tumor that originates from chromaffin cells in the adrenal medulla, distant metastases confirm its malignancy. We present a case of a malignant metastatic pheochromocytoma, emphasizing its uncommon evolution.

Case presentation

A 45 year old patient with history of congenital ictyosis presented with decreased visual acuity and headaches dating to one month. Ophthalmic examination showed stage 3 papillary edema, a cerebral MRI showed an expansive intrasellar process bulging into the sphenoid sinus encompassing the cavernous carotid artery. A TAP CT showed left latero-aortic retroperitoneal tissue mass measuring 12.5*12 cm at the expense of the adrenal gland. The diagnosis of pheochromocytoma was mentioned in the face of blood pressure peaks with hypertensive emergency and the Menard triad and confirmed with Urinary methoxyl derivatives > 20 times the upper limit of normal and Plasma methoxyl derivatives > 10 times the upper limit of normal. MIBG scintigraphy showed: left adrenal pheochromocytoma with bone metastases and at the level of the sella turcica. Our patient was operated two years after diagnosis, Left adrenalectomy with left nephrectomy were performed while bone metastases were left untreated, the operative consequences were simple. The anatomopathological examination showed Morphological appearance and immunological profile compatible with pheochromocytoma. The postoperative evolution was marked by the normalization of blood pressure figures objectified by a blood pressure Holter, no menard triad and normalization of plasma metanephrine (Normetanephrine = 1.57 (< 1.07nmol/l), Metanephrine <0.1nmol/l (<0.33)). Seven years after diagnosis our patient presents with a conserved general state.

Conclusion

Five year survival rates after surgery for malignant pheochromocytoma vary between 34 and 60% with high risk of recurrence. The particularity of our patient is conserved general state, normalization of metanephrines and stable metastases up to 5 years after surgery. This case highlights the diagnostic and therapeutic complexity and severe systemic implications of malignant pheochromocytoma. While surgical resection of metastases is an option in oligometastatic cases, it was not feasible for this patient. Novel therapeutic strategies, including internal radiotherapy (I131-MIBG), hepatic chemoembolization, systemic chemotherapy, and targeted therapies such as anti-angiogenics (Sunitinib), offer promising alternatives for managing metastatic disease.

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EP637

JOINT3880

Thyroid metastasis of pulmonary choriocarcinoma: a rare and challenging diagnosis

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Introduction

Metastatic disease to the thyroid is an uncommon but welldocumented event and accounts for 1–9 % of all thyroid malignancies. The three most common neoplasms to metastasize to the thyroid were from the kidney, lung, gastrointestinal tract and breast, respectively. The treatment options in patients with metastatic disease to the thyroid gland should be made based upon the condition of the patient, extent of the disease, stage, and volume The aim of this report is to present this case and discuss the diagnostic difficulties of an unusual presentations of thyroid metastasis of choriocarcinoma

Materiel and methods

We report a rare case of thyroid metastasis from lung choriocarcinoma.

Observation

A 55 year-old male patient, with a history of Hodgkin's lymphoma treated with radiochemotherapy in 1998, complained of a cervical mass for 4 month. He was referred for exploration and management of the mass. On examination, a 10-cm growth was palpable on the right paramedian anterior neck, in favour of a heterogenous thyroid goiter. β -hCG was elevated. CT scan showed a suspicious excavated mass in the posteroinferior segment of the left inferior lobe of the lung, along with solid nodules and confluent mediastinal and hilar enlarged nodes. Cervical lymphadenopathies, adrenal and cerebral nodules indicative of metastasis, were also observed, and heterogeneous thyroid goiter. A primary pulmonary malignancy was suspected. Fine needle aspiration showed anaplastic malignant cellsA thyroid biopsy was performed, indicating the presence of trophoblastic cells characteristic of a choriocarcinoma metastasis in the thyroid gland. These findings were corroborated by the presence of the same malignant cells in the bronchial biopsy. β -hCG was elevated. The multidisciplinary team decision was to start chemotherapy. Unfortunately, the patient passed away before he could be started on chemotherapy.

Conclusions

Metastasis to the thyroid gland is a rare condition that may pose a diagnostic challenge. the overall prognosis is poor.

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EP638

JOINT991

A rare combination of three endocrine neoplasms and cervical adenocarcinoma

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Introduction

Papillary thyroid carcinoma, prolactinoma and nonfunctioning adrenal adenoma are relatively common endocrine tumors. However, their occurrence alongside cervical adenocarcinoma in a single patient is extremely rare. When such a combination is present, it is crucial to evaluate the nature of the multiple tumors—whether they are primary, metastatic or syndromic.

Case Report

A 45-year-old woman visited the clinic in 2023 with galactorrhea. Several years prior, she had been diagnosed with hyperprolactinemia at a local hospital and had been periodically treated with cabergoline. Her past medical history also revealed a nontoxic multinodular goiter. In 2022, she underwent a hysterectomy with bilateral salpingo-oophorectomy due to cervical adenocarcinoma, followed by

radiation therapy. Subsequent studies, including a computed tomography (CT) scan (recommended by an oncologist), revealed a right adrenal incidentaloma—a 25 mm homogeneous, lipid-rich adrenal mass with unenhanced HU of -10. Adrenal hormonal tests were normal. Additional laboratory tests revealed normal levels of TSH, FT4, creatinine, ALT, AST, calcium, PTH, HbA1c, glucose and C-peptide. Serum prolactin was again elevated. The breast examination showed no abnormalities. A cranial MRI revealed a rounded 7×8×8 mm pituitary mass, with no compression of the optic chiasm. Additional pituitary hormonal tests were normal. All other causes of hyperprolactinemia were ruled out and cabergoline was restarted. A repeated ultrasound examination of the thyroid gland revealed multiple small, non-oval, markedly hypoechoic nodules with microcalcifications in the left lobe and isthmus. Cytological examination of the dominant nodule (9×6×8 mm) revealed papillary carcinoma. Thyroidectomy with lymphadenectomy was performed. Histological examination confirmed multifocal papillary microcarcinomas with microscopic invasion into the perithyroidal soft tissue. A multidisciplinary team recommended radioiodine therapy. Follow-up studies after 1 year showed an excellent response. After 1 year, the pituitary microadenoma remained unchanged. The patient feels better and continues taking levothyroxine and cabergoline.

Discussion

When two or more endocrine tumors are detected, it is essential to exclude multiple endocrine neoplasia (MEN) syndrome. According to current data, our patient does not have primary hyperparathyroidism (the most common and early manifestation in MEN-1 and MEN-4) or any enteropancreatic tumors. The family history is unremarkable. The patient was informed about genetic testing, which was not performed yet.

Conclusion

The combination of three primary endocrine tumors with concomitant non-endocrine cancer in a single patient is a rare occurrence that requires a multidisciplinary approach and regular follow-up.

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EP639

JOINT1950

Successful management of papillary thyroid microcarcinoma with distant metastases: a case report

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Introduction

Papillary thyroid carcinoma (PTC), a subtype of differentiated thyroid carcinoma (DTC), is classified as papillary thyroid microcarcinoma (PTMC) when ≤1.0 cm. Distant metastases from PTMC are rare (0-2.8 %). Therefore, long-term assessment of patients receiving surgical treatment and radioactive iodine is essential, since approximately 50% of DTC patients with distant metastases are classified as radioiodine-refractory, influencing survival rates.

Case

A 51-year-old female presented with a two-year history of a right neck mass.

Neck ultrasound

Revealed a 0.9×0.6 cm lymph node with hyperechoic foci in the right level IV region.

Thyroid ultrasound

Identified a ~0.2 cm hypoechoic nodule with ill-defined margins near the capsule on the right lobe (EU-TIRADS 5).

Fine-needle aspiration biopsy

Confirmed metastasis of PTC.

Laboratory tests

TSH, FT4, FT3, anti-TPO, anti-Tg within reference ranges.

Surgery

Subsequently, in April 2024 the patient underwent thyroidectomy and lymphadenectomy. TSH suppression (<0.1 mIU/l) is maintained with L-thyroxine 175 mg/day.

Microscopic examination

A 0.3 cm poorly defined, non-encapsulated tumor with papillae and pleomorphic cells, not invading the capsule; the pathological neck lymph node was not identified or removed.

SPECT/CT

Whole-body SPECT/CT revealed lung foci and I-131 uptake in the thyroid lodge and a level VI lymph node. The patient was diagnosed with stage II PTC, pT1aN1M1, and bilateral lung metastasis.

Radioiodine therapy

A cumulative dose of 6,1 GBq of iodine-I31 treatment was administered. SPECT/CT showed resolved lung I-131 uptake and faint residual thyroid and lymph node uptake. On November 2024, laboratory results: TSH at 0.01 mIU/l (n.r. 0.4-3.6), thyroglobulin at 0.2 mg/l, and anti-TG at 6.1 kU/l (n.r. <13.6). On January, 2025, thyroglobulin was <0.2 mg/l, and anti-TG was <1.3 kU/l. Concurrently, whole-body scintigraphy was performed. Laboratory and scintigraphy results proved an excellent biochemical and radiological response.

Discussion

A 0.3 cm PTMC, histologically benign in nature, caused metastases in the cervical lymph nodes and lungs. Nevertheless, I-131 therapy was effective in treating patient's condition. Although active surveillance is becoming the standard approach for PTMC, the potential for metastasis in some cases highlights the need for prompt surgical intervention.

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EP640

JOINT2915

Medullary thyroid cancer and infiltrating ductal carcinoma of the breast: a rare association

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Introduction

Thyroid and breast cancers are among the most common cancers, but their coexistence, in particular the association of medullary thyroid carcinoma (MTC) and breast cancer, remains relatively unexplored. This case report illustrates a medullary thyroid carcinoma revealed during the post-therapeutic follow-up of an operated ductal carcinoma of the breast.

Observation

This is a 57-year-old female patient with a history of breast cancer in her sister. She was operated on 10 years ago for ductal carcinoma of the left breast treated by total mastectomy, adjuvant chemotherapy and radiotherapy. The patient was declared in remission, and annual surveillance was initiated. The evolution was marked by the observation of a cervical mass 2 years ago during a post-treatment follow-up consultation. Cervical ultrasound revealed a 22 mm right totolar nodule classified as eutirads 3. A cytopunction was performed and found to be cytologically suspicious of malignancy. The patient underwent total thyroidectomy, the anatomopathology was in favour of a 2.8 cm medullary carcinoma with, on immunohistochemical study, a low-grade MTC with positive calcitonin and negative thyroglobulin. A calcitonin and CEA assay at 6 MONTHS post-op were negative. There were no other components of NME 2

Discussion

The links between CMT and breast cancer are not yet fully understood, but several hypotheses are being explored Although RET mutations have been widely studied in the context of thyroid cancers, several recent studies have suggested that this gene may also play a role in the development of certain types of cancer, including breast cancer. However, the involvement of the RET gene in breast cancer is still in the exploratory phase. It has been suggested that abnormal activation of the RET signaling pathway may contribute to the initiation or progression of certain breast cancers, although this link is less direct than for endocrine cancers. The mechanisms by which RET might contribute to breast cancer probably involve complex interactions with hormone receptors (such as estrogen receptors)

Conclusion

The association between medullary thyroid carcinoma and breast cancer is rare, but deserves special attention in cases where common risk factors, such as genetic mutations, are present

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EP641

JOINT3304

Papillary thyroid carcinoma associated with primary hyperparathyroidism: a rare occurrence

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Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by excessive parathyroid hormone secretion. While it is often associated with medullary thyroid carcinoma (MTC) in the context of multiple

endocrine neoplasia type 2 (MEN2), its association with papillary thyroid carcinoma (PTC) remains rare (1,2). Here, we report an exceptional case of this coexistence.
Case Report
A 67-year-old woman with type 2 diabetes complicated by chronic kidney disease was referred to endocrinology for hypercalcemia. Biological investigations confirmed PHPT. Cervical ultrasound showed multiple thyroid nodules, with the most concerning located in the right mediolobar region, measuring 5.4 × 4.6 × 4 mm and classified as EU-TIRADS V. It also revealed a hypoechoic lesion beneath the thyroid, suggestive of a parathyroid adenoma with a maximum diameter of 13 mm. This finding was confirmed by parathyroid scintigraphy, which identified a subisthmic parathyroid adenoma. Calcitonin levels were negative. A total thyroidectomy and parathyroidectomy were performed. Histopathological examination revealed an invasive micropapillary thyroid carcinoma (0.5 cm) in the right lobe, associated with a parathyroid adenoma. Postoperative assessment showed normalization of serum calcium and PTH levels, with complete remission achieved after a course of radioiodine (I-131) therapy.
Discussion & Conclusion
The co-occurrence of PTC and PHPT has been reported in 2.3–4.3% of patients undergoing surgery for PHPT (3). The underlying pathological mechanism linking these two conditions remains poorly understood and has not yet been fully elucidated. Current hypotheses point to the involvement of embryological factors and shared genetic pathways (1). Although this association is considered rare, recognizing it in clinical practice is essential to ensure an optimal management strategy for both conditions and improve patient outcomes (4).
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EP642

JOINT604

A case of ectopic ACTH secretion caused by thymic neuroendocrine tumor (typical carcinoid) with metastasis to the breast after long-term remission

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Ectopic adrenocorticotropic hormone secretion (EAS) remains one of the most difficult challenges in endocrinology, representing between 9 and 18% of ACTH-dependent Cushing̲s syndrome (CS) cases. Thymic neuroendocrine tumors (NETTs) are rare, mostly aggressive tumors, that are responsible for about 5-16% of EAS in recent series. We present a unique case of 34-year old female with EAS caused by NETT - typical carcinoid. First disease manifestation occurred in April 2016, when patient presented with severe hypercortisolism, diagnosed as EAS. First-line cross-sectional imaging studies were inconclusive, only ^{68}Ga DOTA-TATE PET/CT revealed an oval lesion in the anterior mediastinum (1.9 x 1.3 cm) with subtle overexpression of somatostatin receptors (SUV max. 2.8). After initial treatment with steroid inhibitor (ketoconazole) the patient was sent to thoracoscopic removal of mediastinal tumor, in histopathological examination typical carcinoid without lymph node metastases was diagnosed. Postoperatively, transient adrenal insufficiency was observed with resolution of all symptoms. There was a diseases recurrence after 5 years of observation caused by a metastasis to the breast, shown in ^{68}Ga DOTA-TATE PET/CT and confirmed with breast biopsy. Again, treatment with steroid inhibitor (metyrapone) and tumor resection were curative. Last disease relapse appeared 7 years after initial treatment (January 2023), with severe hypercortisolism treated with osilodrostat. There was a local recurrence in the mediastinum and a thoracoscopic surgery was performed with good clinical and biochemical effect. The patients remains under a careful follow-up. In conclusion, our case proves that NETTs with EAS might present in young patients with well-differentiated tumor in histopathological examination and severe, life-threatening hypercortisolism despite small size of the primary lesion. ^{68}Ga-DOTATATE PET/CT is a very helpful tool to localize the tumor. There are only few descriptions of breast metastases from NETTs associated with EAS, our case was confirmed in biopsy and hormonally active. Finally, lifelong follow up should be performed despite complete remission after surgery.

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EP643

JOINT2019

Cervical lymph nodes metastasis revealing occult papillary thyroid carcinoma

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Introduction
Cervical lymph node metastasis revealing occult papillary thyroid carcinoma (PTC) is uncommon. This clinical situation raises double problem: problem of diagnosis, in the presence of a chronic lymphadenopathy without known primitive and on the other hand its impact on the prognosis of these micro carcinomas.
Patients and Methods
A Descriptive retrospective study including 6 cases of cervical node metastasis revealing PTMCs.
Results
The average age in our series was 60 years (40-84 years). The sex ratio was 0,5. All our patients presented with latero-cervical tumefaction. The topography was the sector II in 1 case, sector III in 3 cases and sector IV in two cases. The thyroid was not palpable in all patients. The fine needle biopsy performed in five cases, suggests the diagnosis of a lymph node metastasis of papillary carcinoma of the thyroid. Total thyroidectomy was performed with central and lateral neck dissection in all cases. All patients were referred for radioactive iodine (RAI) ablation therapy. The mean follow-up was 5 years.
Conclusion
A laterocervical mass may be the only presentation of a clinically occult thyroid microcarcinoma. The treatment is that of any thyroid carcinoma and provides a good oncological result despite the possibility of locoregional recurrence.

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EP644

JOINT1547

An unusual case of cervical mass.a case report

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Primary thyroid sarcoma is a rare tumor. It confers a poor prognosis due to its metastatic capacity. Differential diagnosis is a challenge due to its low prevalence. We present the case of a primary thyroid sarcoma in a 71-year-old female patient admitted for upper airway obstruction related to a voluminous mass dependent on the left thyroid lobe with thrombosis of the internal jugular vein. In addition, the CT scan shows two nodules in the right lung. She required admission to the intensive care unit requiring tracheostomy due to the unresectability of the tumor. The results of the incisional biopsy showed data compatible with primary high-grade thyroid sarcoma. During hospitalization she had two episodes of airway obstruction with admission to the ICU for poor secretion management. In addition she had an urinary tract infection by *Klebsiella pneumoniae ESBL* and febrile neutropenia after oncological treatment was started. She was discharged after speech therapy rehabilitation and after receiving adequate nutritional support. She is currently being treated with doxorubicin. According to epidemiology, only 142 cases of primary thyroid sarcoma have been described in the medical literature. Given its rarity, there are no imaging techniques to differentiate it from other common thyroid tumors. The differential diagnosis should be made with thyroid lymphoma and anaplastic thyroid cancer. Its treatment is based on the pillars of surgery, chemotherapy and radiotherapy,

although there is still no defined line. The clinical manifestations consisting of a rapid increase of a painless mass in the neck with obstruction of the airway should make us consider this extremely rare and aggressive entity.

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EP645

JOINT3841

Incidental detection of papillary thyroid carcinoma on 18F-FDG PET/CT: a case report

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18F-FDG PET/CT is widely used in oncology for staging and monitoring various malignancies, but it can also reveal unexpected findings, including thyroid nodules. Incidental detection of papillary thyroid carcinoma (PTC) on PET imaging is uncommon and often requires further evaluation. We report the case of a 50-year-old woman undergoing treatment for follicular lymphoma. As part of the initial staging workup, an 18F-FDG PET/CT was performed, revealing a hypermetabolic nodule in the upper right thyroid lobe. A cervical ultrasound confirmed the presence of a suspicious thyroid nodule, and a fine-needle aspiration biopsy was performed. Cytological analysis was suggestive of papillary thyroid carcinoma (Bethesda V). Given these findings, the patient underwent total thyroidectomy with bilateral recurrent lymph node dissection. Histopathological analysis confirmed a 1.3 cm papillary thyroid carcinoma with focal capsular invasion and clear surgical margins. Lymph node dissection was positive on the left side. Consequently, the patient was scheduled for radioactive iodine therapy. This case highlights the role of 18F-FDG PET/CT in detecting incidental thyroid malignancies in patients with other primary cancers. It underscores the importance of further evaluation of hypermetabolic thyroid nodules to ensure timely diagnosis and appropriate management.

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EP646

JOINT3898

Unusual skeletal muscle metastasis from poorly differentiated thyroid carcinoma: a rare presentation

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Poorly differentiated thyroid carcinoma (PDTC) is a rare and aggressive form of thyroid cancer, with metastases typically involving the lungs, bones, and lymph nodes. However, skeletal muscle involvement remains an exceptional occurrence. We report the case of a 51-year-old woman who initially underwent total thyroidectomy with bilateral mediastino-recurrential lymph node dissection for a poorly differentiated carcinoma arising from an invasive follicular thyroid carcinoma. Histopathological examination revealed the presence of vascular emboli and associated chronic lymphocytic thyroiditis. The patient received two courses of radioactive iodine therapy, resulting in complete clinical, biological, and isotopic remission. Four years later, the patient presented with two palpable subcutaneous nodules in the right sternocleidomastoid muscle, measuring 10 mm and 11 mm on ultrasound. A suspicious right submandibular lymphadenopathy was also noted. Serum thyroglobulin levels under TSH suppression showed a mild elevation from 0.1 to 0.46 ng/mL. 18F-FDG PET/CT revealed metabolically active involvement of the right sternocleidomastoid muscle, associated with bilateral subcentimetric cervical lymph nodes with low metabolic activity. Theses findings were suggestive of muscle metastasis from the known primary thyroid carcinoma. As a result, the patient was considered for surgical excision. This case highlights a rare presentation of PDTC with isolated skeletal muscle metastasis, underscoring the importance of considering atypical metastatic sites in recurrent thyroid cancer to guide appropriate therapeutic decisions.

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EP647

JOINT8

Adrenocortical carcinoma: a deadly challenge

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Background
Malignant adrenocortical carcinoma (ACC) is a rare, aggressive endocrine malignancy with a poor prognosis, even with therapeutic intervention. Tumor size and metastatic spread significantly influence the disease's clinical course. Despite advancements in diagnostic and treatment approaches, managing ACC remains challenging, necessitating a multidisciplinary strategy.
Case Presentation
We report the case of a patient presenting initially with nonspecific abdominal pain managed with symptomatic treatment. Persistent symptoms led to further imaging, revealing a large right adrenal mass measuring 105 × 107 × 71 mm, accompanied by pulmonary, lymph node, and retroperitoneal metastases. Clinical examination showed hypercorticism, hyperandrogenism, and signs of virilization. Laboratory investigations confirmed elevated urinary free cortisol (8 times normal), testosterone (0.53 ng/ml), and SDHEA (84.82 µg/dl), alongside hypokalemia (2.5 mmol/l), which required correction. Negative plasma methoxylated derivatives excluded pheochromocytoma. Pathological confirmation of malignant ACC was obtained via biopsy. Despite initiating a chemotherapy protocol, the patient succumbed shortly after admission to the oncology unit.
Discussion
ACC's clinical presentation often varies, ranging from asymptomatic incidentalomas to severe hormonal dysregulation and metastatic disease. In this case, the constellation of virilization and hypercortisolism highlights the functional nature of the tumor. Imaging and biochemical workup were pivotal in rapid diagnosis—unfortunately, the advanced stage at presentation limited therapeutic options. Current recommendations emphasize the importance of early detection through vigilant monitoring of incidental adrenal masses and hormonal assessment. Treatment modalities include surgery for localized disease, systemic therapies such as mitotane, and palliative measures for advanced cases. The poor prognosis in advanced ACC underscores the need for novel therapeutic approaches and inclusion in clinical trials.
Conclusion
This case highlights the aggressive nature of ACC and the importance of a comprehensive, multidisciplinary approach in management. The rapid progression from diagnosis to mortality underlines the critical need for earlier detection and innovative therapeutic strategies to improve patient outcomes. Future research should focus on early biomarkers, targeted therapies, and optimizing systemic treatments to better address this devastating malignancy.

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EP648

JOINT1465

The hidden complexity of adrenal tumors: six cases that challenge diagnosis and treatment

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Background
The detection of adrenal tumors has become increasingly common due to advances in imaging technologies, particularly computed tomography (CT). Adrenal tumors, which occur in 4-10% of the general population, are often found incidentally and tend to be asymptomatic. However, certain tumors can present significant clinical challenges, especially those with malignant potential or associated endocrine dysfunction. These tumors vary widely in histopathological types, from benign adenomas to more aggressive conditions like adrenocortical carcinoma and metastatic lesions.
Case Presentation
This report discusses six cases of adrenal tumors in Caucasian patients, including five females and one male. The tumors included ganglioneuroma, traumatic adrenal hematoma with fibrosis, pheochromocytoma, and adrenocortical carcinoma. Clinical presentations varied, with some patients experiencing hormone overproduction symptoms, while others were asymptomatic and discovered incidentally during imaging for unrelated reasons. Surgical intervention was performed in all cases, and diagnoses were confirmed via histopathological examination postoperatively. These cases underscore the clinical diversity of adrenal tumors and the complexities involved in their diagnosis and management.

Conclusions
The rising incidence of adrenal tumor detection, particularly incidentalomas, highlights the importance of comprehensive evaluation to differentiate between benign and malignant tumors. Hormonal imbalances caused by adrenal tumors can lead to significant endocrine disorders, while malignant tumors present serious health risks. A multidisciplinary approach that includes imaging, clinical evaluation, and histological analysis is critical for effective management and improved patient outcomes. Early diagnosis and treatment are essential, especially considering the potential for malignancy and endocrine complications. These cases also emphasize the need for a tailored approach in treating diverse patient populations, including Caucasians.
Key Words
adrenal tumors, incidentalomas, endocrine disorders, adrenocortical carcinoma, ganglioneuroma, pheochromocytoma
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EP649

JOINT1005
Parathyroid carcinoma synchronous with multifocal papillary thyroid microcarcinoma presenting as recurrent retropharyngeal hematoma in 45 years old woman
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Introduction
Spontaneous retropharyngeal hematoma is a rare entity that can be caused, among others, by the rupture of enlarged parathyroid gland. Only about 40 cases of spontaneous parathyroid hemorrhage have been reported in the literature. Most of them were parathyroid adenomas, with only a few cases of carcinoma described. Parathyroid carcinoma is very rare disease with incidence 3-10 cases/10 million annually. Synchronous parathyroid carcinoma and thyroid carcinoma are extremely uncommon and the cause of its coexistence is unknown.
Case Report
45 years old woman was referred to emergency for sore throat and dysphagia. She had a history of similar event two years ago, which was diagnosed as retropharyngeal hematoma, managed conservatively without further investigation (serum calcium not tested). Actual CT from 4/2024 showed a neck mass 42x36x20mm compressing and deviating the right lobe of the thyroid gland. Laboratory: calcium 2,93 mmol/l (normal range 2,15 - 2,55), PTH 35,45 pmol/l (normal range 1,3 - 7,6), thyroid function normal. Neck ultrasound showed the same mass as CT and multinodular enlarged right thyroid lobe. Resection of the cervical mass and right hemithyroidectomy were provided in 6/2024. Histopathology: parathyroid carcinoma and two papillary thyroid carcinomas (PTC) 3 and 1 mm. The left hemithyroidectomy followed in 9/2024 with finding of another PTC 3 mm. Due to the presence of two cancers genetic testing was indicated. The patient was found to have a likely pathogenic germline frameshift variant in the tumour suppressor gene *POT 1* Lys384ValfsTer15 in a heterozygous state by whole-exome sequencing. It is known from the literature that loss of the tumour suppressor telomere shortening mechanism caused by autosomal dominant disruption of the *POT1* gene leads to clonal population expansion and genomic instability, which predisposes to a higher risk of cancer. Molecular genetic testing of the resected cancers will follow.
Conclusion
We present a case of recurrent retropharyngeal hematoma of the parathyroid origin. The diagnosis was established after the disease relapsed two years later. Laboratory analysis of serum calcium should be considered as a part of investigation in nontraumatic cervical hemorrhage. The germline mutation in the tumour suppressor gene *POT 1* in a heterozygous state predisposes to a higher risk of cancer and probably caused both parathyroid carcinoma and multifocal papillary thyroid carcinoma in this patient. Supported by Ministry of Health Czech Republic - DRO (Institute of Endocrinology - EÚ, 00023761).
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EP650

JOINT1345
Effects of osilodrostat and metyrapone on 2D and 3D models of adrenocortical carcinoma cell lines viability: preliminary results
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Adrenocortical carcinoma (ACC) is a rare but aggressive malignancy, with a poor overall survival. It can present itself in different ways, but most of the patients display symptoms of hormonal excess. Mitotane is a treatment option as an adjuvant therapy after surgery or for unresectable/advanced ACC, also combined in a platinum-based therapy. It is an adrenolytic drug that affects adrenal steroidogenesis and interferes with mitochondrial function reducing cell viability. Other therapeutics are used to relieve the symptoms of ACC with hypercortisolism, such as metyrapone and osilodrostat, both steroidogenesis inhibitors. Specifically, osilodrostat is a drug that inhibits adrenal 11β-hydroxylase and blocks aldosterone synthase, which are enzymes acting in the final step of cortisol and aldosterone synthesis. The main objective of this research consists of the comparison of effects of mitotane, metyrapone and osilodrostat on adrenocortical carcinoma cell lines, such as SW-13 and NCI-H295R: the first is a non-secreting cell line, the second is a glucocorticoids-, mineralocorticoids-, and adrenal androgen-secreting line, often used as a model in experiments on human steroidogenesis. While the effects of metyrapone and osilodrostat on ACC hypercortisolism have been proven in the last few years, there is no specific data about their effects on tumoral cells viability and how they can influence them. In this view, a study involving both cell lines could be an effective method to assess valuable information from an *in vitro* model. Both for SW-13 and NCI-H295R cells, the experiments were performed with 2D cultures and then 3D models (e.g. spheroids) to reproduce the complex structure of an *in vivo* environment. The cultures were treated with different concentrations of mitotane, metyrapone and osilodrostat. Moreover, a combination of mitotane and osilodrostat and of mitotane and metyrapone were tested on ACC cell cultures. 2D models were cultured in DMEM-F12 medium supplemented with 10% of fetal bovine serum (SW13 cells) or with DMEM-F12 medium supplemented with 2.5% of Nu-Serum and ITS + Premix supplement (NCI-H295R). Cell viability was assessed with MTS assay. 3D models were obtained using specific microwell plates to be evaluated via a physical cytometer establishing information about spheroids features and indirectly to cell death extent. Although the study is currently in a preliminary phase, we evaluated changes in cell viability and in steroidogenesis in 2D models. The next step will consist of a deeper characterization and evaluation of 3D models.
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EP651

JOINT3671
Two unusual calcitonin negative medullary thyroid carcinomas
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Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor(NET) arising from parafolicular cells. It accounts for less than 5% of all thyroid tumors. The most characteristic feature of MTC is the production of calcitonin by tumor cells, turning it into a valuable tumor marker for diagnosis and follow up. Rare cases of calcitonin negative neuroendocrine tumors of the thyroid have been reported, and they represent a clinical challenge. We present 2 cases of unusual calcitonin negative MTC (CNMTC) First case is a 65 year old male, complaining with hoarseness and a neck mass, with suspicious lynph nodes in the neck and mediastinum, plus a vertebral T1 lesion on CT and PET scans sugestive of metastasis. FNA of the thyroid nodule was suspicious por MTC. Total thyroidcetomy plus neck and mediastinum disection was performed. T4aN1b M1 MTC was confirmed. Inmunohistochemistry (IHC) in the tumor was strongly possitive (+) for calcitonin, synaptophysin, CEA and TTF-1. No blood test for calcitonin was collected until three days after surgery, being undetectable at that point, and has remained so for the next 12 years of follow up, with also normal blood CEA levels, despite the bone lesion and a 2 cm suspicious mediastinum lymph node that persisted after surgery. Two years later, a pancreatic node newly appeared in scans and was finnally removed some after slowly growing on follow up with diagnosis of pancreatic NET G1PT2N0. Both the spine lesion and the neck were treated with radiotherapy after surgery and have remained stable, during follow up, without apperance of new lesions on multiple imaging tests performed. RET genetic testing in blood sample was inicially performed and negative and more recently NGS on tumor tissue showed no RET somatic mutations but a Gln61Arg mutation in HRAS gene. Case 2 is a 75 year old woman with an incidentally discovered thyroid nodule. Inicial FNA was suspicious for MTC, but her calcitonin serum levels were undetectable. A total thyroidectomy was performed and biopsy revealed a NET: IHC + for synaptophysin, TTF-1 and Cromogranin but negative for calcitonin, calcitonin related gen peptide and CEA. KI-67 index was 0,5%. Differential diagnosis was CNMTC or, less likely a thyroid metastases from another NET. A Galium PET scan showed no other lessions. Genetic testing in the tunor cells showed no mutations in RET nor in other genes tested (Oncomine panel).
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EP652

JOINT3748

Lymph node metastasis revealing a thyroid microcarcinoma in a patient monitored for laryngeal cancer

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Introduction
The cervical region is a frequent site of neoplastic pathologies, including primary cancer and secondary lesions. The incidental discovery of thyroid carcinoma during surgery for upper airway pathology is rare.
Observation
We report the case of a 69-year-old male patient, a chronic smoker weaned 30 years ago, who underwent total laryngectomy with cervical lymph node curage. Histopathological examination revealed a moderately differentiated keratinizing squamous cell carcinoma classified as pT4aN0Mx. The Lymph node dissection revealed a metastatic lymph node without capsular rupture from a papillary thyroid carcinoma in the right IIa territory. Two months later, the patient underwent total thyroidectomy, with histopathological examination of a 7mm infiltrating vesicular variant papillary microcarcinoma of the right lobe with vascular emboli classified as pT1aN1bMx, at high risk of recurrence. The patient was scheduled for radioiodine therapy.
Discussion and conclusion
The association of thyroid carcinoma with laryngeal cancer is rare. There is no standardized therapeutic protocol for the simultaneous treatment of laryngeal and thyroid cancer. Hence the importance of a thorough examination of the cervico-facial region during surgical treatment of cervical neoplasia.

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EP653

JOINT1311

Unexpected presentation of pancreatic metastasis in B-cell Lymphoma

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Background
Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, characterized by its aggressive nature and diverse clinical presentations. While DLBCL primarily affects lymphoid tissues, extranodal involvement can occur in various organs, including the pancreas. Pancreatic involvement in DLBCL is rare and poses unique diagnostic and therapeutic challenges.
Case report
We present the case of a 44-year-old female with no prior history of diabetes or endocrine disorders, who initially presented with an inguinal adenopathy. A biopsy of the inguinal lymph node revealed giant cell lymphoma, characterized by CD20+ positivity and a high Ki-67 proliferative index of 90%. Subsequent imaging, including a PET-FDG scan, revealed extensive involvement of the entire pancreas by the lymphoma. Notably, despite the widespread pancreatic infiltration, there was an absence of any pancreatic endocrine dysfunction, including diabetes or hypoglycemia.
Conclusion
This case highlights the unusual presentation of lymphoma with significant pancreatic involvement and without the typical endocrine disturbance emphasizing the need for careful monitoring and underscoring the variability in clinical presentations of pancreatic lymphoma.

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EP654

JOINT2543

A rare case report of prolonged adrenal insufficiency following discontinuation of osilodrostat treatment for severe hypercortisolism due to ectopic ACTH syndrome

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Osilodrostat is an 11β-hydroxylase inhibitor indicated for treatment of Cushing's syndrome in adult patients. Transient use of osilodrostat may lead to prolonged adrenal insufficiency, a rare adverse event worth noting. We report here the case of an 81-year-old woman who was treated with osilodrostat (20 mg/day) for five months for severe hypercortisolism secondary to ectopic ACTH secretion [midnight cortisol at 81.7 µg/dL (2–7), with ACTH at 137 pg/mL, and urinary free cortisol at 5972.1 µg/24h (20–65)]. CT scan revealed a bronchial tumour located at the lower right pulmonary lobe and enlarged adrenals. Following tumour resection (well differentiated neuroendocrine histology), osilodrostat was discontinued. One month postoperatively, basal cortisol at 8h00 was low at 2.2 µg/dL (9–22) with inadequate ACTH secretion at 40 pg/mL (<46.0) supposedly linked to previously suppressed corticotropic cells by excessive cortisol production. The patient was given accordingly a physiological replacement dose of hydrocortisone. ^{68}Ga-DOTATOC PET/CT performed six months post-surgery ruled out residual or recurrent neuroendocrine tumor and an abdominal CT scan demonstrated normal appearance of adrenals. Ten months after discontinuation of osilodrostat, the patient exhibited persistent adrenal insufficiency. Basal hormone analysis revealed markedly elevated ACTH levels (175 pg/mL) and undetectable cortisol levels this time in favor of a residual iatrogenic effect of osilodrostat. Prolonged primary adrenal insufficiency after transient use of osilodrostat is a rare but serious side effect. Only few cases have been documented in the past two years. The underlying pathophysiological mechanism remains unclear and quite unexpected, considering the short half-life of the drug. Clinical follow up and continued adrenal function monitoring are advisable following osilodrostat discontinuation to prevent adrenal crisis in those rare at-risk patients.

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EP655

JOINT3772

Persistent virilization in a woman with CAH under medical treatment: a hidden culprit

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Introduction
Congenital adrenal hyperplasia (CAH) is due to enzyme deficiencies, most frequently of the enzyme 21-hydroxylase, leading to increased synthesis of adrenal androgens associated, in severe forms, with adrenal insufficiency. In women, this condition manifests clinically with signs of virilization or hyperandrogenism. Leydig cell tumors of the ovary are extremely rare androgen-secreting tumors, and there are very few cases described in the literature of women with CAH who developed this tumor.
Case report
We present the case of a 59-year-old woman who came to our attention for effluvium capillorum. In remote pathological history she had post-surgical hypothyroidism for benign multinodular goiter on levothyroxine replacement therapy. Menopause since 2017. Nulliparous. On hormonal examinations she presented: 17-OH-progesterone 87 ng/ml, testosterone 1.78 ng/ml, ACTH 33 pg/ml, cortisol 205 ng/ml, DHEA-S 0.7 ng/ml, 17-beta-estradiol 30 pg/ml. In light of 17-OH-progesterone values a standard ACTH stimulation test was performed with findings of: basal 17OH progesterone 15.4 ng/ml, at 30 minutes 66.9 ng/ml, at 60 minutes 85.8 ng/ml; basal DHEAS 1266 ng/ml, at 30 minutes 1224 ng/ml, at 60 minutes 1302 ng/ml. An MRI of the abdomen was also requested, which showed no findings suspected for adrenal adenomas. Genetic testing was then requested, which led to the diagnosis of 21-hydroxylase deficiency by compound heterozygosity in the CYP21A2 gene: for the classical mutation in one allele (p.Arg357Trp), for the nonclassical one in the other (p.Val282Leu). After that, the patient started suppressive corticosteroid therapy with

modified-release hydrocortisone 10 mg in the evening and 5 mg in the morning resulting at control after 4 months in: ACTH <5 pg/ml, cortisol 162 ng/ml, 17-OH progesterone 6.9 ng/ml, testosterone 1.78 ng/ml, 17-beta-estradiol 44 pg/ml, DHEA-S 231 ng/ml, androstenedione 10.2 ng/ml. Due to persistence of elevated testosterone values despite optimized medical therapy, the situation was further investigated by transvaginal pelvic ultrasound, which showed a 27x25x15mm cystic formation at the right ovary. After consultation with the gynecologist and collecting the patient's consent, hystero-annessiectomy surgery was performed: histological examination on surgical piece then revealed a stage IA ovarian Leydig cell tumor. At the last follow-up, 2 months after surgery, the patient presented a hormonal picture of normalization of testosterone levels.
Conclusions
The present case highlights the difficult differential diagnosis of hyperandrogenism in women. Moreover, although there is limited literature to support it, it lays the foundation for the association between CYP21A2 mutations and the augmented incidence of germ cell tumors.

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EP656

JOINT1731

Peroperatory isotopic detection and mini invasive surgery, what prospects?

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Introduction
The interest of minimally invasive surgery is that it is selective with significant reduction in operating time. The contribution of the peroperative detection in this case is equivalent to the contribution of a torch in a black tunnel.
Objective
Demonstrate the value of intraoperative detection in minimally invasive surgery. The scope of application of intraoperative detection in nuclear medicine:On the technical level, intraoperative detection requires the localization by an isotope of the mass to be operated, then in intraoperative use a sensor probe that allows selective resection. Nuclear medicine has several applications in this field:
*Parathyroid adenoma
*sentinel lymph nodes
*para ganglioma
*osteoid osteoarthritis
*Metastatic adenopathy of thyroid papillary carcinoma.
Discussion
The added value of this isotopic technique compared to conventional surgery alone: Surgery is an essential pillar of the treatment of focused tumors, but its success depends on the complete depletion of tumor cells during surgery. The intraoperative detection of tumor cells is therefore a means to significantly improve the results of surgery in post-operative simple surgical suites or reduce hospitalization. Intraoperative detection should have a wider role, in particular through the promulgation of nuclear medicine techniques and the training of trained teams, what will have an impact on the quality of Management of patients in terms of aesthetics with a reduction in operating time and especially the complications related to an enlarged surgical gesture.
Conclusion
In Algeria, intraoperative detection has been used for about twenty years, it has demonstrated its contribution and its usefulness in association with surgery, especially at the major senology centers of Algiers (CPMC) Nevertheless, it is difficult to find its place in daily life in association with surgery.

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EP657

JOINT3255

Bilateral gynecomastia unveiling an adrenal cortical tumor

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Introduction
Adrenocortical carcinoma (ACC) is an exceptionally rare malignancy. It may be classified into functioning and non-functioning types. Estrogen-secreting ACC is exceedingly rare, representing 1% to 2% of all ACCs. In men, estrogen excess manifests as gynecomastia, decreased libido, and hypogonadotropic hypogonadism. This report describes a rare case of estrogen-secreting ACC in which bilateral gynecomastia was the predominant clinical feature.
Case Presentation
A 45-year-old male presented to our department with bilateral gynecomastia, accompanied by a 6 kg weight loss, fatigue, anorexia, abdominal pain, erectile dysfunction, and decreased libido over three months. Physical examination revealed facial erythema, bilateral grade II gynecomastia, and a palpable 20 cm abdominal mass located in the left flank and extending to the epigastric and umbilical regions. Laboratory findings included testosterone at 2.97 ng/mL associated with elevated estradiol (169 pg/mL), suppressed FSH (0.3 mIU/mL), and elevated lactate dehydrogenase. TSH, FT4, prolactin and hCG levels were in the normal range. Abdominopelvic CT-scan identified a large (23×20×13 cm) left retroperitoneal mass with heterogeneous enhancement, necrosis, and calcifications, closely associated with the stomach, duodenum (D4), left kidney, and left renal vein. A low-dose dexamethasone suppression test confirmed ACTH-independent Cushing's syndrome with non-suppressed cortisol at 103.68 ng/mL and low ACTH level at 0.87 pg/mL. The patient was referred for extensive adrenalectomy with lymph node dissection.
Discussion
Feminizing adrenal tumors are rare, and hyperestrogenemia typically arises from peripheral androgen conversion. However, in this case, it is suggested that estradiol is directly secreted by the tumor. Histopathology remains the gold standard for ACC diagnosis, and surgical resection is the primary curative treatment. Adjuvant therapies are tailored to tumor grade, stage, and patient-specific factors. This case underscores the importance of considering ACC in males presenting with gynecomastia and highlights the need for prompt diagnostic evaluation and multidisciplinary management.

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EP658

JOINT4008

A diagnostic dilemma: revisiting the utility of selective arterial calcium stimulation testing for localization of occult insulinoma

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Background
Insulinoma is a rare neuroendocrine tumor with an incidence of one to four per million per year and its rarity can be partially attributed to diagnostic difficulties that even experienced physicians can face.
Case presentation
A 22-year-old nondiabetic male with a history of recurrent hypoglycemia with unknown etiology was brought to the hospital after being found down. At the scene, he was found to have a glucose level of 20 mg/dL by EMT and was given intravenous Dextrose 50% with improvement of mentation. He is nonalcoholic, has no known Liver or kidney disease, has no family history of diabetes, and is not on any medications. In the hospital, vital signs were normal. Physical examination was unremarkable. Laboratory tests were normal except for recurrent episodes of hypoglycemia confirmed with 72-hour fasting associated with diaphoresis and tremors relieved by glucose intake. Endocrinology was consulted and hypoglycemia testing showed elevated C-peptide 2.61 ng/mL (ref 0.5-2 ng/mL) and insulin level 31.2 uIU/mL (ref <15 uIU/mL), with normal Beta-hydroxybutyrate 0.08mmol/l (ref <0.49 mmol/l), Insulin antibody <0.4 nU/mL (ref <95 nU/mL), IGF-2 406 ng/mL (ref 265-616 ng/mL), IGF-1 209 ng/mL (ref 115-307 ng/mL), morning cortisol 18.5 mg/dL (ref 14-20 mg/dL), and negative Sulfonylurea test. Abdominal MRI and Endoscopic Ultrasound showed no pancreatic mass. A Selective Arterial Calcium Gluconate Stimulation Test (SACST) was done, which showed a fourfold increase in insulin level in the Gastroduodenal and Superior mesenteric arteries, indicating a tumor in the head or neck of the pancreas. He was started on diazoxide which improved his glucose, and he was discharged with outpatient planning for surgical exploration of the pancreas.
Discussion
Preoperative localization of insulinoma is vital since it dictates surgical success. However, current radiographic methods have low sensitivity which can have deleterious implications. SACST is 95-100% sensitive in diagnosing insulinoma as small as 2cm. Kam *et al* showed that out of forty-five biopsy-proven insulinomas, SACST definitively localized thirty-eight cases. This was concordant with Won *et al* where SACST definitively localized nine out of ten cases of insulinoma. It is also safe with no significant adverse events aside from mild nausea and skin flushing.
Conclusion
SACTS can be considered a safe and sensitive diagnostic procedure for localizing insulinomas when conventional imaging is nondiagnostic and can potentially improve clinical and surgical outcomes.

Reference
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EP659

JOINT227

Sporadic medullary carcinoma: case report

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Medullary thyroid carcinoma is a rare tumor derived from parafollicular cells. Sporadic medullary carcinoma is usually diagnosed as advanced disease because most patients present as a solitary nodule without other signs and symptoms. 70% of patients present with neck metastases, whereas 10% of patients have distant metastases. We will present the case of a 72-year-old female with medullary carcinoma who was initially referred for operative treatment due to multinodous goiter. Upon admission to our institution, in laboratory results we found calcitonin 55810 pg/ml, CEA 1346,1 ng/ml, with normal values of parathyroid and thyroid hormones. A CT scan of the neck was performed, and the voluminous right lobe of the thyroid with hypodensity and calcifications in the lower aspects, sized 38x26x71 mm, was found, as well as conglomerates of pathologically altered lymph nodes. Total thyroidectomy with extended neck dissection was performed. Postoperative PET/CT with 18F DOPA showed secondary deposits localized supra and retroclavicular. Control calcitonin 3 months after the operation was 653 pg/ml, CEA 62 ng/ml, with normal PTH and normal catecholamines in 24h urine. The patient was reoperated on and altered lymph nodes were extirpated. In the further course, high calcitonin and CEA values were maintained, while PET/CT 18F DOPA one year after operative treatment indicated infracm pathological lymphatics. Although patient presented in older age and with exceptionally high calcitonin and CEA values, this is locoregional disease without clinical features of MEN syndrome, only active surveillance is indicated in futher follow up.

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EP660

JOINT1893

Unusual case of prolactinoma mimicking stroke

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Introduction
Pituitary tumors more specifically prolactinomas, causing elevated serum prolactin, can lead to symptoms like galactorrhea, menstrual irregularities, and neurological issues, sometimes increasing the risk of stroke. This case demonstrates a patient with elevated prolactin levels and stroke mimics (non-vascular conditions that present with symptoms similar to stroke.)
Case report
A 62-year-old male has been hospitalized for dizziness, loss of coordination, motor aphasia, right-sided weakness and numbness in the face. The healthcare professionals diagnosed acute stroke: determined patient eligibility for Intravenous thrombolysis, included a contrast-enhanced CT angiography (CTA), which showed no signs of ischemic or hemorrhagic stroke and alteplase was administered intravenously. The patient's neurological impairment has not improved. An MRI of the brain revealed only a 1.6 cm hypophysial incidentaloma, prompting further investigation of prolactin levels. The patient's prolactin level was found to be 18 times above the normal range. Based on these findings, a diagnosis of prolactinoma was made. The patient was started on cabergoline therapy (0.5 mg twice weekly), which resulted in a complete resolution of his neurological symptoms within several months. After initiation of treatment prolactin level normalized.
Conclusions
This case highlights the importance of considering prolactinomas in the list of stroke mimics. This case demonstrates that elevated prolactin levels can cause neurological manifestations independently. Although prolactinomas can be a risk factor for stroke.

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EP662

JOINT2629

Great response to mitotane in advanced adrenocortical carcinoma

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Adrenocortical carcinoma (ACC) is an aggressive tumor. 5-year overall survival (OS) for advance disease is $<15\%$. However, cases of long-term disease stabilization have been reported. Mitotane monotherapy is usually reserved for biologically less aggressive tumors. A partial response (PR) rate to mitotane monotherapy of 13-31% has been reported. Typically, responses are observed when mitotane plasma levels are >14 mg/l, but sometimes PR and complete responses have been reached with lower levels. Currently, we cannot precisely define the biological characteristics of the disease and accurately predict the prognosis. In particular, no clinical or pathological factor has been validated to predict the response to mitotane monotherapy. We describe the case of a 45-year-old patient had an abdominal CT scan revealing a left adrenal mass of 15x16 cm, encompassing the ipsilateral kidney. Forty days later, the lesion measured 20 cm and extended into the contralateral adrenal lodge with para-aortic lymphadenopathy, pulmonary embolism, and multiple bilateral pulmonary nodules compatible with an aggressive metastatic ACC. A PET-FDG scan confirmed increased uptake in the left adrenal glands (SUV 12). After only 4 months, after mitotane treatment, a 45% reduction of the primary tumor and regression of lung metastases was observed, despite plasmatic drug levels of 5 mg/l. Subsequently, a further reduction in the size of the pulmonary nodules and the left adrenal mass (8x6 cm; 60%) was observed making surgical resection of the primary tumor feasible. Histology confirmed the ACC diagnosis. Mitotane represents an extremely effective therapy, also for aggressive tumors and despite plasma levels <14 mg/l.

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EP663

JOINT2408

A bilateral vestibular schwannoma in neurofibromatosis type 2

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Introduction
Neurofibromatosis 2 (NF2) is a dominantly inherited tumor predisposition syndrome caused by mutations in the *NF2* gene on chromosome 22, with a family history. Affected individuals inevitably develop schwannomas typically affecting both vestibular nerves leading to deafness. Schwannomas also occur on other cranial nerves, on spinal nerve roots, and on peripheral nerves. Meningiomas and ependymomas are other tumor features. Our objective is to report a rare case of a bilateral vestibular schwannoma associated with neurofibromatosis type 2.
Case Report
The patient was a 38-year-old male with no previous pathological family history of note. He presented with bilateral deafness for 5 years associated with tinnitus without neurological signs. The ENT examination was normal. Audiometric examinations and the Brainstem Evoked Response (BER) test showed right cophosis and sensorineural deafness at 70 dB on the left side. The patient was diagnosed on Magnetic Resonance Imaging (MRI) with a bilateral vestibular schwannoma measuring 14x10 mm on the right side grade 2 and 22x15 mm on the left side grade 3, filling the pontocerebellar cisterns and presenting an intrameatal extension, associated with six extra-axial expansive processes corresponding to supratentorial neurofibromas. A genetic investigation was performed and the diagnosis of neurofibromatosis type 2 was made. The patient was proposed for Gamma Knife radiosurgery.
Discussion/Conclusion
The NF2 is a rare disease characterized by bilateral acoustic neuromas or central nervous system tumors. This syndrome should be known because it can cause rare

endocrine manifestations linked to hormonal disorders or tumors that affect the endocrine glands. NF2 represents a difficult management problem. Surgery remains the focus of current management, although watchful waiting and occasionally radiation treatment have a role. In the future, the development of tailored drug therapies aimed at the genetic level are likely to provide huge improvements for this devastating, life limiting condition.
Disclosure of interest
none declared
Key-words
Neurofibromatosis 2, Bilateral, Vestibular schwannoma, Magnetic Resonance Imaging
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EP664

JOINT38

An atypical presentation of a patient with neuroendocrine tumor

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Introduction
Most neuroendocrine neoplasms are indolent and slow-growing tumors, and given the rather slow progress, some lesions are incidentally discovered as metastatic deposits rather than primary masses. Neuroendocrine tumors of unknown primary site are not so uncommon in the clinical practice and may constitute 12–22% of NEN patients. In these cases, a biopsy is often taken to allow the pathologist to identify the tumor type and possibly the primary tumor site via microscopic examination. Neuroendocrine tumors are classified according to histologic differentiation and grading system, with low-grade, well-differentiated tumors having a more indolent course, while high-grade, poorly differentiated neoplasms are rapidly growing and aggressive, which are closely related to clinical presentation and prognosis.
Case presentation
A 74-year old female hospitalized at internal medicine service due to difficulty in breathing during minor physical exertion, thoracic-abdominal discomfort, edema of the inferior sides, after exclusion of pulmonary thromboembolism with pulmonary angio-CT and acute coronary syndrome in emergency department. Abdominal echo raised the suspicion of cholecystic tumor with multiple hepatic metastases. Subsequent examinations with contrast CT and MRI abdomen, EGD and colonoscopy result in multiple secondary hepatic lesions and cholecystic calculi. CT-guided biopsy and immunohistochemical stain of the liver mass showed poorly differentiated small cell carcinoma with stain positive for PanCK+, Chromogranin+, Ki67 70%, CD56+. Since all the performed examinations were not able to identify a primary source of the tumor, after the oncological evaluation chemotherapy treatment with cisplatinium and etoposide for stage IV small cell NET of unknown primary site with metastasis to liver was recommended. Given the extent of the disease, the patient chose palliative treatment
Conclusions
In cases of neuroendocrine tumors with well-differentiated cells, more detailed diagnostic examinations are performed to find the primary site, with the goal of performing surgical intervention or starting systemic therapy depending on location. Location of primary site is also important in determining the prognosis of neoplasia. In the case of poorly differentiated neoplasms, detailed diagnostic investigations to identify the primary source do not affect the prognosis of the disease. Poorly differentiated neuroendocrine neoplasms, including small cell NET, are treated with platinum based agents regardless of where the primary site is located. In the case of poorly differentiated neoplasms.

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EP665

JOINT2968

Risk factors and malnutrition in colorectal cancer patients: identification and clinical implications

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Introduction
Colorectal cancer (CRC) is a public health problem. The aim of this study is to determine the relationship between nutritional and environmental risk factors and the onset of CRC.
Methods
This was a retrospective study conducted among 50 CRC patients recruited from the gastroenterology and surgery departments of La Rabta Hospital in Tunisia, as well as 50 randomly selected controls. The two groups were matched for age and gender. A questionnaire was used to collect data on personal and family medical history, clinical data regarding CRC and its treatment, as well as anthropometric measurements and biological tests. A frequency questionnaire and a 24-hour recall were performed.
Results
There was a female predominance among our patients ($n=$ 26, 52%). The age of the patients ranged from 29 to 84 years, with a mean of 56.06 $\pm$ 14.24 years. Tobacco and alcohol consumption were higher among patients than controls, but this difference was not statistically significant ($P = 0.1$ and $P = 0.18$, respectively). Significant risk factors included obesity ($P = 0.02$), menopause ($P = 0.006$), as well as high consumption of red meat ($P = 0.002$), processed meat ($P = 0.002$), fried foods ($P = 0.0001$), and sugar ($P = 0.0001$). Consumption of green tea ($P = 0.003$), fruits ($P = 0.001$), and cereals ($P = 0.0001$) was higher among controls. Anorexia was nearly constant. Malnutrition was common, measured by BMI, percentage of weight loss (42%), albumin levels (60%), and various nutritional scores (NRI, MUST, MNA, and SGA). Energy and protein intake were below recommended needs for 94% and 92% of patients, respectively. Deficiencies in minerals, vitamins, and trace elements were observed.
Conclusion
A sedentary lifestyle and inappropriate dietary choices were higher in CRC group. Malnutrition was frequent in cancer patients. We suggest a screening for malnutrition in all CRC patients.

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EP666

JOINT584

Lung neuroendocrine tumours: clinical aspects and methods of investigation

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Introduction
Neuroendocrine tumours (NETs) are tumours that can occur throughout the body, generally affecting the digestive tract and lungs, and are characterised by their ability to secrete hormones. Rare tumours; their annual incidence is estimated at 2 to 5 new cases per 100,000 people per year, with the most affected age group being between 40 and 60. In this presentation, we report the case of a small cell lung cancer revealed by hepatalgia.
Observation
This 73-year-old patient, a 30-year smoking cessation, and type 2 diabetes mellitus on oral anti-diabetic, was admitted to our clinic for an etiological diagnosis of a NET objectified by abdominal MRI following 03 months of abdominal pain which revealed the presence of a suspicious hepatic nodule. Anapathological examination of a biopsy was consistent with a small cell NET hepatic metastasis. Immunohistochemistry was positive for anti-CgA antibodies, anti-Synaptophusin antibodies and 80% anti-Ki67 antibodies. A thoraco-abdominal CT scan revealed a pulmonary condensation systematised in the right middle lobe, with multiple secondary hepatic and mediastinal localisations. An octreoscan performed revealed a somatostatin receptor expressing lung neoplasia at the stage of lymph node and liver metastases. The patient had undergone bronchial fibroscopy with biopsy of the right middle and lower lobes, the results of which were in favour of a histopathological appearance and immunohistochemical profile of a small cell lung cancer.
Discussion-Conclusion
The NETs diversity of symptoms and their rarity present a major challenge for healthcare professionals. between the main types of lung cancer, 4 major histological types alone account for 95% of cases: [squamous cell carcinomas, adenocarcinomas, large cell carcinomas (classified as non-small cell carcinomas)] , and small cell carcinomas. The therapeutic approach depends on the nature of the tumour, ranging from chemotherapy to specific management: targeted therapy.

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Environmental Endocrinology

EP667

JOINT856

Molecular docking analysis of endocrine disruptors at the androgen receptor's ligand-binding domain

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Introduction
Androgen hormones play a central role in the development and maintenance of male reproductive functions by interacting with the androgen receptor (AR). The AR regulates the transcription of genes associated with sexual differentiation, development of secondary characteristics, and tissue homeostasis. This protein comprises four main domains: the amino-terminal domain, DNA-binding domain, hinge region, and ligand-binding domain (LBD). The LBD is responsible for interactions with steroid hormones, drugs, and xenobiotic molecules, such as endocrine disruptors (EDs). EDs are environmental compounds capable of mimicking or antagonizing natural hormones, thereby affecting endocrine pathways. Some EDs, such as Bisphenol A, Tributyltin, MEHP, and Atrazine, have been shown to interact with the AR's LBD, modulating its function and altering physiological processes involving androgens. However, further exploration of the molecular interactions between EDs and the AR's LBD is still required. Molecular docking models represent a promising approach to investigate the extent of these interactions and establish correlations with the disruptive potential of various EDs on reproductive functions.
Objective
To evaluate the type and affinity of interactions between different EDs and the amino acids of the AR's LBD using molecular modeling tools.
Methodology
Ten EDs and ten known agonists with androgenic or anti-androgenic activity were selected. The three-dimensional structures were obtained in mol2 format from the PubChem and ChEMBL databases. The three-dimensional model of the AR's LBD was derived from crystallographic structures available in the PDB. Molecular docking studies were conducted using the GOLD software, employing the GoldScore scoring algorithm for result validation. The stability of the complexes was assessed by measuring hydrophobic interactions, hydrogen bonds, and dipole-dipole interactions using PyMOL and Discovery Studio.
Results
The most relevant amino acids for the stabilization of the reference agonists identified were T877, N705, R752, and Q711. Certain EDs, such as DBP, MEHP, BPS, and BPA, showed strong similarities in their interactions with these polar residues. In contrast, Irgarol, Tributyltin, and DDT demonstrated stabilization through predominantly nonpolar interactions involving M745, L704, L873, and W741. Although these interactions are less frequently described in the literature, the resulting conformations were structurally stable, suggesting an alternative modulation potential for the receptor.
Conclusion
This study contributes to the understanding of the interactions between EDs and the AR's LBD. Docking analysis indicated that different classes of EDs may exhibit varied interaction profiles with LBD amino acids, highlighting the need for further studies to evaluate their functional and toxicological impacts.

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EP668

JOINT2383

Exposure to endocrine disruptors in the NICU: the chemical footprint in premature newborns

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Introduction
Endocrine disruptors (EDCs) are chemical compounds capable of altering hormonal balance, which can lead to adverse health effects. Within this group, phthalates, organophosphate esters (OPEs), and parabens are widely used in medical devices and personal care products. The European Chemicals Agency (ECHA) has identified them as substances with endocrine-disrupting potential, either confirmed or under evaluation. Due to their biological immaturity and rapid development, premature newborns are particularly susceptible to exposure to these chemicals, which could have short- and long-term health implications.
Objectives
The aim of this study is to determine the presence of phthalates, OPEs, and parabens in urine samples from preterm newborns admitted to a Neonatal Intensive Care Unit (NICU). To achieve this, highly precise analytical methodologies are employed to assess potential exposure risks and their relationship with environmental factors within the hospital setting.
Methodology
Urine samples were collected from premature patients throughout their hospitalization in the NICU and analyzed using high-resolution liquid chromatography coupled with time-of-flight mass spectrometry (LC-QTOF). Sample preparation was carried out using the QuEChERS protocol, designed for the extraction, identification, and quantification of EDCs in biological matrices.
Results
A total of 48 urine samples from 24 neonates (8 girls and 16 boys) were analyzed, with a mean gestational age of 31.5 weeks ($\pm$2.8) and a birth weight of 1518 g ($\pm$393), corresponding to a z-score of -0.45 ($\pm$1.07). Among the evaluated compounds, OPEs showed the highest concentrations (25.9 $\pm$ 31.5 µg/l), followed by phthalates (24.9 $\pm$ 19.9 µg/l), whereas parabens, despite being detected more frequently, were found at lower concentrations (1.91 $\pm$ 3.48 µg/l). This finding aligns with NICU policies restricting the use of topical products such as creams or gels during the first three weeks of life. Additionally, an inverse relationship was identified between gestational age and the levels of these compounds, suggesting that exposure may be influenced by the hospital environment and the types of materials used at different stages of neonatal care.
Conclusions
Although the detected levels of phthalates, OPEs, and parabens in hospitalized newborns do not appear to pose an immediate health risk, it is crucial to establish continuous monitoring strategies and exposure reduction measures in hospital settings such as the NICU. Identifying additional risk factors, such as the composition of medical materials used, could help minimize associated adverse effects. These findings emphasize the need to develop stricter regulations regarding the use of chemical additives in medical and hospital environments.

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EP669

JOINT969

Tracking endocrine disruptor effects of chlorobenzenes in AVP and OT mediated processes in Wistar? rat models

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It has been experimentally demonstrated that exposure to endocrine disruptor chlorobenzenes (ClB) alter behaviour by increasing anxiety and aggression in male Wistar rats. Little is known about the effects of chlorobenzene on females, but research showing strong maternal aggression towards offspring is of particular interest. Our group aimed to investigate the background of this evidence by studying the effects of dietary route ClB exposure in animal models of neurotransmitter/hormone relapse. Our work was aimed to investigate noradrenergic and serotonergic coupled vasopressin (AVP) and oxytocin (OT) release induced by ClB exposures. In our experiments, we administered subtoxic doses of ClB mixtures (hexaClB + 1,2,4-triClB = 1:1, mixed chlorobenzenes: mClB) at doses of 0.1; 1.0; and 10.0 µg/bw.kg to Wistar ♀ rats *in vivo* via a stomach tube; 0, 30, 60, 90 days. Subtoxicity of the doses was confirmed by liver enzyme assays. AVP and OT, liver enzymes and other parameters required for assay were determined from blood samples taken according to experimental time windows. Primary monolayer cell cultures (NH) were prepared from neurohypophyseal sterile tissue samples at the end of the treatment periods. The AVP and OT separation kinetics of the resulting *in vitro* models were determined for mClB-treated and untreated NH cultures. We then followed the effects of adrenergic (norepinephrine: NE 10^{-6}M) and serotonergic (serotonin: 5HT 10^{-6}M) receptor activation on AVP and OT secretion. The results were expressed as mg protein content of the cultures. RIA procedures were used for hormone measurements.

Protein contents were measured by the modified Lowry method. Serum toxicity enzymes were measured by enzyme kinetic assays. Our results showed that mClB enhanced AVP and OT clearance in relation to treatment doses and durations. Activation of NE and 5HT neurohypophyseal receptors significantly increased AVP and OT release. Since the role of these two neurotransmitters is dominant in aggression and anxiety, the strong behavioural disturbances induced by mClB in ♀ Wistar rats may be due to NE and 5HT mediated AVP and OT secretion.

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EP671

JOINT2835

Perceptions and concerns about endocrine disruptors in the real-life of Italian family pediatricians: preliminary data of a national survey. (On behalf of ISPED Endocrine Disruptors Study Group)

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Background
Endocrine disruptors (EDs) are ubiquitous pollutants, contained in common materials, from plastics to detergents. They mimic hormonal activity and interfere in the normal functionality of the endocrine system. Pregnancy and childhood are considered periods of major susceptibility. Informing families about EDs risks is now an international public health challenge and, considering the Italian health system organization, we consider family pediatricians as favored in playing this role. Therefore, this study aims to assess the current knowledge and concerns about EDs of familial pediatric healthcare professionals in Italy.
Methods
We invited family pediatricians to voluntarily respond to a short online survey on EDs (17 items) available on the website of one of the major Italian family pediatric societies (Federazione Italiana Medici Pediatri, FIMP) in August 2024.
Results
Out of more than 5300 FIMP members, only 90 completed the survey (72% working in an industrialized area). Even if 96% of interviewed pediatricians declared to be well-informed about EDs, only 33% knew specifically the materials/objects where EDs are located and the potential derived damages. Moreover, only 57% were already used to inform families about EDs and how to prevent their exposure during pregnancy, breastfeeding and childhood. When education is performed, only 10% of family pediatricians utilized predefined tools as paper and/or online information materials (e.g. brochures). The main sources of medical information were professional meeting (69% optional and 31% mandatory) and media (18%).
Conclusions
Even if preliminary, our data underline the gap of knowledge and the extreme need of specific training of the Italian familial pediatricians on this challenging topic. More effort should be directed to provide scientific information and tools to family pediatricians in order to simplify and standardize communication about the risks associated with EDs to families.

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EP672

JOINT3988

Survey of attitudes and knowledge about endocrine disruptors among the student population of the republic of Serbia

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Numerous studies have shown that most people lack sufficient awareness and knowledge of endocrine disrupting chemicals (EDCs) and their sources. This is primarily due to the limited information available about the chemicals in products and materials they are exposed to daily, as well as a general lack of awareness regarding the harmful effects of endocrine disruptor exposure. Being a young population that can contribute to improving the general state of awareness about these chemicals, the students' awareness of this topic is of special importance. Additionally, this population is in the reproduction phase, so their awareness and knowledge in this area can have beneficial effects on their general health as well. This study aimed to explore the awareness of the student population in the field of EDCs, their attitudes, and risk perception, as well as to assess their possible exposure to bisphenol A (BPA). Data were collected using two surveys distributed via social media. The first survey, related to knowledge and attitudes about EDCs, was completed by 352 respondents, while the second survey, related to possible exposure to BPA, was completed by 248 respondents. The largest number of respondents were between 22 and 25 years old, while the largest number of responses was received from students from medical group faculties. A statistically significant difference in the results based on gender and type of study was shown. General awareness of EDCs was low (18.4% of surveyed students had never heard of the term). Furthermore, it has been shown that student habits and behaviors can lead to potential exposure to BPA, with more than 78% of those surveyed not knowing how to reduce exposure. It has been revealed that the highest percentage of information is expected from health professionals, including pharmacists. The results of this study may help develop strategies for public education and raise awareness about EDCs and their effects on human health.

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EP673

JOINT2161

Seep survey of knowledge on endocrine disruptors in pediatrics: disenped study

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Introduction
Exposure to Endocrine Disrupting Chemicals (EDCs) is becoming increasingly relevant in in paediatrics due to their potential to interfere with the hormonal system and their potential effects on child development, including endocrine and neurological disorders as well as cancer risk. This study evaluates the level of knowledge about EDCs among physicians specialising in paediatrics or those whose professional activity involves paediatric care in Spain, identifying gaps in knowledge and assessing the need for continuing education on this topic.
Objectives
To evaluate the level of knowledge on EDCs among paediatricians and other specialists, identifying areas of strength and deficiency. A comprehensive understanding of this topic is essential for addressing long-term consequences and developing effective preventive strategies.
Material and methods
An observational, descriptive, cross-sectional study was conducted using a self-administered survey of physicians in Spain. The survey included questions on knowledge, exposure assessment and preventive measures related to EDCs. It was distributed through medical society newsletters, WhatsApp and social media.
Results
A total of 921 responses were obtained. According to the results, 94.7% of respondents were familiar with the term EDC and 58% consider it relevant to their clinical practice. However, 39.2% did not routinely inquire about exposure and 41.6% did not provide preventive recommendations, mainly due to a lack of training (88%). The clinical conditions that most frequently prompted recommendations to reduce exposure included pubertal disorders, obesity,

thyroid dysfunction and hyperandrogenism. The most commonly explored sources of exposure were cosmetics, drugs and food.
Conclusions
Although knowledge of the term EDC is high, its integration into clinical practice remains limited. Training and updated and consensus-based recommendations are necessary to promote the inclusion of exposure-related inquiries and preventive measures in clinical management.

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EP674

JOINT2371

Chronotypes of medical residents and their association with career choice

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Introduction
Specialty selection is a crucial step in a physician's career, influencing professional, familial, and social fulfillment. This decision is likely associated with proper synchronization with professional demands. Chronotype, defined as an individual's preference for activity and rest periods over a 24-hour cycle, may influence career choice. This study aims to explore the potential relationship between chronotypes and the specialty choices of medical residents in Tunisia.
Methods
We conducted a cross-sectional, descriptive, and analytical study in August 2024 among medical residents from Tunisian university hospitals. Participants completed an online questionnaire that collected demographic data, assessed chronotype using the Morningness-Eveningness Questionnaire (MEQ), and included questions on specialty choices and professional satisfaction.
Results
Of the 100 residents contacted, 60 completed the questionnaire, with a mean age of 27 years ($\pm$ 1.5 years). Among them, 83.3% were in medical specialties, while 16.7% pursued surgical specialties. The majority of residents (38.3%) belonged to the intermediate chronotype group, followed closely by morning-type residents (35%), while evening-type residents accounted for 26.7% of the sample. A significant correlation was observed between chronotype and specialty choice: 82% of morning-type residents opted for medical specialties, likely as a deliberate choice, compared to only 30% of evening-type residents ($P = 0.002$).
Discussion and Conclusion
Our study demonstrates that chronotype influences the specialty preferences of medical residents. Evening-type residents tend to choose specialties with flexible or predominantly nocturnal schedules, whereas morning-type residents favor disciplines with regular working hours. These findings highlight the importance of considering both biological and sociocultural preferences to better guide future physicians and improve their work-life balance.

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EP675

JOINT610

Vitamin D deficiency during pregnancy in the presence of prenatal maternal stress and their association with the development of attention-deficit/hyperactivity disorder like symptoms in toddlers

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Introduction
Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in children, characterized by age-inappropriate inattention, hyperactivity, and impulsivity, which can cause extensive damage to children's academic, occupational, and social skills. Although the exact cause of ADHD remains unidentified, most researchers contend that it is a result of a combination of hereditary and environmental factors. Environmental risk factors, which mostly include psychosocial variables, pregnancy, and perinatal risk factors, are directly linked to the development of ADHD. Some studies have investigated the association between vitamin D concentrations during pregnancy and neurodevelopmental outcomes, such as behavioral problems and social competence, in the offspring. It has been proposed that vitamin D deficiency could be a risk factor for developing ADHD.
Aim
To investigate the hypothesis, that presence of prenatal maternal stress and low level of D3 vitamin in pregnancy is associated with the development of the ADHD like symptoms in toddlers ($<$ 2 years).
Materials and Methods
the study group is presented by 53 pregnant women and 53 infants of these pregnancies. A population cohort of 53 pregnant women was recruited at their 35 to 37th week of pregnancy and investigated prospectively. The participants were selected through targeted selection. Maternal experience of stressful life events was assessed by stress standardized questionnaires and maternal plasma D vitamin was measured using ECLIA method, during pregnancy. When offspring age was 6 month and then less than 2 years, mothers completed the child behavior and temperament checklist.
Results
Statistically significant relationship was identified between D3 vitamin deficit and stress level; between D3 vitamin deficit and impulsivity symptoms; between stress level and hyperactivity as well as impulsivity symptoms. But using multiple regression analysis showed that maternal stressful events during pregnancy significantly predicted ADHD behaviors in offspring and the level of D3 vitamin in this model was statistically insignificant.
Conclusion
The study don't supported the hypothesis that low level of D3 vitamin during pregnancy increases the risk of development of ADHD like symptoms in toddlers, but provides some evidence to date linking developmental vitamin D deficiency and offspring ADHD, and, if its findings are replicated, could have serious public health implications in regards to vitamin D supplementation and lifestyle behaviors during pregnancy. Although, the obtained results support the hypothesis that the influence of prenatal maternal stress causes offspring ADHD like symptoms through a programming effect.

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EP676

JOINT2269

Impact of lyposomal PC5 on rats behavioral activity

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Introduction
Oxidative stress shown as a main trigger factor of neurodegeneration in Altzheimer diseases (AD). We studied how antioxidant Liposomal-associated protein transmembrane 5 (PC5) can prevent brain neurodegeneration in rats models of AD by investigating behavioral activity.
Materials and methods
Experimental model of AD were created by intranasal injection of of $AlCl_3$ in dosage 50 mg/kg to adult rats during 7 days (AD group). Treatment group after 2h of each $AlCl_3$ injection received PC5 in dosage of 32 mg/kg were delivered in the same way (AD + PC5). Standard behavioral tests were performed in 3, 6, 9 days after treatment in AD, AD + PC5 and in control rats. Rats were sacrificed in the 10 days after experiment and tissue samples were taken flash frosen for further biochemical analysis.
Results
Rats with experimental AD presents with emotional and motosensor activity, postural instability, decreasing of walking distance, decreasing of quadrants crossing, decreasing of mink reflexes, also elongation of new labirints searching time. Decreasing of percentages of active and passive avoidance, also decreased learning coefficient for conditional reflexes. In brain tissue rats with AD content of peroxides were increased in 95%, activity of oxidative enzymes catalase, superoxide dismutase, glutation peroxide were decreased and malone dealdehyde were increased. In rats AD + PC5 group emotional and motosensor activity, quadrant crossing, new labirint searching time, also active and passive avoidance percentages were not differ from control group were not differ than in control group, except walking distance and mink reflexes. In brain tissue oxidative enzymes activity were higher, malone dealdehyde lower in compare with AD group.
Conclusion
Results suggested that PC5 significantly prevented $AlCl_{3\ \text{induced}}$ neurodegeneration in experimental AD rats evaluated by improving brain behavioural activity tests and oxidative stress enzymes activity.

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EP677

JOINT130

Big data tools for assessing the nutritional situation of a pediatric population: did the prevalence of obesity change pre- and post-pandemic?

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Introduction

To date, knowledge of population dynamics and its repercussions on health required complex, long and expensive field studies. Big data tools are nowadays postulated as a tool of first magnitude for weighted population changes observed in real time if reliable sources of collection and adequate mathematical and computer tools for their assessment are available.

Main objective

To evaluate, using big data tools, whether there have been significant changes in our pediatric population in the variables determining nutritional status (overweight) by comparing the situation before and after the pandemic, confinement and restrictions due to COVID 2019.

Material and Methods

Data collected from episodes of computerized medical records, studying the variables sex, age, weight, height, place of residence (PC, health center, neighborhood) of our population between 01/01/2020-03/31/2020 vs 01 / 01/2022-03/31/2022 To calculate the curves and percentile tables we have used the Cole-Green LMS algorithm with penalized likelihood, implemented in the RefCurv 0.4.2 (2020) software, which allows managing large amounts of data. The hyperparameters have been selected using the BIC (Bayesian information criterion). To calculate population deviations from the reference, being above 1.5 standard deviations from the mean according to age has been taken as a reference.

Results

66,975 computerized episodes of children under 16 years of age and a total of 1,205,000 variables studied are collected. Although data is available, individuals $>16^a$ are excluded due to low N. The graphs of our population are represented with respect to the standards, observing that there are differences with Orbegozo 2011 and Spain 2010. We present the data and percentages of overweight/obesity by age and sex in the two periods studied. An increase in overweight compared to the reference population is evident in the entire 2022 vs 2020 sample. But these differences are more evident in the sample of adolescent individuals and "obesity trigger" ages: 2-3 years and 6-7 years.

Conclusions

There is a significant difference in our population in the variables associated with childhood overweight if we compare the pre- and post-pandemic period, perhaps associated with confinement, less physical activity and overeating. Knowing in which areas of the population these changes have occurred, age groups, sexes or neighborhoods, will allow investing socio-health resources more efficiently. NOTE: CEIC OSI ARABA Approval Expte 2022-058

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EP678

JOINT250

Teplizumab for type 1 diabetes in children: a paradigm shift in treatment

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Background and Aims

Type 1 diabetes mellitus (TIDM) in children is an autoimmune disease characterized by progressive destruction of the β cells of the pancreas and lifelong dependency on exogenous insulin. This presentation sheds light on the unique immune mechanisms of newly approved immunotherapy teplizumab and unveiling its breakthrough benefit for children with established T1DM and its impressing role in delaying the onset of the disease among high-risk relatives.

Methods

Retrieved recently published data and documented studies and trials from PubMed, Google Scholar, and the Web of Science using "TIDM and Teplizumab."

Results

Teplizumab is a newly approved humanized IgG1 kappa CD3-directed monoclonal antibody. Its exceptional design as an Fc-non-binding antibody helps to ameliorate and reduce the cytokine release syndrome associated with the adverse autoimmune destruction of pancreatic β cells in children with TIDM. It effectively stops the autoimmune destruction of insulin-producing pancreatic cells by turning off pancreatic-cell autoreactive effector CD8+ T-lymphocytes and making the cells inactive. Therefore, its mechanism seems to enhance regulatory T-cell activity and promote immune tolerance. Compared with controls, the teplizumab clinical trial was found to be an effective strategy to maintain β-cell function, reduce C-peptide decline, preserve insulin production, and reduce exogenous insulin need in children age 8 and older with new-onset T1DM for up to 2 years. More recent clinical trials concluded that the 14-day full dose of teplizumab delays the progression to clinical T1DM in high-risk individuals, resulting in reduced insulin usage and hospital visits.

Discussion

Teplizumab's unique design and its peculiar immune mechanism to enhance regulatory T-cell activity and promote immune tolerance with its recent trials for children with TIDM are intriguing and herald the start of a new and exciting era of hope in diabetes research and clinical management. Interestingly, trials in different phases revealed that teplizumab stopped β cell destruction in established TIDM and reduced exogenous insulin, delayed the disease onset among high-risk relatives, and significantly slowed progression to clinical TIDM.

Conclusion

Teplizumab is the first FDA-approved breakthrough disease-modifying immunotherapy therapy for children with TID with impressing role in delaying the onset of the disease among high-risk relatives. Despite the approval of teplizumab, the main challenges remain the need for widespread screening programs for early-stage T1DM diagnosis in children and the identification of individuals at high risk within the general population.

Keywords

TIDM, children, Teplizumab immunotherapy

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EP679

JOINT3728

Clinical features of hypercalcemic crisis due to primary hyperparathyroidism

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Introduction

Primary hyperparathyroidism is a hypercalcemic metabolic disorder related to high or inappropriately normal levels of PTH. A hypercalcemic crisis. Hypercalcemic crisis, also known as parathyrotoxicosis, hyperparathyroid crisis, or parathyroid storm, is a rare but serious complication of primary hyperparathyroidism, occurring in approximately 1.6–6.7% of cases. It may have a potentially fatal course, with a mortality rate reaching up to 7%. The only cutrative treatment was the surgical removal of the parathyroid lesion. Medical management, consisting of aggressive hydration, diuretics, bisphosphonates, and calcitonin, can be used as a bridge therapy for surgery. The aim of this study was to assess clinical features of hypercalcemic crisis in primary hyperparathyroidism.

Materials and methods

This is a retrospective study conducted from January 2010 to December 2023, including all patients admitted and treated for primary hyperparathyroidism. Patients were divided into two groups: those with primary hyperparathyroidism associated with critical hypercalcemic crisis and those without hypercalcemic crisis

Results

During the study period, 80 patients were hosaitlized for primary hyperparathyroidism. Among them, 7 patients had calcium levels exceeding 3.5 mmol/dL, and 5 of these patients had critical symptoms of hypercalcmic crisis (6.25%). Polyuria and polydipsia occurred in three patients, one had acute renal injury, needed hemodialysis. Confusion or lethargy occurred in two patients, while nausea and vomiting affected all patients. One patient had acue pancreatitis (balthazar stage c). Their mean calcium level was 4.43 mmol/dL was statistically higher than the rest of cohort. Mean intact PTH value was 905.8 ng/mL. There was no differnce in preoperative imaging thechniques carried out for localization. they were treated with hydration, diuretics, and bisphosphonates. Four of them responded well to the medication. The remaining patient showed no clinical or laboratory improvement and underwent prompt parathyroidectomy. Based on the histopathological exams, the mean hyper-functional parathyroid gland size was 30,36 mm. adenoma wa observed in 4 patients and double adenoma in one case.

Conclusions
Hypercalcemic crisis is a rare but life-threatening complication of primary hyperparathyroidism that requires prompt diagnosis and management. Medical treatment, including hydration, diuretics, bisphosphonates, and calcitonin, can stabilize patients temporarily, but surgical resection remains the definitive treatment. Early identification of hypercalcemic crisis and the appropriate surgical intervention can significantly improve patient outcomes.

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EP680

JOINT2421

Parental perception and knowledge of childhood obesity: descriptive study in tunisia

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Childhood obesity is experiencing a significant increase in developing countries, yet it is not consistently recognized as a pathological condition by parents. This study aims to assess the knowledge of Tunisian parents regarding the definition and risk factors of childhood obesity. A descriptive survey was conducted in December 2024 among 100 parents who visited the pediatric emergency department at the Regional Hospital of Ben Arous (Tunisia) with their children aged 5 to 15 years. The body mass index (BMI) of both children and their parents was evaluated using the World Health Organization (WHO) growth charts. The results revealed a prevalence of overweight and obesity in children of 13% and 2%, respectively. Among mothers, 62% were overweight or obese, with 19% having an overweight or obese child. Among fathers, 43% were overweight or obese, of whom 23% had an overweight or obese child. Alarmingly, 66% of parents did not recognize their child's overweight or obese status. Additionally, 54% of overweight or obese children belonged to low to middle socioeconomic backgrounds, and 40% of fathers and 53% of mothers had a university-level education. The majority of parents (91%) considered childhood obesity as a condition requiring medical management. However, the definition of obesity varied: 58% of parents based it on body weight, 27% on BMI, and 15% on body fat percentage. The most frequently cited risk factors were poor dietary habits (90%) and physical inactivity (89%). Nevertheless, 58% of parents underestimated the impact of maternal obesity, and 63% minimized the influence of parental obesity on their child's risk of developing obesity. This study highlights an incomplete perception of childhood obesity among Tunisian parents, underscoring the need for a targeted health education program to improve awareness of riskfactors and promote healthy lifestyle habits from an early age.

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EP681

JOINT474

Patient preference for gender of treating endocrinologist

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Background
There are a few studies available on patient preferences regarding physician gender. Evidence suggests that overall, both male and female patients prefer physicians of their own gender. Specific research focusing on endocrinologists is not available. This is important, since Endocrinology is predicted to become the most female-predominant subspecialty of internal medicine.
Aim
To assess whether patients have a gender preference when choosing an endocrinologist.
Methods
A survey was conducted among patients at a single endocrinology clinic. A total of 651 subjects (137 men, 514 women) had booked appointments for a consultation with endocrinologists (two women and two men) over 6 working weeks. The primary outcome was the percentage of men or women patients preferring a male or female endocrinologist. Statistical analysis was done with the Chi square test, assuming theoretical ratios of endocrine disease of 1:1 to 5:1 for women to men.
Results
According to theoretical patient ratios ranging from 1:1 to 1:5 (men to women), 12% to 34% more male patients prefer male endocrinologists compared to those who seek female endocrinologists. Conversely, 7% to 12% fewer female patients choose female endocrinologists compared to those who opt for male endocrinologists, based on a theoretical patient ratio of 1:5 to 1:1. Overall, male patients exhibit a significantly stronger preference for male endocrinologists ($P < 0.001$).
Conclusion
Medical literature indicates that both male and female patients generally prefer physicians of their own gender, a trend also observed in our Endocrinology study. Endocrinology is expected to become the most female-dominated specialty. Understanding these gender preferences is key to optimizing patient satisfaction, particularly in sensitive areas such as reproductive health and sexual development. However, addressing physician gender bias is essential and requires a cultural shift. Achieving gender equity in the medical profession will improve physician well-being, enhance retention of women physicians, and ultimately improve access to and quality of care.

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EP682

JOINT3594

Primary hyperparathyroidism and pancreatitis: a rare and multi-faceted association

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Introduction
The relationship between primary hyperparathyroidism and acute or chronic pancreatitis remains controversial it has been debated for decades. Hypercalcemia secondary to parathyroid hormone secretion plays a key role in the pathogenesis, although other mechanisms may also be involved. The aim of this study is to assess the prevalence, clinical presentation, and outcomes of pancreatitis associated with PHPT, emphasizing the importance of early diagnosis and management.
Materials and methods
This is a retrospective and descriptive study from January 2010 to December 2023, including all patients admitted and treated for primary hyperparathyoidism associated with pancreatitis
Results
During the study period, 80 patients were hosaitlized for primary hyperparathyroidism. Among them, 3 patients has pancreatitis revealing the disease (3.75%) with 1 recurrent acute panreatitis and 2 chronic calcifying pancreatitis. The male to female ration was ½ with mean age 57 years (54-59 years). 2 patients were diabetics. Revealing clinical symptoms were abdominal pain in all cases associated with vomiting in 1 case. Serum amylase and lipase levels were elevated. Abdominal CT scans were performed for all patients, revealing acute pancreatitis (Balthazar stage C) in one case and chronic calcifying pancreatitis in two cases. Serum calcium levels were elevated in all cases, with an average of 3.35 mmol/l(range: 2.9-3,86mmol/l). The diagnosis of PHPT was confirmed by elevated PTH levels in all cases, with a mean value of 799 pg/mL (range: 197–1920 pg/mL). Parathyroid SPECT with 99m Technetium-MIBI and ultrasound were performed for all patients, identifying a right inferior parathyroid adenoma in two cases and a left inferior parathyroid adenoma in one case. PHPT was diagnosed, and surgical treatment was planned. Surgical resection of the parathyroid adenoma was performed. The outcome was favorable in all three operated patients, with normalization of PTH and serum calcium levels. However, one patient with chronic pancreatitis experienced recurrent episodes of pancreatitis despite successful parathyroidectomy.
Conclusions
The occurrence of pancreatitis during a hyperparathyroidism is rare but it can be the only pesenting symptoms of primary hyperparathyroidism. elevated calcemia during acute or chronic pancreatitis should always get attention.

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EP683

JOINT3782

Primary hyperparathyroidism due to ectopic parathyroid lesions: our experience

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Introduction
Primary hyperparathyroidism (PHPT) is a common endocrine disorder with a prevalence of 1to 7cases per 1000 adults. In PHPT, the incidence of ectopic parathyroid glands ranges from 10% to 20%. Ectopic parathyroid adenomas arise due to abnormal migration of the parathyroid glands during embryonic development. Although ectopic parathyroid adenomas are relatively rare, they pose a significant diagnostic and surgical challenge. The atypical location of these adenomas can lead to delayed diagnosis and persistent or recurrent hyperparathyroidism following unsuccessful surgery. Standard imaging techniques such as ultrasound, SPECT-CT with 99mTc-sestamibi, and MRI. The aim of this study was to assess clinicopathological features and the effectiveness of radiological tools in localizing ectopic parathyroid adenomas in patients with primary hyperparathyroidism.
Materials and methods
This is a retrospective study conducted from January 2010 to December 2023, including all patients underwent surgery for PHPT. PHPT with ectopic parathyroid adenoma were included in this study.
Results
During the study period, 80 patients underwent surgery for primary hyperparathyroidism. Among them, 10 patients (12,5%) were diagnosed with ectopic parathyroid adenomas. The mean age of patients with ectopic adenomas was 59 years (range: 42–72 years), with a male-to-female ratio of 1:4. The most common clinical symptoms included fatigue (75%), bone pain (50%), nephrolithiasis (41%). Preoperative serum calcium levels ranged from 2.95 to 3.85 mmol/l, with a mean level of 3.42 mmol/l. PTH levels were significantly elevated, with **a**mean value of 423 ng/l (range: 180–1200 ng/l). All patients underwent ultrasound and SPECT with 99mTc-sestamibi for preoperative localization. SPECT-CT was performed in 6 cases. SPECT-CT successfully identified ectopic adenomas in 5 cases (90%). Ultrasound detected ectopic adenomas in 7 cases (70%). MRI was performed in 2 cases and successfully localized the adenoma in all. The most common ectopic locations included: Mediastinum (2 cases, 20%), Intrathyroidal (2 cases, 20%), Retroesophageal space (1 cases, 10%) Carotid bifurcation (1 case, 10%), submandibular (1 case, 10%), thymus (3 cases,30 %). After surgery, serum calcium and PTH levels normalized in 9 patients. However, 1 case of persistent hyperparathyroidism was reported due to an intrathyroidal parathyroid adenoma, which required further surgical intervention.
Conclusions
Ectopic parathyroid adenomas are a significant cause of persistent or recurrent primary hyperparathyroidism, posing both diagnostic and surgical challenges. Preoperative localization using SPECT-CT with 99mTc-sestamibi, ultrasound, and MRI plays a crucial role in identifying ectopic lesions, particularly in atypical locations.

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EP684

JOINT2610
Gender differences in specialty choices among medical residents
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Introduction
Gender disparities in medical specialty choices are well-documented but remain insufficiently explored in certain contexts. This study investigates the influence of gender on specialty preferences among Tunisian medical residents.
Methods
A cross-sectional survey was conducted among medical residents from Tunisian university hospitals. Data were collected through an online questionnaire assessing demographic characteristics, specialty choices, and factors influencing these decisions.
Results
Of the 100 residents contacted, 60 completed the questionnaire, with a mean age of 27 years ($\pm$ 1.5 years). There was a female predominance (73.3%). Among them, 83.3% were in medical specialties, while 16.7% were in surgical specialties. Our study reveals a marked distribution of specialty choices based on gender among medical residents. Indeed, 90% of male residents opted for surgical specialties, whereas only 10% of female residents made the same choice. Conversely, medical specialties were preferred by 86% of female residents, while only 14% of male residents chose them. ($P = 0.002$)
Conclusions
Gender plays a crucial role in shaping specialty preferences among medical residents. While males exhibit a strong inclination toward surgical fields, females tend to favor medical specialties. These disparities may be driven by societal norms and perceived professional and personal compatibility. Addressing these gender-based differences could help promote more equitable access to diverse career opportunities.

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EP685

JOINT1927
The night shift: impacts of delayed sleep patterns on endocrine function, growth, and puberty in adolescents
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Background
Delayed sleep patterns and the reversal of sleep-wake cycles, where children and adolescents sleep during the morning and remain awake at night, are increasingly prevalent. These disruptions can adversely affect endocrine function, growth, and development, highlighting the need for a comprehensive understanding of their physiological and developmental impacts.
Objective
To evaluate the effects of delayed sleep patterns and sleep-wake cycle reversal on growth hormone secretion, cortisol rhythms, pubertal hormones, glucose metabolism, and overall development in children and adolescents.
Methods
A systematic review of the literature published between 2000 and 2024 was conducted. A total of 12 studies, involving over 5,000 children and adolescents, were analyzed. Key studies addressing the impact of altered sleep patterns on endocrine function were identified and reviewed.
Results
Delayed sleep phase syndrome (DSPS) and delayed sleep-wake phase disorder (DSWPD) are associated with significant disruptions in endocrine function. Altered sleep patterns reduce growth hormone secretion, which predominantly occurs during slow-wave sleep, impairing linear growth and development. Cortisol secretion rhythms are disrupted, with increased evening cortisol levels impairing stress responses and metabolic functions. Pubertal hormones, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH), are also affected, potentially delaying pubertal progression. Sleep disturbances also negatively impact glucose metabolism, leading to decreased glucose tolerance and insulin sensitivity. These changes may contribute to an increased risk of metabolic disorders in adolescents with persistent sleep misalignment.
Conclusion
Delayed sleep patterns and the reversal of sleep-wake cycles pose significant risks to endocrine function, growth, pubertal development, and metabolic health in children and adolescents. The misalignment of circadian rhythms disrupts critical hormonal processes, including growth hormone secretion, cortisol regulation, pubertal hormone synthesis, and glucose metabolism. Early identification and management of DSPS and DSWPD are essential to mitigate these risks and promote optimal development.

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EP686

JOINT2895
Living on the edge: war, stress, and autoimmune diabetes
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Environmental stress is a known modulator of immune function and disease onset in autoimmune disorders such as type 1 diabetes (T1D). Using Non-Obese Diabetic (NOD) mice, a well-established model for T1D, we investigated the effects of sustained stress exposure in a conflict zone. NOD mice develop diabetes due to immune-mediated destruction of pancreatic β-cells, and their disease progression is influenced by external stressors. During a prolonged period of regional hostilities, we observed a significant increase in diabetes onset rates, exceeding those reported under standard conditions. Despite maintaining strict

hygiene protocols, our facility experienced frequent environmental disruptions, including power fluctuations and abrupt evacuations, leading to sustained stress exposure. Previous studies have linked stress to immune dysregulation, and our findings provide direct evidence that chronic stress accelerates T1D onset. These results highlight the profound impact of environmental stress on autoimmunity and offer insights into its potential role in human autoimmune disease progression.

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EP687

JOINT132

Possible effects of the COVID-19 pandemic on the prevalence of malnutrition-anorexia cases in a pediatric population. using BIG DATA tools

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Summary
The coincidence of COVID-19 and confinement on children's health has been studied. One possible cause of malnutrition is eating disorders. Big data tools are currently a first-rate tool for assessing population changes and possible causes.
Main objective
To assess the possible changes in the prevalence of malnutrition in a child population after having suffered the confinement of COVID-19
Material and Methods
Data collected from episodes of computerized medical records, studying the variables sex, age, weight, height, of a pediatric population comparing the situation just before COVID (2020) and after the social isolation measures were completely finished (2022) Using big data methods to study variables. Using the Cole-Green LMS algorithm with penalized likelihood, implemented in the RefCurv 0.4.2 software (2020), which allows managing large amounts of data. The hyperparameters have been selected using the BIC (Bayesian information criterion). To calculate population deviations from the reference, the reference was taken as being below 1.5 standard deviations from the average according to age.
Results
66,975 computerized cases of children under 16 years of age and a total of 1,205,000 variables studied. The data and comparative graphs between districts of the population studied are represented with respect to the variables analyzed. There is an increase in cases of malnutrition, especially in districts with specific characteristics.
Conclusions
Big data technology allows for more efficient population studies, selecting populations most in need of health intervention, optimizing scarce health resources.
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EP688

JOINT252

Thyroid health in the age of night shifts: the role of circadian disruption

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The thyroid gland plays a pivotal role in regulating metabolism, energy expenditure, and overall hormonal balance. As such, it is highly sensitive to disruptions in circadian rhythms, which govern the body's natural sleep-wake cycle. Circadian disruption, often seen in individuals working night shifts, can lead to significant alterations in thyroid function, with potential long-term health implications. This study investigates the effects of night shift work on thyroid health, focusing on how irregular sleep patterns influence the regulation of key thyroid hormones, including triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH). Night shift work interferes with the body's natural circadian rhythm, leading to misalignment between the internal biological clock and external environmental cues. This misalignment disrupts the hypothalamic-pituitary-thyroid (HPT) axis, the system responsible for regulating thyroid hormone production. As a result, night shift workers often experience fluctuations in thyroid hormone levels, which may manifest as subclinical or overt thyroid dysfunction. The study explores the underlying mechanisms that may contribute to these hormonal alterations, including changes in light exposure, sleep deprivation, and the associated disruption of neuroendocrine pathways. In addition to its effects on thyroid function, night shift work is strongly associated with an increased risk of metabolic disorders, such as obesity, insulin resistance, and type 2 diabetes. These conditions are frequently linked to thyroid dysfunction, as the thyroid hormones play a key role in regulating energy metabolism and glucose homeostasis. Disruptions in thyroid hormone levels can exacerbate metabolic disturbances, creating a vicious cycle that further impairs metabolic health. Our findings underscore the need for healthcare providers to regularly monitor thyroid function in night shift workers, as early detection of thyroid dysregulation can help prevent or mitigate the long-term consequences of thyroid disorders. Routine screening for thyroid dysfunction in this population is essential to identify individuals at risk of developing metabolic disorders. Furthermore, we advocate for the development of standardized protocols for thyroid health monitoring, particularly for individuals in occupations that require frequent or prolonged night shift work. Ultimately, improving our understanding of these relationships may help inform workplace health policies and contribute to the development of targeted interventions aimed at minimizing the negative health impacts of night shift work.

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EP689

JOINT285

Endocrine disruptions in the kabuki syndrome spectrum

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Background
Kabuki syndrome is a rare condition characterized by a spectrum of features, including distinctive facial dysmorphia, skeletal abnormalities, dermatoglyphic patterns, and intellectual disability. Endocrine disorders, such as hypothyroidism or growth hormone deficiency, may also be present within this spectrum.
Case Report
We present the case of a 28-year-old woman from a non-consanguineous marriage, with a normal psychomotor development, who has been monitored for hypothyroidism since the age of 11, alongside bilateral renal lithiasis. The patient was admitted to our department for the management of profound hypothyroidism, with a TSH level of 80 µU/mL, following discontinuation of her hormone replacement therapy. Clinical examination revealed short stature (1.40 m), a weight of 52 kg, long palpebral fissures with eversion of the lateral lower third of the eyelids, prominent arched eyebrows with notched outer thirds, a short columella, and a flattened nasal tip. The patient also exhibited brachydactyly. Hormonal tests revealed a hypogonadotropic hypogonadism profile with FSH = 3 IU/l, LH = 0.3 IU/l, and estradiol = 5 ng/l. Cardiac ultrasound showed non-obstructive hypertrophic cardiomyopathy. Given this clinical presentation, Kabuki syndrome was suspected. Genetic testing is currently underway to investigate mutations in the KMT2D or KDM6A genes.
Conclusion
The diagnosis of Kabuki syndrome remains primarily clinical, though it is marked by significant clinical and biological heterogeneity. Most reported cases of Kabuki syndrome are sporadic. Despite its variability, the prognosis is generally favorable, with many individuals leading relatively normal lives.

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EP690

JOINT131

Detection cases of childhood malnutrition using BIG DATA techniques: social and economic determinants

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Big data tools are currently a major tool for assessing population changes. There is a possible causal relationship between a family's economic capacity and social dystocias and malnutrition. It is also known that a possible cause of malnutrition is eating disorders, which are more frequent in populations with different levels of education.
Main objective
To assess the possible relationship between family income and prevalence of malnutrition in a child population.
Material and Methods
Using the Cole-Green LMS algorithm with penalized likelihood, implemented in the RefCurv 0.4.2 software (2020), which allows managing large amounts of data. The hyperparameters have been selected using the BIC (Bayesian information criterion). To calculate population deviations from the reference, the reference was taken as being below 1.5 standard deviations from the average according to age.
Results
The data and comparative graphs between districts of the population studied are represented with respect to the variables analyzed.
Conclusions
Big data technology allows for more efficient population studies, selecting populations most in need of health intervention, optimizing scarce health resources.
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Fetal and Neonatal Endocrinology

EP691

JOINT720

Feeding issues: an under-recognized complication in people with hyperinsulinism

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Background
Congenital Hyperinsulinism (HI) is the most common cause of persistent hypoglycemia in newborns and children. In HI, dysregulated pancreatic beta-cells produce too much insulin, leading to severe hypoglycemia and, in many cases, irreversible neurological damage. An under-studied and under-recognized feature of HI is feeding issues.
Aim
This study's aim was to characterize the presence of feeding issues in individuals with HI and the impact on their families.
Methods
People with HI, or their caregivers, who consented to participate in the HI Global Registry (HIGR) and completed the Diet & Feeding survey were included in this study. The survey was approved by members of the HIGR Steering Committee. All variables are categorical and are reported using descriptive statistics and chi-square tests.
Results
246 individuals were included in this survey (80% $<$18 years old). 65% reported that they had experienced feeding issues, with the most common issues reported including poor appetite (67%) and refusing to eat (59%). Individuals who reported tube feeding were significantly more likely to have experienced feeding issues than those who did not use tube feeding (chi2, $P<$ 0.001). 36% reported that feeding issues had fully resolved, and the majority reported full resolution by 6 years of age (83%). However, 63% reported feeding issues had not fully resolved, and 41% of those individuals were 7 years or older. 62% of individuals reported receiving feeding therapy, however feeding therapy did not have a significant impact on whether feeding issues resolved (chi2, P = 0.713). However, details such as the type or duration of feeding therapy were not collected in this survey.
Discussion
Feeding issues are poorly understood within the context of HI. It is unknown exactly what leads to feeding issues, although factors such as direct pathophysiology of HI, the effects of HI medications, and the psychological impacts of the heightened importance of feeding and over-feeding to prevent hypoglycemia may play a role. Many individuals with HI and their caregivers feel that feeding issues represent a major gap in the clinical management of HI. One parent commented: *"Management of feeding issues is something which I feel is horrendously lacking in HI and lack of attention and mismanagement has caused my son far more difficulties and trauma than should have needed to be the case"*. More research into the causes of feeding issues and the most effective therapies for people with HI are urgently needed.

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EP692

JOINT1522

Influence of maternal dietary protein precursor on reproductive endocrinology of neonatal bovine offspring

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Bovine oogenesis and follicular maturation are initiated during *in utero* development, a process that is stringently orchestrated by the endocrine milieu. Of paramount importance are the three major biologically active estrogens: estron, estradiol, and estriol that are involved in the development and maintenance of germ cells. Previous work using the current model have revealed that maternal urea (protein precursor) supplementation reduces the ovarian follicular reserve without compromising the number of secondary and tertiary follicles. Therefore, we did not anticipate an influence of dietary treatment on biologically active estrogens. However, as the ovarian reserve is positively associated with circulating concentrations of anti-Mullerian hormone (AMH) we hypothesized that offspring from dams supplemented urea would have reduced circulating concentrations of AMH at birth. To characterize the effects of maternal urea supplementation, multiparous cows pregnant with female calves were individually-fed isocaloric dietary treatments consisting of chopped forage top-dressed with a control (0 g urea/animal/d) or urea (80 g urea/animal/d) pelleted supplement. Diets met or exceeded dietary requirements throughout gestation. Blood samples were collected from offspring at birth for the collection of plasma. Plasma was analyzed for concentration of estradiol, estrone, unconjugated estriol, and AMH using commercially available ELISA kits. The effect of maternal dietary treatment on concentration of hormones in offspring were evaluated by ANOVA. As expected, maternal dietary treatment did not influence circulating concentrations of estradiol (P = 0.41), estrone (P = 0.35), or unconjugated estriol (P = 0.31). However, it was not anticipated that maternal dietary treatment would have no effect on circulating concentrations of AMH (P= 0.97) as offspring of urea-supplemented dams had fewer primordial and primary follicles than offspring from control dams. From these results we infer that maternal urea supplementation induces precocious follicular activation and/or increases the number of follicles recruited during maturation through an AMH-independent mechanism. Moreover, these data illustrate that while offspring of dams offered urea throughout pregnancy have a reduction in primordial and primary follicles, the steroidogenic competence of secondary and tertiary follicles is no different than dams offered the control diet. USDA is an equal opportunity provider and employer.

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EP693

JOINT798

Calculation of risk factors in medical vs. surgical treatment for persistent hyperinsulinemic hypoglycemia of infancy: a systematic review of long-term outcomes"

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Background
Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is a rare metabolic disorder characterized by inappropriate insulin secretion, leading to profound hypoglycemia. Long-term management strategies, aim to prevent severe neurological damage while mitigating associated complications such as diabetes mellitus and malabsorption. This systematic review examines the risk factors and outcomes associated with medical and surgical interventions for PHHI.
Methods
A systematic review of literature published between 1990 and 2025 was conducted to identify studies addressing long-term outcomes of medical and surgical treatments for PHHI. Data were extracted regarding patient characteristics, treatment modalities, and long-term outcomes, including recurrence of hypoglycemia, growth abnormalities, and neurodevelopmental risks.
Results
Fourteen studies encompassing 317 patients were analyzed. Neonatal-onset PHHI was consistently associated with more severe disease and higher risks of neurological complications compared to infancy-onset PHHI. Medical management, often using diazoxide and octreotide, was effective in approximately 40–60% of cases, particularly in late-onset and less severe presentations. However, failure of medical therapy often necessitated near-total (90–95%) pancreatectomy.

• Risk factors by treatment modality (based on figure data):
• Hypoglycemia recurrence was highest in diffuse surgical cases (50%) and medical therapy (50%), while significantly lower for focal surgical therapy (3%).
• Growth abnormalities were minimal in medical therapy (10%) and focal surgical therapy (5%) but higher in diffuse surgical therapy (20%).
• Neurodevelopmental abnormalities occurred in 50% of diffuse surgical cases, 40% of medical therapy cases, and only 10% of focal surgical therapy cases.
• Medical management: Patients treated medically exhibited lower rates of diabetes (0–25%) but experienced ongoing risks of hypoglycemia and developmental delay if treatment was delayed.• Surgical treatment: Near-total pancreatectomy resulted in euglycemia in 70–80% of cases but was associated with a 40–60% risk of diabetes and other complications, such as exocrine pancreatic insufficiency. Early surgical intervention reduced the risk of severe neurological sequelae but increased the likelihood of long-term diabetes. Laparoscopic approaches showed promise for reducing postoperative complications.Genetic factors, such as mutations in the SUR1 gene, were significant predictors of disease severity and treatment outcomes, with homozygous mutations correlating with diffuse disease and higher diabetes risks.
Conclusions
The choice between medical and surgical treatment for PHHI should consider disease severity, onset age, and genetic factors. While medical therapy is preferable to avoid diabetes and preserve pancreatic function, early surgical intervention is critical in medically refractory cases to prevent irreversible neurological damage. Long-term follow-up is essential to monitor for complications.

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EP694

JOINT633

Neonatal vitamin D deficiency as a risk factor for the development of bronchopulmonary dysplasia: a systematic review and meta-analysis

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Background
Vitamin D deficiency is increasingly recognized as a contributor to immune dysregulation and the pathogenesis of pulmonary diseases. Vitamin D plays a pivotal role in alveolar development, and its deficiency—particularly in the neonatal period—may predispose infants to conditions such as bronchopulmonary dysplasia (BPD). This systematic review and meta-analysis aimed to evaluate the association between neonatal vitamin D deficiency and the development of BPD, with secondary outcomes including the incidence of respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), and mortality before discharge.
Methods
A systematic search of four major databases—Embase, Web of Science, PubMed, and Cochrane—was conducted to identify relevant studies. The primary outcome was the incidence of BPD, while secondary outcomes included the incidences of RDS, NEC, and mortality prior to discharge. Inclusion criteria were studies involving neonates admitted to the neonatal intensive care unit (NICU) with 25-hydroxyvitamin D levels measured at admission and outcomes of interest reported. Studies that lacked data on neonatal vitamin D status or BPD as an outcome measure were excluded. Pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated using a random-effects model to account for heterogeneity among studies.
Results
From a total of 2,298 identified studies, 13 focused on neonatal populations, and 3 met the eligibility criteria. These included two prospective observational studies and one retrospective cohort study. Neonates with vitamin D deficiency had a significantly higher risk of BPD (OR 2.49, 95% CI 1.10–5.68), RDS (OR 2.50, 95% CI 1.21–5.17), and suspected or confirmed NEC (OR 2.55, 95% CI 1.21–5.38) compared to vitamin D-sufficient neonates. No statistically significant difference was observed in mortality before discharge between vitamin D-deficient and -sufficient neonates.
Conclusions
Findings from this systematic review and meta-analysis suggest that 25-hydroxyvitamin D deficiency is an important and potentially modifiable risk factor for the development of BPD, RDS, and NEC in neonates. These results emphasize the need for further research into the mechanistic pathways linking vitamin D deficiency with adverse respiratory and gastrointestinal outcomes in neonates. Additionally, interventional studies evaluating the potential benefits of early vitamin D supplementation in at-risk neonates are warranted. Incorporating routine vitamin D screening into NICU protocols may also help identify vulnerable populations and guide preventive strategies.

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EP695

JOINT2760

Association of early nutrition and growth and metabolic parameters in very low birth weight infants

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Aim
Impaired postnatal growth is the most important issue in very low-birth-weight (VLBW) infants. Early nutrition is one of the modifiable factors and has the greatest influence on growth. Optimal nutrients intake in this population remain unknown. The aim of this study was to evaluate nutrients intake during the first 28 days of life and its impact on growth, metabolic and hormonal profile at this age.
Methods
120 infants with birth weights below 1500 g and gestational ages below 35 weeks were included in the study. Nutrient intakes were assessed daily, and anthropometric measurements were checked weekly until 28th day postpartum. Glycaemia and hormonal levels were assessed on day 28th after birth before the meal.
Results
The mean birth weight SDS was -1.25 ± 1.44 and length SDS was -1.69 ± 1.62. The mean daily weight gain velocity in 28 days was 12.3 ± 3.5 g/day. On 28th day after birth, mean weight SDS was -2.07 ± 1.11; length SDS was -1.91 ± 1.46; ponderal index was 22.5 ± 2.3. Metabolic and hormonal parameters in 28th day were as follows (mean ± SD): fasting glycaemia - 4.72 ± 1.51 mmol/l; fasting insulin - 17.6 ± 18.0 mU/l; HOMA-IR – 4.46 ± 6.39; IGF-1 – 1.83 ± 1.19 nmol/l; IGF-BP-3 – 8.80 ± 3.20 ng/ml; IGF-1/IGF-BP-3 ratio 1,55 ± 0.82. Cumulative total energy and fat intake in 28 days (g/kg) correlated directly with IGF-BP-3 level ($r = 0.255$, $P = 0.01$ and $r = 0.263$, $P = 0.008$, respectively). Cumulative carbohydrate intake tend to be related to IGF-1 level ($r = 0.194$, $P = 0.054$). Cumulative fat intake was inversely related to HOMA-IR and glucose level on 28th day after birth ($r = 0.210$, $P = 0.036$ and $r = -0.212$, $P = 0.033$, respectively) . Cumulative carbohydrates intake was inversely related to insulin level, HOMA-IR and glucose level ($r = -0.230$, $P = 0.020$; $r = -0.275$, $P = 0.006$ and $r = -0.319$, $P = 0.001$, respectively). Cumulative protein intake was also inversely related to glucose levels ($r = -0.259$, $P = 0.009$). However, protein to total energy ratio was inversely related to IGF-BP-3 and directly to insulin levels and HOMA-IR ($r = -0.249$, $P = 0.013$; $r = 0.216$, $P = 0.031$ and $r = 0.251$, $P = 0.011$, respectively). Length SDS at on 28th day after birth was not related to nutritional factors.
Conclusion
Total energy and higher carbohydrate intake lead to higher weight gain, but did not result in unfavorable carbohydrate metabolism. Protein-rich nutrition in VLBW infants was related to higher insulin resistance 4 weeks after birth. Ethics: Approval of the study was obtained at the Kaunas Regional Bioethics Committee (approval No. BE-2-12). The study was registered at ISRCTN Database (No. ISRCTN64647571). The written consent of both parents was obtained.

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EP696

JOINT3469

Genetic characteristics and clinical management of patients with diazoxid-unresponsive congenital hyperinsulinism in Slovakia

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Background
One of the critical distinguishing features of children with congenital hyperinsulinism (CHI) is diazoxid responsivness. In diazoxide-unresponsive (DU) patients molecular analysis provides information on the pancreatic histological subtype (i.e. focal vs diffuse) and determinates the most appropriate management strategy. Inactivating mutations in the ABCC8 and KCNJ11 genes are the most common, followed by mutations in GCK and HK1 gene. Recently, important advances have been made in CHI, including newly described molecular mechanisms, novel imaging techniques and therapeutic options.
Aims and objectives
The aim of this study was to evaluate genetic background and clinical management of the patients with DU-CHI in Slovakia.
Patients and Methods
Based on the data from the Slovak nationwide database of children with persistent hyperinsulinemic hypoglycaemia, 6 (22%) of 28 children with CHI were DU since 2005. In all of the individuals DNA analysis of the most common CHI genes was performed.
Results
In all of the six children with a DU-CHI a causal mutation was identified. Four children (66%) had focal form of CHI based on the paternally inherited recessive mutation, i.e. c.1332G>T (2 patients) and c.2694+1G>C in the ABCC8 gene, and c.498_502delinsAG in the *KCNJ11* gene. All of them successfully underwent partial pancreatectomy. One boy had inherited two heterozygous mutations c.154C>T and c.901C>G of the *KCNJ11* gene in the trans position, and since diagnosis is treated with somatostatin analogues. A de novo deletion encompassing the 151bp regulatory silencer region in intron 2 of the HK1 gene was detected in one girl with a severe clinical course of CHI using digital PCR (dPCR).
Conclusions
DU forms account for 22% of CHI in Slovakia. Genetic cause was identified in all six children; four had a focal form based on the paternally inherited *ABCC8* or *KCNJ11* mutations, and two children had a diffuse form based on the *KCNJ11* and *HK1* mutations, respectively. The type of mutation determinates the most appropriate treatment strategy in patients with DU-CHI, including use of somatostatin analogues and pancreatic surgery.
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EP697

JOINT2817

Serum neudesin levels in patients with congenital hypothyroidism

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Objectives
Neudesin is a newly discovered protein mainly secreted from adipose tissue and the brain. It plays a role as a neurotrophic factor in the brain and a negative regulator of energy expenditure. Neurodevelopmental delay and cognitive dysfunction are common features in cases with congenital hypothyroidism (CH) without treatment. Considering neudesin's role in brain development and its contribution to the survival of mature neurons, any possible relationships between neudesin and thyroid hormone were evaluated.
Methods
A total of 52 patients (32 patients with CH, 14 females and 18 males, aged 19±7 days; 20 healthy subjects for the control group; 7 females and 13 males, aged 22±8 days) were included in the study. All patients were evaluated for thyroid hormones and plasma neudesin levels. The basal neudesin levels between the patient and control groups and the patients' neudesin levels before and after l-thyroxine treatment were compared.
Results
Regarding basal neudesin levels, there was no statistically significant difference (6.77±6.41 vs 7.93±7.04 ng/mL) ($P = 0.552$) between the CH and control groups respectively. However, neudesin levels increased following one month of therapy (6.46±6.63 vs 12.85±18.74 ng/mL) in the CH group; this difference was statistically significant ($P = 0.019$).
Conclusion
Although there was no difference in basal neudesin levels between the patient and control groups, neudesin levels increased with treatment. However, more extensive and different studies are needed to understand the pathophysiological role of this relationship in the disease or the recovery process.

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EP698

JOINT3856

Evaluation of clinical characteristics of syndromic and non-syndromic monogenic diabetes presented at neonatal and childhood period in a highly consanguineous population

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Aim
Monogenic diabetes (MD) accounts for the underlying aetiology of a small group of diabetes cases characterized by a single gene mutation. Given its heterogeneous course, identifying the relevant gene mutation and describing its characteristics is fundamentally important for the management and genetic counselling. In this study, we assessed a large series of patients with syndromic and non-syndromic MD who presented during neonatal and childhood periods.
Methods
A total of 46 patients with syndromic and non-syndromic MD from 41 families who presented between 2010 and 2022 were included. Family history, clinical and laboratory characteristics, and molecular genetics analysis results were obtained from hospital records.
Results
A mutation was detected in 44 of 46 (95.6%) patients. In non-syndromic MD, *ABCC8/KCNJ11* mutations ($n = 6$), *INS* mutations ($n = 5$), and *GCK* mutations ($n = 5$) were the most prevalent underlying causes. PTF1A mutations ($n = 11$) and EIF2AK3 mutations ($n = 9$) were most commonly observed in syndromic MD. The rates of parental consanguinity were 64.7% in patients with non-syndromic MD and 96.3% in patients with syndromic MD ($P = 0.015$). A successful transfer from insulin to sulfonylurea (SU) therapy was achieved in 2 patients with *ABCC8* and two patients with *KCNJ11* mutations.
Conclusion
In our large cohort, we found a high detection rate of underlying genetic causes (95.6%) for neonatal and childhood-onset MD which was attributed to enrichment by the high rate of consanguinity. Biallelic and syndromic forms were highly prevalent, especially within consanguineous populations. In patients with MD who have consanguineous parents, biallelic gene mutations that cause syndromic and non-syndromic diabetes should be prioritized in molecular genetics analysis.

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EP699

JOINT801

Managing daily challenges in congenital hyperinsulinism: impacts and solutions for improved quality of life"

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Background
Congenital hyperinsulinism (CHI) is a rare disorder caused by excessive insulin secretion, leading to persistent hypoglycemia. CHI poses significant challenges for patients and caregivers, affecting dietary, medical, cognitive, and social aspects of life. Effective strategies are essential for improving quality of life (QoL) and long-term outcomes.
Objective
To summarize the daily challenges in CHI management and propose strategies to address them, focusing on dietary, medical, cognitive, social, and long-term aspects, as well as therapeutic advancements.
Methods
A systematic review of studies published between 1990 and 2025 identified key challenges and solutions across multiple domains. Data from 16 studies were analyzed, including patient cohorts and reviews on QoL impacts and management strategies.
Results
1. Dietary Management: CHI requires frequent meals or high-protein, low-carbohydrate diets. Severe cases may need overnight feeding or gastrostomy. Personalized dietary plans and continuous glucose monitoring (CGM) reduce caregiver burden.
2. Medical Management: Lifelong medications, such as diazoxide and somatostatin analogs, pose challenges due to side effects and administration burden. Long-acting therapies like lanreotide lower treatment frequency, while caregiver training in device management enhances outcomes.
3. Cognitive and Physical Impact: Recurrent hypoglycemia can cause developmental delays and poor school performance. Early physical and cognitive therapies, coupled with school accommodations, improve outcomes.
4. Social and Psychological Impact: Social isolation and emotional stress affect both children and caregivers. Inclusive activities and counseling alleviate these challenges.
5. Caregiver Burden: Constant vigilance and financial strain create stress. Respite care and financial support programs help alleviate these pressures.
6. Therapeutic Advancements: PET/CT imaging distinguishes between focal and diffuse CHI, enabling tailored interventions. Long-acting therapies improve QoL by reducing treatment burden. Advocacy and standardized care protocols support families globally.
Conclusions
Effective CHI management requires addressing daily challenges to improve patient and caregiver QoL. Advances in therapies, genetic testing, and imaging have significantly mitigated these challenges, though financial and logistical barriers remain. Further research should explore long-term impacts of personalized therapies and global access to advanced care.
Keywords
Congenital hyperinsulinism, quality of life, dietary management, somatostatin analogs, caregiver burden, PET/CT imaging, advocacy programs.
Conclusions
CHI management requires a multidisciplinary approach addressing medical, dietary, psychological, and social challenges. Personalized interventions, advanced technologies, caregiver support, and long-term care strategies are crucial to improving outcomes and quality of life for affected families.
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EP700

JOINT3475

Neonatal hypocalcemic seizures revealing asymptomatic maternal hyperparathyroidism: case report and literature revue

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Introduction
Primary hyperparathyroidism during pregnancy is a rare condition increasing both maternal and perinatal morbidity and mortality. Thus, early detection and prompt surgery are essential, with the optimal timing being during the second trimester, which is considered safe. Maternal hyperparathyroidism can cause severe neonatal hypocalcemia and hypocalcemic tetany, affecting approximately 50% of infants born to mothers with untreated disease. Neonatal hypocalcemia results from prolonged parathyroid suppression due to chronic maternal hypercalcemia and the sudden cessation of maternal calcium transfer after delivery. The aim of this study is to highlight the importance of early diagnosis and management of maternal primary hyperparathyroidism during pregnancy to prevent neonatal complications, particularly hypocalcemic seizures.
Materials and methods
We present a case of recurrent neonatal tonico-clonic seizures due to undiagnosed asymptomatic maternal hyperparathyroidism.
Results
A fifteen-day-old male infant was presented to pediatric emergency department because of recurrent tonico-clonic seizures. Physical examination was normal. Ca level was 1.5 mmol/l, PTH levels was relatively low: 16 pg/mL. Transient hypoparathyroidism was considered as the cause of hypocalcemic seizures. The patient's mother had no complaints, nor a medical history. Her physical examination was normal. Biochemical evaluation revealed a serum total Ca level of 3,05 mmol/l. Serum phosphate level was 0,38 mmol/l. Urinary Ca was also elevated to 705 mg/24H. The PTH level was found to be 603 pg/mL while 25(OH) D level was low: 25 ng/mL. Parathyroid SPECT was performed with 99m Technetium-MIBI revealing a right inferior parathyroid adenom. Asymptomatic primary hyperparathyroidism was diagnosed and surgery was planned.
Conclusions
Unrecognized maternal hyperparathyroidism can suppresses fetal parathyroid activity and impairs the parathyroid response to hypocalcemia after birth. Based on our review of the literature, surgery is the preferred definitive treatment and is deemed safe and effective when performed during the second trimester of pregnancy.
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EP701

JOINT269

Novel mutation in TBX1 in a neonate with hypocalcemic seizures and digeorge syndrome

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Background
The 22q11.2 region covers approximately 30 genes, including TBX1, the mutation of which has been show to cause the 22q11.2 deletion syndrome. We report the case of a neonate with a novel heterozygous TBX1 mutation who experienced hypocalcemic seizures.
Case report
A 9-day-old female newborn was admitted to the pediatric neurological department to investigate recurrent focal tonic-clonic seizures. On admission, the physical examination was normal. The video-electroencephalography (EEG) was performed and ictal recording showed focal tonic and clonic seizures with bilateral propagation. Routine blood tests revealed hypocalcemia, total serum calcium of 1.66 mmol/l (2.15–2.8 mmol/l); and hyperphosphatemia, 3.42 mmol/l (1.25–2.5/mmol/l) with normal liver and kidney function, normal vitamin D level and negative inflammation markers. The parathyroid hormone levels were low on two occasions, 0.7 pg/ml and 0.3 pg/ml (1.3–9.3 pg/ml), respectively. The treatment consisted of controlling the seizures and correcting the hypocalcemia. A loading dose of phenobarbital (20 mg/kg) was administered, followed by oral administration. Since the seizures persisted, levetiracetam was added which led to seizure remission. The antiepileptic treatment with phenobarbital decreased serum calcium levels despite the simultaneous administration of calcium supplements. Calcium supplementation was started intravenously and, continued via the oral route. Hypoparathyroidism was transient and the treatment of hypocalcemia was stopped at the age of 2 months. Considering the association of neonatal hypocalcemia with hypoparathyroidism and seizures, DiGeorge Syndrome as well as other genetic disorders were taken into account. FISH did not reveal a 22q11.2 microdeletion. Further genetic analysis showed a novel T box-1 (TBX1) heterozygous mutation (c.337C>T; p.Gln113*). Over the next 4-month follow-up period the infant developed normally, without any seizures. EEG normalized and antiepileptic therapy was gradually discontinued.
Conclusion
A novel heterozygous TBX1 mutation was identified as a cause of neonatal hypocalcemic seizures and DiGeorge syndrome. We emphasize the importance of further genetic evaluation in infants with hypoparathyroidism without 22q11.2 deletion for detecting TBX1 mutations.
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EP702

JOINT314

Necrolytic migratory erythema following prolonged continuous subcutaneous Dasiglucagon administration: a case report

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Backrgound
Congenital hyperinsulinism (CHI) is a rare but severe disorder characterized by persistent hypoglycemia due to unregulated insulin secretion. Dasiglucagon, a synthetic glucagon analogue, has emerged as a promising treatment for CHI due to its stability and ease of use in continuous subcutaneous infusion. However, long-term safety data remain limited. Here, we describe a case of necrolytic migratory erythema (NME), a rare and severe dermatologic condition, associated with prolonged continuous subcutaneous dasiglucagon therapy.
Case
A male infant with CHI caused by compound-heterozygous mutations in *ABCC8* was treated with continuous subcutaneous dasiglucagon after standard therapies, including intravenous glucose, diazoxide, and octreotide, failed to achieve glycemic control. Initial dasiglucagon therapy with 20–60 µg/h was effective; however, after several weeks of treatment, the patient progressively developed erythematous, scaly skin lesions. This condition was accompanied by significant malnutrition, evidenced by a consistent downward trajectory across multiple weight percentile lines in serial measurements, along with zinc deficiency and hypoaminoacidemia. Based on the patient's history and clinical presentation, we strongly suspected necrolytic migratory erythema (NME). Given the patient's severe skin condition a central line was chosen to ensure secure intravenous access and targeted intravenous substitution of zinc, trace elements, amino acids, and fatty acids was initiated to treat malnutrition. While we initiated further diagnostic workup for NME, the patient developed Staphylococcus aureus-associated central line sepsis. Consequently, continuous subcutaneous dasiglucagon administration was tapered and the therapy was discontinued after a total of five months. The patient underwent subtotal pancreatectomy to manage persistent hypoglycemia. Postoperatively, his condition improved significantly, with resolution of the skin lesions and normalization of nutritional parameters through targeted supplementation. As expected, diabetes mellitus developed, requiring insulin therapy.
Discussion
Dasiglucagon has shown significant promise in managing severe hypoglycemia, owing to its rapid glucose-raising effects. While short-term use has demonstrated efficacy and tolerability across various therapeutic indications, our case of prolonged continuous use in CHI, which was complicated by the development of NME, underscores the critical importance of rigorous monitoring during extended treatment. Monitoring should prioritize the early identification of potential adverse effects, including dermatological conditions, amino acid and zinc deficiencies, and alterations in weight trajectory. Although this case report does not establish a direct causal relationship between continuous dasiglucagon therapy and NME, it emphasizes the need for vigilant long-term use, multidisciplinary care, and further research to enhance the understanding of its safety profile and optimize therapeutic strategies.

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EP703

JOINT3729

Evaluation of a new guideline for the early detection and management of neonatal hypoglycaemia

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Introduction
Neonatal hypoglycaemia is the most common metabolic condition in neonates. It affects up to 15% of all neonates and 50% of neonates born with risk factors. However, there is still no international consensus on treatment thresholds and management strategies for neonatal hypoglycaemia. In March 2020, a new standard operating procedure (SOP) for the "early detection and treatment of neonatal hypoglycaemia" for newborns born after 35 weeks of gestation was introduced at the Paediatric and Obstetric Clinic of the University Hospital Düsseldorf. The development of this SOP was based on an extensive review of various international guidelines. The SOP provides a preventative approach for children with risk factors for neonatal hypoglycaemia and includes standardised blood glucose screening and treatment of hypoglycaemia if necessary. The aim of this study is to compare a retrospective (pre-SOP) and a prospective (post-SOP) cohort to investigate whether the SOP has improved the early detection and management of hypoglycaemia and whether the number of severe or prolonged hypoglycaemia has decreased. It will also compare the frequency of hypoglycaemia, the number of blood glucose measurements, the rate of transfer to the paediatric clinic, the duration of treatment with intravenous glucose, and the overall inpatient treatment.
Methods
The study includes a total of 607 children born at the University Children's Hospital Düsseldorf, 280 born before to the implementation of the new SOP (before March 2020) and 327 born after the implementation of the new SOP. The cohorts were matched for sex, birth weight, gestational age, and risk factor for neonatal hypoglycaemia.
Results
All patients have been enrolled in the study. Data collection is currently being completed. We then plan to perform statistical analyses and present the final data at the conference.
Conclusion
Given the high incidence of hypoglycaemia in neonates, it is of great interest to determine whether the new standard can detect hypoglycaemia more frequently, prevent profound hypoglycaemia, reduce the number of severe and prolonged hypoglycaemic episodes and thus prevent possible negative consequences due to brain damage. However, the 'costs' of interventions also need to be analysed, including patients who have received interventions but are unlikely to have benefited from them. It is only through such analyses that evidence-based guidelines can be developed, which is urgently needed for an issue as important as neonatal hypoglycaemia to improve the approach for future generations.

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EP704

JOINT1695

Cloudy blood, clear diagnosis: homozygous GP1HBP1 mutation in a 20 day old neonate

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Background
Severe hypertriglyceridemia and dyslipidemia in infancy are rare, often presenting with nonspecific signs that complicate early diagnosis and management. Genetic causes, such as mutations in key triglyceride metabolism proteins, are frequently implicated. GP1HBP1 (Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1) is critical for the interaction between lipoprotein lipase (LPL) and triglyceride-rich lipoproteins. Mutations in GP1HBP1 impair triglyceride clearance, leading to extreme hyperchylomicronemia, characterized by markedly elevated triglycerides, lipemia retinalis, and risk of acute pancreatitis[1]. Early recognition of genetic hyperlipidemias is crucial for prompt intervention and prevention of complications[2].
Case Presentation
We report a 20-day-old neonate presenting with fever and incidentally noted cloudy blood samples. Lipid profile showed extreme hyperlipidemia: total cholesterol 702 mg/dL, triglycerides 12,583 mg/dL, HDL 51 mg/dL, and VLDL 2,517 mg/dL. The infant, born full-term with no neonatal complications, had no xanthomas, xanthelasmas, or family history of dyslipidemia. Fundoscopy revealed lipemia retinalis; abdominal ultrasound was normal. Genetic testing identified a homozygous pathogenic GP1HBP1 variant, confirming autosomal recessive chylomicronemia syndrome[1]. Management included a low-fat maternal diet (as the infant was exclusively breastfed) and omega-3 fatty acid supplementation (2 g/day)[3].
Discussion
This case highlights the need to consider genetic dyslipidemias in neonates with severe hypertriglyceridemia. GP1HBP1 mutations disrupt LPL activity, causing impaired triglyceride metabolism[1]. Management focuses on dietary fat restriction, omega-3 supplementation, and close monitoring to prevent complications like pancreatitis and cardiovascular disease[2,3]. Early genetic diagnosis facilitates targeted management and family counseling.
Conclusion
This report underscores the importance of early recognition and a multidisciplinary approach in managing severe neonatal hyperlipidemia due to GP1HBP1 mutations, optimizing outcomes in rare genetic dyslipidemias.
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EP705

JOINT799

Unraveling genotype-phenotype interactions in congenital hyperinsulinemic hypoglycemia: implications for targeted therapies and diazoxide responsiveness

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Background
Congenital Hyperinsulinemic Hypoglycemia (CHI) is a rare disorder of insulin dysregulation caused by genetic mutations that impair the function of pancreatic β-cells. Accurate genotype-phenotype correlations and understanding of therapeutic responses, including to diazoxide, are crucial for effective diagnosis and management. This review examines molecular findings, diazoxide response rates, and alternative therapies for CHI, focusing on phenotype and genotype relationships.
Methods
A systematic review of studies published from 2013 to 2025 was conducted, analyzing genetic variants, clinical phenotypes, and diazoxide response rates. Data were extracted from verified studies on key genotypes (e.g., ABCC8, KCNJ11, GLUD1, HNF4α, GCK, and INSR) and phenotypes (e.g., diffuse, focal, atypical, and transient CHI).
Results
Data from 546 patients across 14 studies revealed distinct patterns in diazoxide response by genotype and phenotype.
• Genotype-based responses:
• ABCC8 and KCNJ11 mutations, the most common genetic causes of CHI, showed low response rates to diazoxide (40% and 50%, respectively).
• GLUD1 mutations had high response rates (81%), while GCK mutations were moderately responsive (71%).
• HNF4α mutations exhibited the highest response rates (90%), whereas INSR mutations were poorly responsive (30%).
• Phenotype-based responses:
• Diffuse CHI, often associated with severe neonatal presentations, had a low response rate (35%).
• Focal CHI, typically caused by paternal ABCC8 mutations with somatic loss of heterozygosity, showed the highest response rate (90%) after surgical resection.
• Atypical CHI demonstrated variable diazoxide responsiveness (50%), reflecting its heterogeneous etiology.
• Transient CHI, common in mild and perinatal cases, had a high response rate (80%) with medical therapy.
• Therapeutic insights:
• Long-acting somatostatin analogs, such as octreotide and lanreotide, provided effective alternatives for diazoxide-unresponsive diffuse and atypical CHI cases.
• Emerging therapies, including GLP-1 receptor antagonists, showed promise in preclinical studies for severe CHI unresponsive to standard treatments.
Conclusions
The genotype and phenotype of CHI strongly influence therapeutic outcomes, particularly diazoxide responsiveness. Diffuse and severe forms often require alternative therapies or surgery, while milder forms respond well to medical management. Comprehensive molecular and phenotypic analysis is essential for tailoring treatment and improving long-term outcomes in CHI. Further research into personalized therapeutic approaches and emerging treatment options is warranted.
Keywords
Congenital hyperinsulinism, ABCC8, KCNJ11, diazoxide, somatostatin analogs, GLP-1 receptor antagonists, genotype-phenotype correlation.
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EP706

JOINT953

"Genotype and phenotype-driven probability of therapeutic response in congenital hyperinsulinism"

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Background
Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in neonates and infants, caused by dysregulated insulin secretion. The probability of response to diazoxide, first-line therapy, and other medical or surgical treatments varies based on genetic mutations and phenotypic presentations. Understanding these factors is crucial for optimizing treatment strategies.
Objective
To evaluate the probability of therapeutic response in CHI based on genetic mutations and phenotypic factors, highlighting genotype-phenotype correlations.
Methods
A literature review of studies between 2000 and 2024 was conducted, focusing on the influence of genetic mutations (ABCC8, KCNJ11, GLUD1, HNF4A, and HNF1A) and phenotypic factors (histological subtypes, age of onset) on diazoxide response and other treatment outcomes. Data were synthesized to calculate probabilities of therapeutic success.
Results
1. Genetic Factors and Diazoxide Response:
• KATP Channel Mutations (ABCC8, KCNJ11):
• Dominant mutations: High probability of diazoxide response (>70%), as partial loss of function allows diazoxide to activate the KATP channel.
• Recessive mutations: Low response probability (<30%), associated with severe diffuse CHI due to complete channel dysfunction.
• Other Mutations:
• GLUD1: Very high response probability (>80%) due to effective suppression of insulin secretion with diazoxide.
• HNF4A/HNF1A: High probability (>80%), associated with mild forms of CHI.
2. Phenotypic Factors:
• Histological Subtype:
• Focal CHI: Response probability depends on mutation; lesions are often curable with lesionectomy.
• Diffuse CHI: Low diazoxide response probability (<20%); near-total pancreatectomy often required.
• Age of Onset:
• Neonatal CHI: Severe phenotype with low diazoxide response.
• Later-Onset CHI: Milder phenotype with higher diazoxide responsiveness.
3. Alternative Therapies:
• For diazoxide-unresponsive cases, therapies such as octreotide, lanreotide, and CGM-assisted glucose monitoring are effective, particularly in severe or diffuse CHI.
Conclusions
The probability of therapeutic response in CHI is highly dependent on genotype and phenotype. Diazoxide is effective in patients with dominant KATP mutations, GLUD1, and HNF4A mutations, while recessive KATP mutations and diffuse CHI predict poor response. Individualized treatment strategies based on genetic and phenotypic profiling are essential to optimize outcomes in CHI patients.
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EP707

JOINT3718

The role of surgery in the 3rd trimester in the management of hypercalcaemia in pregnancy

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Introduction
Hypercalcemia during pregnancy, while uncommon, is not exceedingly rare. The management of hypercalcemia in pregnancy can be particularly challenging with the approach largely depending on the trimester in which the condition is diagnosed. Treatment strategies include conservative management, medical therapy, or, in some cases, surgical intervention.
Case
A 30-year-old woman was reviewed in the antenatal clinic at 12 weeks of gestation, with blood tests revealing hypercalcemia. Her calcium level was 2.89 mmol/l, parathyroid hormone (PTH) level was elevated at 8.24 pg/ml, urinary calcium was 9.1 mg/24h, and vitamin D level was 58 nmol/L. She was asymptomatic at the time. An ultrasound of the parathyroid glands revealed a left superior parathyroid adenoma. She was referred to the surgical team for consideration of surgery. While awaiting surgical intervention, she was advised to increase her oral fluid intake. Due to delays in the surgical consultation during the second trimester, she was initiated on Cinacalcet therapy. However, she later developed polyhydramnios, prompting an urgent and successful parathyroidectomy at 30 weeks of gestation. Following the surgery, her calcium level normalized to 2.33 mmol/l. She subsequently delivered a healthy baby without complications.
Discussion
Hypercalcemia can be caused by a variety of conditions including primary hyperparathyroidism, malignancy, sarcoidosis, and certain medications. In pregnancy, primary hyperparathyroidism is the most common cause, and the management of hypercalcemia is contingent upon the trimester in which the diagnosis is made. Treatment options may include conservative measures such as intravenous fluids, medical therapies like Calcitonin or Cinacalcet, and surgical intervention. Surgical treatment is generally recommended in the second trimester to prevent both maternal and foetal complications. In cases of symptomatic

hypercalcemia, surgical intervention may be indicated later than the 2nd trimester as seen in this case.
Conclusion
Surgical intervention for hypercalcemia during pregnancy is typically recommended in the second trimester. However, surgery may be necessary in the third trimester, particularly in cases of symptomatic hypercalcemia. In this case, the patient developed polyhydramnios, likely secondary to hypercalcemia, and parathyroidectomy was performed at 30 weeks of gestation which helped manage symptoms and prevented further foetal complications and resulted in an uncomplicated delivery of baby.

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EP708

JOINT863

Clinical experience with various persistent congenital hyperinsulinisms in a single tertiary care center: a case series

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Introduction
Congenital hyperinsulinism (CHI) is a disease group characterized by inappropriate insulin secretion leading to hypoglycemia. Genetic testing helps diagnose diseases, select effective treatments, and provide genetic counseling for families. Disease-causing single nucleotide variants affecting more than 30 genes are reported to cause persistent hyperinsulinism. F-DOPA PET CT imaging is also used to identify patients who may require surgical treatment. Medical treatment of hyperinsulinism includes medications such as diazoxide, somatostatin analogues, calcium channel blockers, and glucagon. We would like to review six cases experienced in our hospital and share information on appropriate treatment for this condition.
Cases
There were 6 patients with persistent congenital hyperinsulinism, 3 were diagnosed with hyperinsulinemia in the neonatal period due to hypoglycemia that occurred on the day of birth, and 3 were diagnosed with congenital hyperinsulinism after visiting the hospital due to convulsions and hypoglycemia after infancy. All 6 patients started treatment with diazoxide, and 4 patients continued treatment with diazoxide, but 1 patient developed significant pulmonary hypertension while taking diazoxide and was changed to octreotide, and the remaining 1 patient changed to octreotide because his blood sugar was not sufficiently controlled with diazoxide, but could be changed back to diazoxide at 3 years of age and continued to take diazoxide until the age of 8. In the genetic panel test, no mutations were found in 2 patients, and ABCC8 gene mutations were found in 3 patients. One patient with an ABCC8 mutation stopped taking diazoxide at age 8, was diagnosed with diabetes mellitus at age 13, and is currently taking oral hypoglycemic agents. F-dopa PET-CT was performed to two patients in whom no genetic mutation was detected, and both were confirmed to have diffuse type of CHI.
Conclusions
Diazoxide is an approved oral drug for the treatment of hyperinsulinism, despite the possibility of rare but serious side effects such as pulmonary edema or hypertension. Serious side effects including pulmonary hypertension should be kept in mind when administered to neonates. The clinical manifestations of permanent congenital hyperinsulinism are diverse, so careful attention is needed to ensure appropriate treatment.

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EP709

JOINT803

Comparative outcomes of medical and surgical management in children with persistent neonatal hyperinsulinemic hypoglycemia: a focus on long-term growth, metabolic, and developmental implications"

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Background
Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in neonates and infants, posing significant challenges in management. Hypoglycemia during the neonatal period is particularly difficult to control due to the severity and variability of the disease. While medical treatments such as diazoxide or octreotide are often first-line, they fail in severe or diazoxide-unresponsive cases, necessitating surgical intervention, such as partial or near-total pancreatectomy. Long-term outcomes of these treatments vary significantly, impacting growth, metabolic control, and neurodevelopment.
Objective
To compare the outcomes of medical vs surgical treatments in managing persistent neonatal hypoglycemia caused by CHI, focusing on growth, metabolic, and developmental outcomes.
Methods
This review consolidates data from 20 studies published between 1990 and 2023, involving over 2,000 patients with CHI. Studies were evaluated based on treatment modalities (medical or surgical), long-term outcomes related to growth, metabolic health, and neurodevelopment, and genetic correlations.
Results
• Growth Outcomes: Patients on medical therapy generally demonstrated normal growth trajectories, provided hypoglycemia was well-controlled. Surgical interventions, particularly near-total pancreatectomy, resulted in significant growth impairments in some studies. For instance, Soliman *et al*. (1998) reported height scores of -2.57 SD, reflecting growth retardation, while most patients in Beltrand *et al*. (2012) maintained normal growth.
• Metabolic Outcomes: Medical therapy successfully managed hypoglycemia in approximately 50-71% of patients, with diazoxide efficacy varying based on genetic mutations. Surgical treatments resolved hypoglycemia in 97% of focal CHI cases but were less effective in diffuse CHI, with 50% experiencing persistent hypoglycemia post-surgery. However, near-total pancreatectomy carried a high risk of insulin-dependent diabetes (40-96%) and exocrine insufficiency.
• Developmental Outcomes: Neurodevelopmental delays were observed in both groups, particularly in patients with prolonged or inadequately controlled hypoglycemia. Surgical patients exhibited higher rates of neurobehavioral deficits (up to 55% in Rasmussen *et al*., 2020), while early and effective medical management mitigated these risks in many cases.
Conclusion
Management of CHI remains challenging, with both medical and surgical treatments presenting unique benefits and risks. Medical therapy is effective for many cases but is limited in severe, diazoxide-unresponsive CHI. Surgical intervention, while curative in focal disease, is associated with long-term complications, including diabetes and neurodevelopmental delays. Early diagnosis, individualized treatment plans, and multidisciplinary care are essential to optimize outcomes. Future advancements in genetic analysis and novel therapies are urgently needed to improve the prognosis for these patients.

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EP710

JOINT375

Hypoglycemia screening before discharge in newborn identified as at risk

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Neonatal hypoglycemia is a common metabolic disturbance that can adversely affect neurological development. Current guidelines focus on screening and managing hypoglycemia in the first 24 h of life, yet some asymptomatic at-risk infants experience hypoglycemia between 24 to 48 h, with limited recommendations for this critical period. This study aims to assess glucose screening at 48 h of age to ensure safe discharge for asymptomatic neonates at risk of hypoglycemia. A prospective cohort study was conducted from July 2023 to May 2024 at a tertiary care hospital. Asymptomatic neonates aged 48-60 h with gestational ages between 34-41 weeks, identified as at risk for hypoglycemia, were enrolled. Blood glucose levels were measured using both a glucometer and standard plasma glucose testing. Among the 139 newborns included in the study, the incidence of hypoglycemia varied significantly between glucometer (10.8%)

Table 1. Laboratory values of cases

Factors	Unadjusted odds ratio (95%confidence interval)	Adjusted OR (95%CI)
Type of feeding before discharge		
Breastfeeding	Reference	Reference
Infant Formula	0.22 (0.04, 1.2)	0.17 (0.03, 1)
Breastfeeding and Infant Formula	1.30 (0.54, 3.13)	1.27 (0.52, 3.12)
Discharge weight		
> 2,500 gm	Reference	Reference
≤ 2,500 gm	2.22 (1.03, 4.78)	2.46 (1.09, 5.57)

and standard plasma glucose (48.9%) measurements. Infants with discharge weights below 2500 grams were twice as likely to experience hypoglycemia (OR: 2.221, $P = 0.042$). Despite a strong correlation ($r=0.725$,$P < 0.001$) between glucometer and plasma glucose readings, glucometers tended to overestimate glucose levels, particularly at lower glucose concentrations.

Conclusion

There is a high incidence of hypoglycemia among asymptomatic neonates identified as at risk before discharge. Asymptomatic neonates with risk factors for hypoglycemia who have a discharge weight of $\leq$ 2,500 grams should be screened for hypoglycemia at 48 to 60 h of age to ensure their safe discharge from the hospital.

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EP711

JOINT2836

New insights into hypothalamic dysfunction: schaaf-yang syndrome in two infants

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Objective

To delineate the chronological progression and pathophysiological effects of *MAGEL2* mutations in infants with Schaaf-Yang syndrome, focusing on associated endocrine disorders and developmental dysfunctions such and characteristic dysmorphisms.

Methods

A detailed review of clinical, hormonal, and genetic data from two infants with Schaaf-Yang syndrome, including the onset of specific endocrine characteritics and developmental features, particularly those related to *MAGEL2* mutations.

Results

AVP-D Both infants presented with symptoms of arginine vasopressin deficiency (AVP-D) such as hypernatremia and polyuria from the neonatal period, highlighting disturbances in hypothalamic function. **Hypopituitarism:** Manifestations of growth hormone deficiency and transient adrenal insufficiency were noted early in life, typically emerging within the first few months. **Delayed Hyperinsulinism:** Diagnosis of hyperinsulinism occurred at seven and eleven months, managed with diazoxide and octreotide, reflecting progressive pancreatic beta-celldysfunction. **Genetic Insights:** Infants displayed *de novo* truncatingmutations in the *MAGEL2* gene (c.1996dup and c.1912C>T), which correlate with more severe phenotypic manifestations. **Developmental Dysmorphisms:** Both infants exhibited characteristic facial features (broad forehead, almond-shaped eyes, flattened nasal bridge, thin upper lip) and finger contractures associated with oligohydramnios, highlighting the prenatal impact of *MAGEL2* mutations.

Conclusion

The profound endocrine and developmental manifestations in Schaaf-Yang syndrome underscore the criticalrole of *MAGEL2* mutations in disrupting hypothalamic functions. These mutations not only impair hormone regulation leading to AVP-D, hypopitutarism and hyperinsulinism but also affect prenatal development, contributing to distinct facial dysmorphisms and contractures. This detailed understanding is crucial for developing targeted interventions and managing the complex endocrine dysfunctions in SYS, facilitating improved outcomes through proactive and informed therapeutic strategies.

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EP712

JOINT3337

A case of PURA syndrome characterized mainly by hypotonia and hypersomnia

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Background

PURA syndrome (OMIM: 616158) is a neurodevelopmental disorder caused by heterozygous pathogenic variants in the PURA gene (5q31.3), which encodes a DNA/RNA-binding protein critical for neuronal myelination, synaptic plasticity, and cell cycle regulation. Characterized by neonatal hypotonia, feeding difficulties, hypersomnolence, and global developmental delay, this syndrome needs to be clinically differentiated from diseases such as Prader-Willi syndrome with hypotonia and developmental delay.

Clinical Case

An 8-month-old male presented with profound axial hypotonia (inability to lift head or roll over), hypersomnolence (18 hour/day), and delayed motor milestones. Neonatal history included respiratory distress syndrome, intraventricular hemorrhage (Grade II), and periventricular leukomalacia. Neurological examination revealed normocephalic head, intact visual tracking, absent auditory orientation, and preserved tendon reflexes. Serial evaluations excluded metabolic disorders (normal tandem mass spectrometry), cardiac defects (unremarkable echocardiography), and negative 15q11 methylation analysis. Trio whole-exome sequencing identified a de novo heterozygous PURA frameshift variant (NM_005859.5:c.523del, p.Asn175Thrfs50) in exon 1, classified as pathogenic (PVS1, PS2, PM2). At 3-year follow-up, the patient exhibited severe motor delay (non-ambulatory, absent sitting balance), growth restriction (<3rd percentile), and language impairment (no meaningful words). Neuroimaging showed persistent white matter hyperintensities. Management included enteral nutrition support, vitamin D supplementation, and intensive neurorehabilitation. This report delineates the natural history and molecular confirmation of a novel PURA frameshift variant.

Conclusion

This case reinforces the core phenotype of PURA syndrome: neonatal-onset hypotonia, hypersomnolence, and irreversible neurodevelopmental deficits. The identified exon 1 truncating variant likely disrupts PUR-alpha's N-terminal domain, impairing its role in mRNA transport and translation. Given the lack of disease-modifying therapies, we advocate standardized surveillance protocols encompassing EEG (for seizure risk), spine imaging (scoliosis progression), and swallow studies. This study delineates the clinical and molecular characteristics of a novel PURA-associated syndrome. The variant (NM_005859.5:c.523del, p.Asn175Thrfs50) expands the mutational spectrum, correlating with extreme hypersomnolence severity.

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EP713

JOINT3004

Cardiometabolic function in offspring, mother and placenta after assisted reproductive technology (COMPART)

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Background

The increasing rate of infertility drives rapid advancements in assisted reproductive technology (ART). Improved cryopreservation techniques have significantly increased the use of embryos that have been frozen/thawed (frozen embryo transfer; FET) in ART. FET offers benefits over conventional fresh embryo transfer (fresh-ET) by reducing some pregnancy complications associated with fresh-ET. However, F*et al*so carries increased obstetric and perinatal risks, such as preeclampsia, increased birthweight and increased risk of being born large for gestational age (LGA). Both preeclampsia and LGA is known to predispose children to obesity and later cardiometabolic diseases.

Aim

The study aims to uncover the mechanism underlying the altered obstetric outcomes and fetal growth following FET and to determine the health implications for the children. The study hypothesizes that the freezing/thawing induces epigenetic changes in the embryo causing fetal and placental overgrowth. This leads to preeclampsia and LGA and potentially impacts cardiometabolic health in the children.

Methods

The prospective cohort will include 600 pregnant women, partners and offspring, equally comprised of pregnancies achieved after ART with FET, ART with fresh-

ET and naturally conceived (NC) pregnancies. The study includes extensive data collection from medical records, questionnaires, laboratory tests and clinical examinations. The pregnant women undergo three examinations during pregnancy to assess biomarkers of preeclampsia and maternal metabolism and growth factors. Fetal growth is determined by serial ultrasound scans. Epigenetic and transcriptomic profiles in placenta and cord blood is investigated upon delivery. The children are examined at three months of age with evaluation of body composition by an air displacement plethysmography scan and a dual-energy X-ray absorptiometry scan. Cardiometabolic biomarkers and hormones of minipuberty are analyzed in blood samples. To determine the genetic contribution to phenotypic traits, single-nuclei-polymorphism genotyping is performed and a polygenic score for major cardiometabolic traits calculated. The study commenced May 2024, currently 201 participants are enrolled and 25 children born.

Outcomes and scientific impact

The study is powered to detect a difference in birthweight (SDS) between FET, Fresh-ET and NC. Secondary outcomes are grouped into work packages and compared between the groups. WP2 (pregnancy): incidence of preeclampsia, WP3 (placenta): placental weight, WP4 (child): fat percentage, WP5 (epigenetics): DNA methylation in cord blood and placenta, WP6 (genetics): deviation from genetically determined birthweight. Several exploratory outcomes are defined. We expect our study to identify key mechanisms related to outcomes after FET that could inform clinical practices and improve long-term health for mothers and children conceived after ART.

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EP714

JOINT582

Update on the association of prenatal and postnatal exposures to acetaminophen and neurodevelopmental disorders

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Introduction

Acetaminophen (paracetamol) is traditionally considered a safe medication for the management of fever and pain in pregnant women and in children. Although several studies have reported that postnatal exposure to acetaminophen in susceptible children is associated with neurodevelopmental disorders, data on its neurodevelopmental impact after prenatal exposure are controversial. This review presents an update on the association of prenatal and postnatal exposures to acetaminophen and neurodevelopmental disorders.

Methods

A systematic search of literature was conducted using the search terms acetaminophen, endocrine-disrupting chemicals, prenatal exposure, postnatal exposure, and neurodevelopmental disorders.

Results

Acetaminophen, a widely used over-the-counter medication, is a non-opioid antipyretic and analgesic drug. It is used by more than 50% of pregnant women for the treatment of fever and pain. Neurodevelopmental disorders can affect all types of populations and cause high cost to the economy. Although some studies have suggested that prenatal exposure to acetaminophen is associated with high incidence of neurodevelopmental disorders in the offspring (e.g., autism spectrum disorder and attention-deficit/hyperactivity disorder), a sibling control analysis of a large population of children exposed to acetaminophen through pregnancy ($n = 185{,}909$) showed that there is no significantly increased risk of autism, attention-deficit/hyperactivity disorder, and intellectual disability in children exposed prenatally. In contrast, most studies of postnatal exposure to acetaminophen have reported that the use of acetaminophen in susceptible infants and children is associated with multiple neurodevelopmental disorders. Acetaminophen intake during pregnancy has also been reported in association with increased male reproductive and urogenital disorders (e.g., cryptorchidism and hypospadias) likely due to the endocrine-disrupting properties of the medication. These findings have important implications for the management of fever and pain in pregnant women and in children. Because of the economic and psychological burden of neurodevelopmental disorders, it is urgent to conduct more high-quality studies with adequate control to assess the association of prenatal use of acetaminophen and neurodevelopmental disorders before proposing clinical guidelines. However, until proven otherwise, pregnant women should have limited use of acetaminophen (e.g., lowest effective dose for the shortest possible time).

Conclusion

It is well established that the postnatal exposure to acetaminophen can increase the risk of neurodevelopmental disorders in children. However, the neurodevelopmental consequences of prenatal exposure to acetaminophen are not clearly established and require further investigations. Until proven otherwise, it is recommended that the intake of acetaminophen during pregnancy be reduced as much as possible.

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EP715

JOINT2916

The neonatal TSH screening as an indicator of the iodine status in newborns in bulgaria: actual data 2021-2024

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Current WHO guidelines consider that under an adequate iodine intake $< 3\%$ of the newborns (NB) should have TSH levels of > 5 mU/l at screening. The neonatal TSH screening was implemented in 1993. A new National Program focused on sustainable elimination of iodine deficiency disorders took place in 1994 and universal salt iodization for the whole country became mandatory. According to ICCIDD criteria Bulgaria was declared as "Iodine sufficient" in 2007.

Aim

To analyze the age-adjusted TSH distribution and provide actual data connected to the iodine intake in NB's between 2021-2024.

Material&Methods

Data from 177 607 NB (84.37% of all screened NB) aged 3rd-5th day of life were analyzed by TSH (DELFIA^{R} Perkin Elmer) in dried blood spots from 28 Bulgarian districts (107 maternities) between 2021-2024. Results: compared to 2006/2007 (2.8% of NB $>$ 5 mU/l) the proportion of NB with TSH $>$ 5 mU/l increased to 6.18% between 2021-2024 for the entire country. According to the TSH cut off 5 mU/l only one district was completely iodine sufficient during the entire period. Other districts showed fluctuations between sufficiency and mild iodine deficiency. Therefore the neonatal TSH distribution corresponds to mild iodine deficiency.

Conclusions

The neonatal TSH monitor was implemented as a constant part of the complex iodine monitoring program early at national, regional and hospital level. Despite a lot of factors influencing the TSH distribution, targeted actions are now necessary in order to proof and further evaluate the alarming situation of mild iodine deficiency appearing again in the country in the NB's as the most sensitive and vulnerable population for development of mental deficits.

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EP716

JOINT1076

A rare case of a male infant in mini-puberty presenting with premature pubarche and non-classical congenital adrenal hyperplasia

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Background

Nontumorous premature pubarche is rare in infants, as the physiological variations in the gonadal and adrenal axes during mini-puberty make etiological diagnosis challenging.

Purpose

To report a case of self-limited premature pubarche in a 5^{+}-mo-old male infant with nonclassical congenital adrenal hyperplasia (NCCAH).

Methods

Case study.

Results

A 5^{+}-mo-old male infant was referred to our clinic due to be found with the presence of pubic hair for 8 days. Being the second child of non-consanguineous

Chinese parents, he was born by cesarean section due to premature rupture of membranes in pre-term with appropriate weight and length in good condition (36^{+5} weeks, 2500g,48cm). At 3-mo-old, he was diagnosed with"eczema"and administered with topical glucocorticoids intermittently for 2^{+} months until now. At 4-mo-old, serum 17OHP was tested to be 2.63 ng/ml due to vomiting. Physical examination revealed thick and long pubic hair on the mons pubis-without hyperpigmentation or enlargement of the penis. His height (–0.04 SDS) and weight (-0.9 SDS) were normal for his age. Laboratory test: E_2 21 pg/ml, T 0.67 ng/ml, P 0.20 ng/ml, DHEAs 3.34μmol/L, cortisol 8.6μg/dl, ACTH 10.2 pmol/L, androstenedione(A^4) $<$1.05 nmol/L. Serum β-hCG, AFP and CEA were normal. At 7^{+}-mo-old(one month after topical steroid withdrawal), the patient was admitted to the hospital due to slightly aggravated pubic hair development. Physical examination revealed scattered large patches of papular rash on the trunk, one acne on the face, and 4 ml testis. GnRHa (triptorelin) 60-minute stimulation test: FSH 1.05→3.02 IU/L, LH 1.13→11.39 IU/L; 8-hour ACTH stimulation test: 17OHP 2.01→18.03 ng/ml, cortisol 5.8→48.8μg/dl, P 0.30→1.8 ng/ml, E_2 12→51 pg/ml, T 0.38→0.13 ng/ml, A^4 $<$1.05→1.29 nmol/L, $DHEA_S$ 1.57→1.92μmol/L. Bone age was 9 months. Testicular ultrasound, adrenal CT, pituitary MRI did not show any abnormalities. Due to his elevated base and ACTH-stimulated serum 17OHP concentration, Whole exome sequencing and *CYP21A2* gene analysis (Sanger sequencing and MLPA) were performed and revealed negative result. At 3y3m, the boy's pubarche spontaneously resolved at age 10^{+}-mo-old after a slightly increase and darkening for one more month, with no other signs of virilization, and growth velocity remained normal.

Conclusions

We report a rare self-limited premature pubarche case of a male infant in mini-puberty with biochemical NCCAH. The premature pubarche is not related to NCCAH.

Key words

Mini-puberty, non-classical congenital adrenal hyperplasia, premature pubarche.

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EP717

JOINT3300

A macrosomic preterm baby with hypoinsulinemic hypoketotic hypoglycemia: a diagnostic puzzle

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Introduction

In cases of hypoketotic hypoglycemia mimicking hyperinsulinism, pathogenic variants in post-receptor signaling cascades lead to autonomous activation of insulin signaling in target tissues, causing severe hypoglycemia with low or undetectable insulin. This report highlights the challenges in diagnosis and management of hypoinsulinemic hypoketotic hypoglycemia (HHH) and discusses available treatment options.

Case Report

A male neonate was born at 33 weeks gestation to non-consanguineous parents, with a weight of 2440 g (+2.2 SDS), mild dysmorphic features and a cleft palate. A capillary blood glucose (BG) on day 12 was 29 mg/dL and a critical blood sample taken during this hypoglycemic episode revealed serum glucose of 32mg/dL, insulin of 0.65mIU/L, c-peptide of 0.285ng/ml, ketones of 0.2mmol/l and adequate counter-regulatory hormone levels (cortisol 21.9μg/dL, growth hormone 10.9μg/L). Glucagon elicited glucose response without lactate elevation. The patient exhibited cyclical hypo/hyperglycemic episodes during 2-hourly feeding with continuous glucose-monitoring (27-383 mg/dL; time in 55-140 mg/dL range: below 4% and above 9%). Persistent hypoglycemia despite a glucose infusion rate (GIR) of up to 8 mg/kg/min required diazoxide and hydrochlorothiazide. Hypoglycemia persisted despite GIR of 17 mg/kg/min, suggesting diazoxide unresponsiveness. Despite treatment including methylprednisolone (2 mg/kg/day), octreotide (40 mg/kg/day), nifedipine (4x100 mg/kg/dose) and glucagon infusion (1 mg/kg/hour), hypo/hyperglycemia cycling persisted, necessitating continuous nasogastric feeding and octreotide by pump, successfully stabilizing BG. Rapid genetic testing for *ABCC8* and *KCNJ11* variants at Exeter were unremarkable. Next-generation sequencing analysis for *ABCC8, AKT2, CACNA1C, CACNA1D, CREBBP, DNTTIP1, EP300, FOCAD, FOXA2, GCK, GLUD1, GPC3, HADH, HNF1A, HNF4A, INSR, KCNJ11, KDM6A, KMT2D, MAFA, MAGEL2, NSD1, PHOX2B, PMM2, RNF10, SLC16A1, TRMT10A*, and *HK1* variants were also unremarkable. Whole exome sequencing re-analysis for hypoglycemia-associated conditions has been initiated. On continuous feeding at three months old the baby had an episode of hypoglycemia (48.9 mg/dL) with concurrent insulin $<$0.04 mIU/L and c-peptide 0.03 ng/ml confirming HHH. The patient died due to septic shock from complications of influenza pneumonia.

Discussion and Conclusion

HHH is a rare and heterogeneous disorder that can clinically resemble congenital hyperinsulinism (CHI) or other metabolic diseases and may be misdiagnosed, as in this case.. Pathogenic variants in the **phosphoinositide-3-kinase (PI3K)-AKT-mTOR signaling cascade,** have been implicated in HHH, and should be considered in cases of CHI with low measurable insulin levels. Continuous feeding systems, which have demonstrated efficacy in recent reports of HHH ultimately achieved euglycemia in the presented case, although the mTOR inhibitor, sirolimus, has also been effective in some cases.

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Growth Axis and Syndromes

EP719

JOINT922

The effects of long-acting pegylated recombinant human growth hormone (jintrolong) on body composition and bone mass in transitional growth hormone deficiency

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Objective

The aim of the present study was to evaluate bone mineral density (BMD) and body composition (BC) of patients with transitional growth hormone deficiency (TGHD) treated with once-weekly PEGylated recombinant human growth hormone (Jintrolong) (PEG-rhGH).

Methods

This study was a prospective, multicenter, single arm study with a total of 66 weeks, encompassing a 2-week screening phase, a 12-week dose-adjustment period, and a 52-week treatment phase. The initial dose was 1 mg/w, with subsequent adjustments based on individual IGF-1 levels. BMD and BC were evaluated using dual energy X-ray absorptiometry (DEXA) at baseline, 38 weeks, and 64 weeks.

Results

A total of 31 subjects were included, including 23 males (74.2%) and 8 females (25.8%) with a mean age of 20.46 years. Mean doses in dose stabilization were 3.40 mg/week. The compliance rates nearing 100%. Following a 64-week therapeutic intervention, there was a significant improvement in the IGF-1 Standard Deviation Score (SDS), which increased from a baseline value of -3.07 to -1.38 (P $<$0.001). Significant improvement in BC was observed, manifesting as percentage of body fat (Fat %) decrease by 2.7% (P $<$0.001) and LBM increase by 4.54 kilograms (P $<$0.001), corresponding to a 12% change rate over 64 weeks. Although the lumbar BMD Z-score did not demonstrate statistical significance, there was a numerical increment observed, with an increase of 0.43, elevating the score from -1.54 at baseline to -1.12 post-treatment. In the evaluation of lipid metabolic profiles, a notable decrease was observed exclusively in triglyceride concentrations, which significantly declined from a mean of 1.50 mmol/l to 1.14 mmol/l (P = 0.018). Meanwhile, there was no statistically significant difference in the changes in low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c) and total cholesterol (TC), but there was a tendency for HDL-c to increase.

Conclusion

Our findings indicate that PEG-rhGH therapy is effective in enhancing lean body mass and reducing body fat percentage. These results suggest that PEG-rhGH, with high adherence, may be beneficial in improving BC and BMD in patients with TGHD.

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EP720

JOINT2145

Overgrowth: one patient, two syndromes

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Background
Sotos syndrome (SS) and Tatton-Brown-Rahman syndrome (TBRS) are two overgrowth syndromes characterized by distinct somatic features and intellectual disability. SS is caused by a heterozygous pathogenic variant in the NSD1 gene, while TBRS is caused by a heterozygous pathogenic variant in the DNMT3A gene.
Case
A 5-year-old patient presented to our hospital with vomiting and unsteadiness of gait. Imaging revealed a neoplasm occupying the third and fourth ventricles of the brain. Histological analysis confirmed the diagnosis of medulloblastoma. On clinical examination, the patient exhibited a height greater than 5 standard deviations (SD) above the mean and a weight greater than 2.5 SD according to the WHO 2006 growth charts. Somatic features were consistent with those seen in SS. Suspecting an overgrowth syndrome, genetic analysis was conducted using exome sequencing (Next Generation Sequencing). This revealed a pathogenic heterozygous variant in the NSD1 gene (c.6455G>A, p.(Arg2152Gln)) and a pathogenic heterozygous variant in the DNMT3A gene (c.2644C>T, p.(Arg882Cys)). Genetic testing of the parents revealed no similar variants, leading to a diagnosis of de novo SS and TBRS.
Conclusion
We present the first case of a patient diagnosed with both SS and TBRS, both arising de novo, in association with medulloblastoma. SS occurs in approximately 1 in 14,000 live births, while TBRS has an incidence of <1 in 1,000,000. Both SS and TBRS are typically transmitted in an autosomal dominant manner, with de novo mutations being the most common cause. Interestingly, the patient's parents are first cousins (with first cousin paternal grandparents), which is known to increase the risk of inherited diseases. However, this patient developed two separate de novo mutations. Both SS and TBRS are associated with an increased risk of neoplasia, particularly within the hematopoietic system. To our knowledge, this is the first case of medulloblastoma reported in a patient with SS, although a previous case of TBRS with medulloblastoma has been described. This case emphasizes the importance of thorough genetic investigation when encountering a patient with an overgrowth syndrome, as clinical features alone may not provide an unambiguous diagnosis. Additionally, while rare, solid tumors should not be overlooked in these patients, and a careful assessment for tumor-related signs and symptoms is crucial.

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EP721

JOINT1264

Clinical and genetic characteristics of cornelia de lange syndrome: a retrospective study of 20 pediatric patients in China

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Background
Cornelia de Lange Syndrome (CdLS) is a rare genetic disorder characterized by a range of developmental and physical anomalies. This study aims to evaluate the clinical characteristics and genetic variations in 20 pediatric patients diagnosed with CdLS.
Methods
We compared clinical characteristics of 20 patients grouped by genotypes based on whole exon sequencing and performed subgroup analyses according to the presence or absence of null variants.
Results
Comprehensive clinical evaluations revealed that 70% of the patients experienced prenatal growth retardation and short stature, while 85% exhibited global developmental delays. Craniofacial dysmorphisms, such as synophrys, short noses, and anteverted nares, were highly prevalent, observed in up to 90% of the cohort. Additional manifestations included skeletal abnormalities (80% exhibited small hands and/or feet), skin manifestations (30% with hirsutism or mottled skin) , and sensory impairments (20% with hearing loss). Genetic analysis identified variants in the NIPBL (75%), SMC1A (15%), and RAD21 (10%) genes. Null mutations, which result in complete loss of protein function, were significantly associated with the classical CdLS phenotype and corresponded with more severe clinical manifestations, including heightened intellectual disability. Three patients received growth hormone treatment, displaying diverse responses.
Conclusions
Our findings underscore the heterogeneity of clinical presentations in CdLS and emphasize the critical role of the mutation type in determining disease severity. These results warrant further investigations to optimize management strategies and improve understanding of the functional significance of the identified variants.

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EP722

JOINT521

Development of AI-based growth prediction models for children with growth disorders: a 3-year analysis using the lg growth study

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Background
Growth hormone (GH) treatment is effective in improving growth outcomes in children with various growth disorders, including growth hormone deficiency (GHD), idiopathic short stature (ISS), small for gestational age (SGA), and Turner syndrome (TS). However, individual responses to GH therapy vary, necessitating predictive models to guide personalized treatment strategies. Previous models have primarily focused on short-term outcomes using regression methods. This study aimed to develop machine learning-based models to predict growth outcomes up to 3 years after treatment initiation and improve accuracy through ensemble learning, using data from the LG Growth Study (LGS). Turner syndrome patients were limited to females.
Methods
Prepubertal children with GHD, ISS, SGA, and female children with TS were included in this study. Clinical and demographic features were collected at the screening visit, including baseline height and weight, age, sex, mid-parental height, bone age, diagnosis, and initial GH dose. Machine learning models (TabNet, XGBoost, LightGBM, CatBoost) were used to predict growth outcomes at 1-, 2-, and 3-years post-treatment. A Weighted Ensemble model was constructed using root mean squared error (RMSE)-based weights. Model performance was evaluated using mean absolute error (MAE), mean squared error (MSE), RMSE, mean absolute percentage error (MAPE), and the coefficient of determination (R^2).
Results
The Weighted Ensemble model achieved superior accuracy for 1-year predictions with an RMSE of 1.95 and R^2 of 0.983. TabNet demonstrated better performance for mid-term predictions, achieving RMSEs of 2.975 (R^2 0.961) at 2 years and 3.674 (R^2 0.937) at 3 years. The Weighted Ensemble maintained overall stability and consistent performance. However, predictions beyond 3 years showed a decline in accuracy across all models.
Conclusion
This study demonstrates that AI-based models can provide accurate growth predictions for children with various growth disorders over the first 3 years of GH treatment. TabNet showed the highest performance in mid-term predictions, while the Weighted Ensemble offered overall stability. Future research should aim to improve long-term prediction accuracy by integrating additional clinical data and advanced time-series methods.

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EP723

JOINT2187

The molar ratio of IGF-1/IGFBP-3 serves as a biomarker for evaluating the therapeutic efficacy of recombinant human growth hormone

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Background
Insulin-like growth factor-1 (IGF-1) is widely recognized as a key parameter for monitoring the therapeutic effects of rhGH and guiding treatment adjustments. However, the majority of growth responses are influenced by the concentration differences between IGF-1 and IGFBP-3. For biologically active substances, the molar ratio of IGF-1/IGFBP-3 more accurately reflects changes in biological activity. Therefore, this study aims to investigate the value of the IGF-1/IGFBP-3 molar ratio in assessing the therapeutic efficacy of rhGH.
Methods
This study included 67 children with short stature who received recombinant human growth hormone (rhGH) treatment. Participants were categorized into three groups based on etiology: growth hormone deficiency (GHD) ($n = 18$), idiopathic short stature (ISS) ($n = 37$), and small for gestational age (SGA) ($n = 12$). The primary outcome measures included the changes in IGF-I SDS and the IGF-I/IGFBP-3 molar ratio SDS at baseline and at 3, 6, 9, and 12 months post-treatment, as well as their correlation with the rhGH treatment dose and changes in height SDS. The treatment effect was also evaluated (a ΔHt-SDS $\geq$ 0.5 SDS increase in height standard deviation within 1 year of treatment was considered a good treatment effect).
Results
After one year of rhGH treatment, all groups showed significant increases in IGF-1 SDS, IGF-1/IGFBP-3 molar ratio SDS, and height SDS compared to baseline ($P < 0.05$). During the treatment period, rhGH dose was positively correlated with both IGF-1 SDS ($r = 0.773$, $P < 0.001$) and IGF-1/IGFBP-3 molar ratio SDS ($r = 0.843$, $P < 0.001$). The trends in IGF-1 SDS and IGF-1/IGFBP-3 molar ratio SDS paralleled those in height SDS. Among the 46 patients with a good treatment response, the IGF-1/IGFBP-3 molar ratio SDS was significantly higher compared to those with a poor response ($P < 0.01$).
Conclusion
The molar ratio of IGF-1/IGFBP-3 is an important biomarker for evaluating the therapeutic effect of growth hormone and provides a theoretical basis for formulating individualized clinical treatment strategies.
Key words
Growth hormone deficiency; Small for gestational age; Idiopathic short stature; Recombinant human growth hormone; Molar ratio of IGF-1/IGFBP-3

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EP724

JOINT3548

Celiac disease and short stature: sometimes it is not just gluten

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Introduction
Celiac disease (CD) is an autoimmune disorder in which gluten ingestion triggers an immune response, leading to small intestinal damage and impaired nutrient absorption. This can result in various symptoms such as diarrhea, weight loss, fatigue, and bloating, though some patients may be asymptomatic. CD is also associated with extra-intestinal complications, including endocrine manifestations. In some cases, short stature may be the only clinical sign of CD. The primary treatment is a strict, lifelong gluten-free diet (GFD). We present a case of a female patient with CD and idiopathic Growth Hormone (GH) Deficiency (GHD), underlying the need for continuous monitoring of growth response post-GFD.
Methods
A 10-year, 6-month-old prepubertal girl (Tanner stage I) was evaluated for short stature. Her growth rate was 2.5 cm/year, and her height and weight were below the 3rd percentile. Her medical history was unremarkable, except for chronic constipation since infancy, managed with macrogol. Laboratory tests revealed IGF-1: 71 ng/ml, tTG-IgA: 116.4 U/ml, and IgA: 144 mg/dL. A gastroenterological evaluation, including biopsy, confirmed mild chronic enteritis consistent with a malabsorption syndrome. She was started on a GFD and monitored every six months.
Results
After two years on a GFD, her tTG-IgA levels normalized, but her growth rate did not improve as expected. Further endocrinological assessment confirmed GHD. The patient started GH therapy, and over the next four years, she gained 25.5 cm in height.
Conclusion
GH secretion should be evaluated in children with CD who fail to achieve expected growth recovery despite adherence to a GFD and normalized tTG-IgA levels. The exact pathophysiological link between CD and idiopathic GHD remains unclear, but their coexistence suggests a potential association. This case highlights the importance of a multidisciplinary approach in the early diagnosis and management of growth disorders in children with CD. Pediatric endocrinologists and general pediatricians should be monitoring growth response post-GFD initiation to ensure timely intervention if GHD is present.
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EP725

JOINT3778

Rare case of DPH1 syndrome: report of a patient with two novel variants

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Introduction
Diphthamide-deficiency (DPH1) syndrome is a rare autosomal recessive neurodevelopmental disorder characterised by variable degrees of developmental delay, dysmorphic features, sparse hair, hand/foot and genital anomalies, short stature and central nervous system malformations. To date, less than 20 cases have been reported in the litterature. Here, we present a case of patient with two novel DPH1 gene variants.
Case presentation
A one year old boy was referred to the pediatric endocrinology clinic for non autoimmune hypothyroidism (TSH 13.8 μIU/ml). The patient was a full term infant presenting with mild psychomotor delay, sparse hair, strabismus, syndactyly, valgus deformity of the feet and a history of unilateral cryptorchidism and bilateral inguinal hernia. His growth development was normal. Thyroid ultrasound was unremarkable and treatment with levothyroxine was initiated. Neurologic evaluation after normalisation of thyroid function confirmed a mild psychomotor delay (mostly hypotonia). During followup, patient's growth velocity progressively declined with his height falling below parental target. Bone age was delayed by one year. Laboratory testing confirmed growth hormone (GH) deficiency and GH treatment was started. Brain MRI revealed a mild ventricular dilatation, a thin corpus callosum and a small sized pituitary gland. As part of the investigation of the patient's multiple pathologies, whole exome sequencing (WES) study was performed, detecting a maternally inherited heterozygous c.907-1delG intronic variant expected to lead to a loss of protein function (in silico analysis) and a paternally inherited c.284C>T (p. Thr95Met) variant) variant of unknown significance in the *DPH1* gene.
Conclusion
Loss of function *DPH1* gene variants affect diphtamide biosynthesis, a post-translationaly modified histidine residue crucial for cell division and embryonic development, leading to cell death and growth defects. We report two novel *DPH1* variants, in a patient with clinical features consistent with those previously described in DPH1 syndrome. Although further studies are required to confirm the functional impact of these variants, this case highlights the expanding genotypic spectrum of DPH1 syndrome and emphasizes the importance of considering this diagnosis in patients with compatible clinical presentation.
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EP726

JOINT1506

Osteogenesis imperfecta/ehler danlos overlap syndrome

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Ehlers–Danlos syndrome (EDS), osteogenesis imperfecta (OI), and cutis laxa (CL) are three rare and heterogeneous connective tissue disorders. Patients with these syndromes have similar manifestations and unpredictable prognosis, making a misdiagnosis highly probable. Osteogenesis imperfecta/Ehlers–Danlos (OI/EDS) overlap syndrome is a recently described disorder of connective tissue, characterized by mutation of *COL1A1* (17q21.33) or *COL1A2* (7q21.3) genes. 3-year-old boy 2nd born of a non-consanguineous parentage with no significant

antenatal and neonatal complaints presented with a delay in attaining age-appropriate milestones. The child had history of recurrent fractures following trivial injuries. The first fracture occurred at the age of one year, affecting the first metacarpal bone of the right hand. The second fracture took place at one and a half years, involving the radius on the right. The third was located at the proximal phalanx of the left toe. The mother had also noted easy bruising. Failure to thrive was noted during follow up visits. Evaluation revealed short stature (85cm, -3 SDS), poor weight gain (10 kg, -3SDS). His head appeared large, he had frontal bossing, blue sclera, generalized joint laxity, hypotonia, contractures in the fingers of the left hand, and loose skin folds. His Beighton score was 7/9. Investigations done revealed normal serum calcium (2.57 mmol/l), vitamin D (147 nmol/l), alkaline phosphatase (233 IU/L) and parathormone levels (1.8 pmol/L). Other endocrinological causes of short stature were ruled out. Additionally, the DXA scan report confirmed the presence of osteoporosis (Z score -3.8 SD). Echocardiography done was normal. History of similar complaints was noted in the father, he had walked late, history of recurrent fractures and hyper mobile joints. His Beighton score was 7 out of 9. A suspicion of collagenopathy, specifically Ehlers-Danlos syndrome, osteogenesis imperfecta spectrum was raised. Whole exome sequencing done showed a pathogenic, heterozygous mutation in the COL1A2 gene on intron 9, variant c.432 + 1G > A which was suggestive of combined osteogenesis imperfecta and Ehlers Danlos Syndrome type 2 which has an autosomal dominant inheritance. Genetic testing of the father not done due to financial constraints. The child has been started on bisphosphonate therapy with zoledronic acid and is on regular follow up. OI/EDS overlap syndrome is a rare collagenopathy requiring high clinical suspicion for diagnosis. This case underscores the role of genetic testing in confirming the disorder, especially with a positive family history. Early bisphosphonate therapy can reduce fracture risk, thereby enhancing the quality of life for affected individuals.

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EP727

JOINT3459

Growth hormone testing in prader willi syndrome: our experience with glucagon test

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Background
Prader-Willi Syndrome (PWS) is a rare genetic disorder characterized by neonatal hypotonia, hyperphagia, obesity and multiple endocrine abnormalities, including short stature and growth hormone deficiency (GHD). In Italy, the "Note AIFA 39" regulates the use and refund of Growth Hormone (rGH) therapy by the National Health System. In PWS children treatment with rGH can be started without stimulation tests to demonstrate GHD. However, after the achievement of final height, stimulation tests must be taken to confirm GHD before resuming treatment in PWS late adolescents and adults. Most studies use the growth-hormone-releasing hormone plus arginine (GHRH-arginine) test or, less frequently, the insulin tolerance test (ITT). Due to the shortage of GHRH-arginine, starting from October 2023, AIFA authorized the use of glucagon stimulation test (GST) to assess GH status in GHD adult patients. Few data are available on GST in PWS.
Aim
This study aims to investigate GHD with GST in PWS patients during the transition phase.
Methods
We retrospectively analyzed peak GH concentrations in ten late adolescent PWS patients followed at our Center (5 males and 5 females; median age 16,1 y; median BMI 25,7 kg/m^2) who underwent GST after discontinuing GH treatment for at least 4-6 weeks. These patients discontinued treatment at achievement of final height as defined by a growth velocity $<$ 1 cm/year and the epiphyseal closure demonstrated by bone age evaluation. GHD was defined as a peak GH concentration (GHp) $<$ 3 ng/ml.
Results
Three patients met the criteria for GHD status (peak GH concentration $<$ 3 ng/ml) and resumed growth hormone therapy. Instead, seven patients suspended the therapy as the peak GH concentration was higher than cut-off. A moderate negative correlation was found between GHp and BMI (r = -0.52, P = 0.123), suggesting that GH response decreased with increasing BMI, but no significant correlation with age was observed. Gender did not significantly influence GH response.
Conclusions
GST is a reliable, safe and inexpensive alternative to the GHRH-arginine test for diagnosing GHD in adult PWS patients. However, BMI-related criteria should be considered, especially in overweight and obese patients. Resuming GH therapy in GHD adult PWS patients during the transition phase showed positive effects in order to preserve body composition and quality of life. Further studies are needed to define the accuracy of GST for GHD screening in PWS during the transitional age.

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EP728

JOINT3849

Disease activity drop-off in elderly patients with active acromegaly over a median follow-up period of ten years: a longitudinal, restrospective study

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Introduction
GH-IGF-1 axis activity declines with aging. Acromegaly. Central GH regulation is retained at least in part in acromegaly, despite autonomous GH secretion. However, changes of GH-secreting tumor function in the elderly remain unclear.
AIM
To investigate GH-IGF-1 axis functional changes overtime in GH-secreting adenomas in terms of acromegaly disease activity in relation to advancing age.
Methods
A retrospective, longitudinal study involving 31 adult patients with active acromegaly was conducted at a single centre over an extended follow-up period from February 2008 to October 2024. At each visit, comprehensive patient data were collected including acromegaly-specific medical history, detailed medication history (start date, duration, dosage, and withdrawal information), biochemical parameters (from a single laboratory) and comorbidities. Acromegaly control was assessed using IGF-1 ULN (ULN1) alone or in relation to ongoing therapy as a product of each [for cabergoline (cab), octreotide (octr), lanreotide (lan), pegvisomant (peg)] drugs daily dose and the corresponding ULN value (ULN1*cab dose, ULN1*octr dose, ULN1*lan dose, ULN1*peg dose). This analysis was also repeated for IGFBP-3 (ULN2) and the relative product based on drug daily dose (ULN2*cab dose, ULN2*octr dose, ULN2*lan dose, ULN2*peg dose).
Results
Serum IGF-1 ($p < 0.001$), IGFBP-3 ($p < 0.001$), ULN1 ($p < 0.001$), and ULN2 ($p < 0.001$) trajectories overtime were inversely related to the time to disease relapse/onset. The inverse trajectory over time was particularly evident for ULN1*cab dose ($p < 0.001$), ULN1*octr dose ($p < 0.001$), and ULN1*peg dose ($p < 0.001$). The same trajectories showed a similar trend for ULN2*cab dose and ULN2*peg dose. The temporal trajectories of ULN1*lan dose (P = 0.278) and ULN2*lan dose did not change significantly over time (P = 0.409). The ULN2*octr dose trajectory overtime showed a trend in reduction but did not reach statistical significance (P = 0.064).
Conclusion
This study suggests that disease activity decreases in older acromegalic patients by the progressive evolution towards a less aggressive disease. Significantly, this research demonstrates as novel observation a decline in the ULN of IGF-1 (ULN1) and IGFBP-3 (ULN2) over time, even after adjusting for daily medication dosage. Improving knowledge on the natural history of acromegaly disease in terms of disease activity modifications during aging and long-term follow-up will enable optimizing therapeutic decisions and drug dosage titration finally minimizing the risk of overtreatment.

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EP729

JOINT2527

Clinical heterogeneity of sanjad sakati syndrome: experience from a single tertiary center in kuwait

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Background
Sanjad-Sakati Syndrome (SSS) is a rare autosomal recessive disorder predominantly reported in individuals of Arab descent. The hallmark endocrinological feature of SSS is primary hypoparathyroidism.
Aim
To define the clinical phenotypes and common complications of SSS in a Kuwaiti cohort.
Subjects and methods
This retrospective study included 17 patients from 14 families with SSS who were diagnosed, treated, or referred for follow-up at our center between 2005 and 2024. Their data were collected and analyzed.
Results
Seventeen patients (10 females, 59%) were recruited with median age of 10.7 years. Consanguinity was present in 9/14 families (64%). All patients were homozygous for *TBCE* founder mutation (c.155_166del; p. Ser52-Gly55del). One patient was additionally homozygous for the c.157+8A>T splice-site variant in intron 2 of ABCD4 gene, associated with methylmalonic aciduria and homocystinuria- an association not previously reported with SSS. The mean age of presentation was 34 days, primarily due to symptomatic hypocalcaemia. The main referral reasons were neonatal seizures (10/17), apnea (2/17) and poor activity (3/17). Dysmorphic features were present in all patients, including deep seated eyes, low set ears and peaked nose. Hypomagnesemia was observed in 24%, and 59% developed bilateral medullary nephrocalcinosis (median age: 3.5 years), with one of them progressing to end stage renal disease. All patients have hypoparathyroidism, while 18% have autoimmune hypothyroidism, 18% have adrenal insufficiency, and 41% experienced delayed puberty. Additionally, one patient has autoimmune hyperthyroidism, and one has growth hormone deficiency. Gastrointestinal manifestations included gastroesophageal reflux disease (41%), chronic constipation (18%) and recurrent intestinal obstruction (18%). Immune dysfunction was observed in 18%, characterized by reduced CD4 counts and low antibody response to vaccines. Ophthalmologic abnormalities were noted in 35%, including refractive errors and corneal opacity in one patient. Bilateral basal ganglia calcifications were present in 29%, with epilepsy diagnosed in two patients. MRI brain findings in three patients revealed corpus callosum and white matter volume loss with small pituitary gland. Nocturnal ventilatory support with bi-level positive airway pressure was required in 35% of patients. The mortality rate was 18% with septic shock as the leading cause of death.
Conclusion
SSS is a rare multisystem genetic disorder with significant morbidity and mortality. The novel association with ABCD4-related methylmalonic aciduria and homocystinuria expands the genetic and phenotypic spectrum of the disease. Given the high burden of complications, early diagnosis, multidisciplinary management, and vigilant long-term follow up are essential for optimizing patient outcomes.

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EP730

JOINT2716

Short stature in CHARGE syndrome

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CHARGE syndrome is a rare monogenic syndrome of congenital defects with a diverse clinical picture, occurring with a frequency of 1: 100 thousand births. CHARGE syndrome is caused by a disturbance in the function of the CHD7 gene, which encodes a protein that is a transcription regulator that binds to elements in the nucleoplasm and enhances the biogenesis of ribosomal RNA (another transcription element). The name CHARGE is an acronym of the first letters of the following developmental defects: C (coloboma) eye cleft (80-90%), H (heart defect) heart defect (60-85%), A (atresia choanae) choanal atresia (55-85%), R (retarded growth) growth and cognitive development disorder (70-85%), G (genital hypoplasia) genital abnormalities (53-100%) E (ear anomaly) dysmorphia of the auricles and hearing loss typical of the syndrome. In approximately 90% of patients, agenesis of the semilunar canals also occurs. Clinical diagnosis of CHARGE syndrome requires the detection of four defects from the group of major criteria or three major and three minor criteria, as well as confirmation of a pathogenic variant in the CHD7 gene. Short stature is one of the minor criteria. There may be many causes of growth deficiency: difficulties in feeding, co-occurrence of systemic defects or growth hormone deficiency. The aim of the study is to assess the effectiveness of growth hormone treatment in children with CHARGE and short stature. An analysis of 29 patients with CHARGE syndrome confirmed by a mutation in the CHD7 gene was carried out. The youngest of the analyzed patients is 6 months old, the oldest is 24 years old. The average birth weight is 2997.4 g, length 52.1 cm. All analyzed patients were burdened with developmental defects, as many as 83% of patients have a heart defect. Growth < 3pc was found in 76% of patients, but only two patients are currently treated with growth hormone due to somatotropin-dependent pituitary insufficiency. During the treatment they did not achieve 3pc height, but an improvement in growth was achieved, expressed as a decrease in the standard deviation of growth.
Conclusions
1. The vast majority of children with CHARGE syndrome are short, but only a few patients are qualified for the diagnosis of somatotropin hypopituitarism and qualified for treatment with recombinant growth hormone.
2. Only two patients with CHARGE syndrome (6.9%) analyzed in the study are treated with rhGH. As a result of using rhGH, an improvement in growth velocity was achieved.

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EP731

JOINT1224

15q26.3 Deletion effect on growth: a case report

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Introduction
Insulin-like growth factor 1 (IGF-1) is essential for prenatal and postnatal growth, acting through the IGF1 receptor (IGF1R), a tyrosine kinase encoded by the IGF1R gene, located on the distal arm of chromosome 15 (15q26.3). Deletions of 15q26 are rare chromosomal abnormalities, typically associated with a variable degree of intrauterine growth restriction (IUGR), postnatal growth failure, developmental delay, microcephaly, intellectual disability, among other congenital anomalies.
Case Report
A five-year-old girl was referred to endocrinology clinic for short stature. Family history revealed a short stature mother (147.5 cm, -2.42 SDS) and an otherwise normal-height family, without consanguinity. Pregnancy was uneventful until 34 weeks of gestation, when IUGR and microcephaly were detected. A C-section was performed at 35 weeks and 5 days. Birth somatometry: height 42.7 cm [-1.5 standard deviation score (SDS)], weight 1930 g (−1.40 SDS) and head circumference 29.5 cm (-1.6 SDS). Due to prenatal ultrasound findings, genome-wide array analysis was performed in cord blood. A 214 kb terminal deletion at a single copy of 15q26.3 was reported, resulting in a partial deletion of IGF1R. She was followed-up at general paediatrics, with a height around -2 SDS until 12 months. She was lost to follow-up during COVID-19 pandemic. From three-years-old on, the height has been around -3 SDS. At the first visit: height 96.3 cm (-2.78 SDS), weight 12.4Kg (-2.83 SDS) and BMI 13.4kg/m2 (-1.42 SDS). Neither dysmorphic features nor development delay were noted. Growth velocity was 4.3 cm/year. Laboratory investigation showed adequate IGF1 [204.0 ng/ml, reference range (RR): 63.6-250.0] and IGF binding protein 3 (4.14 µg/ml, RR: 2.203-5.202) levels; a female karyotype (46, XX); bone age of 3 years old. The 15q26.3 deletion was also identified in the mother. The patient remains under regular follow-up with the endocrinology team and growth hormone (GH) therapy is being considered.
Discussion
This patient's findings suggest a partial IGF-1 resistance, resulting in short stature. The deletion at 15q26.3 might explain these findings. Heterozygous mutations typically reduce IGF1R expression or impair signalling, rather than complete receptor loss. The variable phenotype, which is not yet fully understood, presents a management challenge as in our case. The positive effects of GH treatment may result from its direct stimulatory action or elevated IGF-1 levels, which are expected to activate partially insensitive receptors.

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EP732

JOINT2357

Is L-dopa test effective in detecting adrenal insufficiency with preliminary diagnosis of growth hormone deficiency in children with short stature?

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Background

Growth hormone(GH) deficiency in children is characterized by impaired linear growth and reduced growth velocity, necessitating confirmation through two GH stimulation tests. At the time of diagnosis, approximately 4% of children with GH deficiency exhibit concomitant adrenocorticotropic hormone(ACTH) deficiency, a prevalence that increases to 12% over the course of follow-up. The insulin tolerance test(ITT) is regarded as the gold standard for assessing both cortisol and GH secretion; however, its clinical application is constrained by potential risks and the requirement for close medical supervision.

Objective

This study aims to evaluate the effect of the L-dopa stimulation test on cortisol secretion in pediatric patients with short stature.

Materials-Methods

This retrospective study included 160 pediatric patients(74 females, 86 males) who underwent the L-dopa stimulation test for the assessment of GH deficiency at the Pediatric Endocrinology Clinic between January 2010 and December 2023. Serum cortisol concentrations were measured at the 90th and 120th minutes of the test. Patients with a peak cortisol response <18 µg/dL subsequently underwent a low-dose(1 µg) ACTH stimulation test to further evaluate adrenal function. Clinical, anthropometric, and biochemical data were extracted from medical records and subjected to statistical analysis.

Results

The mean age of the individuals was 9.5 ± 3.6 years, with 74(46.3%) female and 86(53.7%) male patients. The mean height standard deviation score (SDS) was -2.70 $\pm$ 0.89, the mean weight SDS was -1.84 $\pm$ 1.11. The mean peak GH response was 7.04 $\pm$ 5.28 ng/ml following the clonidine stimulation test and 5.55 $\pm$ 4.21 ng/ml following the L-dopa test. A total of 61 patients exhibited a peak cortisol response <18 µg/dL during the L-dopa test. Among these, 26 underwent a low-dose ACTH stimulation test, and 9 patients (34.6% of those tested; 5.6% of the total cohort) were diagnosed with adrenal insufficiency, defined as a peak cortisol response <18 µg/dL. These patients were initiated on oral hydrocortisone therapy. Comparative analyses between patients with normal vs impaired ACTH test responses (<18 µg/dL vs. ≥ 18 µg/dL) revealed no statistically significant differences in peak cortisol response to the L-dopa test, peak GH response to clonidine or L-dopa, age at presentation, gender, weight SDS, or height SDS.

Conclusion

The L-dopa stimulation test may represent a valuable adjunctive tool for the evaluation of cortisol sufficiency in pediatric patients undergoing assessment for suspected GH deficiency. However, further prospective studies with larger sample sizes and standardized protocols are warranted to validate its diagnostic accuracy and clinical utility in detecting adrenal insufficiency.

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EP733

JOINT2690

Treatment responce of the growth hormone in 3M syndrome: a single center experience

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Introduction

3MSyndrome is autosomal recessive inherited dwarfism, characterized by pre and postnatal growth retardation. 3Msyndrome develops as a result of biallelic loss of function mutations in cullin7(CUL7), obscurin-like1(OBSL1), and coiled-coil domain- containing protein8 genes(CCDC8) are responsible for p53 dysfunction, growth hormone(GH) and/or IGF1 resistance. The aim of this study is to evaluate the the growth hormone(GH) axis and response to GH treatment in 3M syndrome patients.

Methods

Medical records of eight patients followed up with short stature in our Pediatric Endocrinology department and diagnosed with 3M syndrome based on the results of genetic tests, between 2015 and 2024 were recorded. Serum basal levels of IGF1 were determined using immunoradiometric assays. All patients underwent a growth hormone stimulation test(GHST) were performed with levodopa and clonidine. Insulin-like growth factor(IGF) generation test was performed on those with sufficient GHST results.

Results

A total of 8 patients(four males and four males)from 7 families with 4,94(3,5–11,7) years median age at the time the GH treatment started were included in this study and were followed for one to eight years. Out of 7 families, six were consanguineous, one unrelated. All of the patients were born at term. The mean SDSs of birth weight and length of the patients were $-3,15 \pm 1$, $-4,0 \pm 0.60$, respectively. The median height SDS at admission was $-4,30((-7,27)$-$(-2,75))$SDS, and the median midparenteral height SDS was –0,76SDS($(-1,68)$- (-0,27)). The partial deficiency was detected in three cases, severe deficiency in one case. IGF generation test was performed in three cases and all were responsive. Despite described growth hormone (GH) insensitivity in 3M syndrome, all our patients either with GH deficiency or with normal GH levels were treated with GH. The percentile improved in all patients. The median annual growth velocity in the first year of treatment (6,1 cm/year) and in last follow up (5,85 cm/year) was higher compared to pre- treatment levels(5,3 cm/year) (p:0,017). The final height SDS of two cases were – 4,3 SDS and – 4,11SDS because of closure of the growth plates.

Discussion

Although the annual height growth rates of patients under treatment are insufficient, their final heights have been found to be higher compared to those of patients who were followed without treatment in the literatüre. Even the absence of worsening in height SDS in patients receiving growth hormone may be considered as a good response to treatment. It is difficult to reach a conclusion about the efficiency of GH treatment in 3M syndrome patients.

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EP734

JOINT3674

"A shared GHSR gene variant in children with short stature and growth hormone deficiency: potential clinical relevance"

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Background

Growth hormone secretagogue receptor (GHSR) mutations are implicated in growth disorders due to disrupted growth hormone (GH) regulation. We describe three pediatric cases with short stature, all carrying the same genetic variant in GHSR (c.422G>T; p.Arg141Leu). This variant, classified as a variant of uncertain significance (VUS), is suspected to have clinical relevance, particularly in cases from a geographically clustered region with consanguineous backgrounds and consistent phenotypic features of partial growth hormone deficiency (GHD).

Cases and Clinical Details

We evaluated three unrelated consanguineous cases from nearly the same geographic area within the United Arab Emirates:

- **Case 1:** 4-year-old female, birth weight 3.2 kg, height SDS -2.5, weight SDS -2.97. Bone age lagged at -1.24 SDS. Arginine-stimulated peak GH level was 6.71 ng/ml. Serum IGF-1 was 57 ng/ml, and IGFBP-3 was 1,767 ng/ml. NGS stature panel revealed a heterozygous GHSR c.422G>T variant. MRI of the sella showed a small anterior pituitary gland.
- **Case 2:** 7-year-old male, birth weight 3.2 kg, height SDS -2.42, weight SDS -2.4. Bone age lagged at -1.52 SDS. Peak GH with arginine stimulation was 6.78 ng/ml. IGF-1 was 31.8 ng/ml, and IGFBP-3 was 1,847 ng/ml. The stature panel identified a homozygous GHSR c.422G>T variant. MRI revealed a small anterior pituitary.
- **Case 3:** 9-year-old male, birth weight 3.2 kg, height SDS -2.87, weight SDS -3.13. Bone age lagged at -1.87 SDS. Peak GH level was 2.95 ng/ml. IGF-1 was 42.1 ng/ml, and IGFBP-3 was 2,486 ng/ml. A homozygous GHSR c.422G>T variant was identified. MRI of the sella also showed anterior pituitary hypoplasia.

Results

All three patients exhibited features of isolated partial GHD, with suboptimal peak GH responses on stimulation testing despite low-normal IGF-1 and IGFBP-3 levels. The shared GHSR mutation (p.Arg141Leu), identified as autosomal dominant or recessive, may contribute to impaired GH axis regulation. The small

anterior pituitary volumes in all cases suggest a structural component related to the variant's pathogenicity.
Conclusion
The recurrent GHSR c.422G>T (p.Arg141Leu) variant in patients from nearly the same geographic area with consistent phenotypic presentations highlights a potential disease-causing role. While classified as a VUS, our findings support further investigation of its contribution to partial GHD. Longitudinal follow-up and functional studies may help clarify its pathogenicity and guide therapeutic decision-making.

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EP735

JOINT682

Development of a minimum dataset (MDS) for the monitoring of growth hormone therapy in children with prader willi syndrome (PWS) - a globe-reg initiative

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Introduction
Recombinant Human Growth Hormone (GH) was approved in the US (2000) and Europe (2001) for children with Prader-Willi Syndrome (PWS) to improve growth and body composition, with reported benefits in cognition, motor skills and behaviour. However, longer term safety and efficacy data of GH in PWS are still lacking and may be difficult to interpret due to lack of consistency in data collection among studies. This study aimed to identify the minimum dataset (MDS) that could be measured in a routine clinical setting across the world, to minimise burden on clinician data entry and improve quality of data collection to facilitate future studies on long term outcomes.
Methods
The study was undertaken by the PWS Expert Working Group in GloBE-Reg, an international registry platform which supports studies on long-term safety and effectiveness of drugs. Twelve clinical experts on PWS from 10 countries and two patient representatives collaborated to develop this recommendation, based on previously published methodology (Chen *et al*. Horm Res Pediatr 2023). Data fields that achieved 70% consensus in terms of importance qualified for the MDS, provided <50% deemed the item difficult to collect. Several anomalies to the MDS rule were discussed to formulate the final MDS recommendation.
Results
In total, 294 items were compiled from routine clinical practice with 33 redundant items removed and 261 items subjected to the grading system. 151/261 items achieved consensus as important data to collect when monitoring children with PWS on GH treatment, while 218/261 items were deemed easy to collect. Combining both the criteria for importance and ease of collection, 126 items fulfilled the MDS requirement. Four items were designated as core data, two were computed fields, five reassigned as non-MDS, 13 removed as unrelated to safety and effectiveness and 65 were merged into 18 fields. Several anomalies which did not fulfill MDS criteria were also extensively discussed to determine its validity within the MDS, in particular family history of Type 2 diabetes, change of GH therapy (if applicable) and adherence, to produce the final MDS recommendations of 58 items; of which 24 are only to be completed once.
Conclusions
This exercise has identified by consensus the minimum dataset considered necessary, which can be collected through real-world data, to provide consistency and comparability in global studies for monitoring the safety and effectiveness of GH in children with PWS, applicable to the current daily preparations and potential newer long-acting GH.

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EP736

JOINT3305

Three decades of growth hormone therapy in prader-willi syndrome: insights from belgium

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Background & Aim
Prader-Willi Syndrome (PWS) is a rare neurodevelopmental disorder characterized by neonatal hypotonia, feeding difficulties, short stature, behavioural problems, and early-onset hyperphagia leading to progressive obesity. Early diagnosis and a multidisciplinary approach are crucial for managing all these features. This study provides a detailed characterization of the Belgian PWS cohort and evaluates the effectiveness of recombinant human growth hormone (rhGH) therapy.
Patients & Methods
Clinical and auxological data were retrieved from BELGROW, a national database of rhGH-treated patients maintained by BELSPEED (Belux Society for Pediatric Endocrinology and Diabetology), from 1986 until 2021. Baseline characteristics and rhGH treatment outcomes were assessed, including changes in height standard deviation (SD) scores (HSDS).
Results
A total of 123 patients with PWS (50% male) were analysed. Most patients (115/123) were included after 2001. The most common genotype was paternal deletion (53%), followed by maternal uniparental disomy (mUPD) (35%), imprinting disorder (5%), and atypical deletion or translocation (3%). Preterm birth was reported in 21%, and 23% met the criteria for small for gestational age (SGA). Reduced fetal movements were noticed in 79% of pregnancies, and all patients exhibited neonatal hypotonia. Obesity (BMI > 2 SD) was observed in 53%. All patients received rhGH, with the youngest starting at 4.8 months. The median (Q1:Q3) age at therapy initiation was 3.57 years (1.11; 6.54), with a median dose of 0.031 mg/kg/day (0.026:0.035). After two years, HSDS increased by +1.3 SD. Mean weight increased by +0.9 SD, but body mass index (BMI) remained stable (Δ 0.1 SD). Scoliosis was reported in 17% at therapy onset. A subgroup of 52 patients was followed until therapy cessation at a mean age of 15.2 years (12.9–17.5). In this group, rhGH therapy began at a mean age of 7.35 years (4.44–10.69). HSDS improved from -2.2 (-3.1 to -1.1) at initiation to -1.23 (-1.19 to -1.15) at cessation. In addition to multidisciplinary care, patients who started treatment before age 6 ($n = 22$) showed a trend toward a more favorable BMI outcome, with an average SDS decrease of -0.38, compared to a negligible change (+0.02) in those who started later ($P = 0.19$). Patients with a deletion were less frequently obese than those with mUPD.
Conclusions
These findings highlight the effectiveness of rhGH therapy in real-world clinical settings for patients with PWS. Treatment significantly improves height and helps maintain BMI stability, reinforcing the importance of early intervention and long-term management in this population.

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EP737

JOINT2602

New evidence of growth hormone treatment benefit on bone mineralization during transition from paediatric to adult care in a growth hormone deficient french cohort

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Introduction
Growth hormone deficiency (GHD) is a rare condition. During childhood (CoGHD), when GHD is confirmed by the hormonal tests, a treatment by growth hormone (GH) is usually introduced. The transition period between paediatric and adult care represents a challenging time. Convincing GHD patients with optimized final stature and their families, to continue GH treatment on such conditions may be complicated. More data need to be collected to better understand the effects of GH treatment during this period, especially for bone health.
Objective
The objective of this study is to describe the bone mass density (BMD) and Zscore evolution during transition period in our CoGHD cohort patients, whether they have received GH treatment in adulthood or not.
Materiel and Methods
We conducted a retrospective study based on our CoGHD patients who had their transition care from 1st January of 1994 to 1st September of 2021. We included all CoGHD patients with a first evaluation (EVAL1) during transition care, and another evaluation (EVAL2) at least 6 months after EVAL1. We described two different populations from our cohort: CoGHD patients continuing GH treatment during more than 6 months between EVAL1 and EVAL 2 (GHT), and CoGHD patients receiving maximum 6 months of GH treatment between the two evaluations (GH0).
Results
162 patients from our 282 CoGHD cohort, were included. In this population, 57 have been treated with GH therapy for 6 months or less (GH0), and 105 continued GH treatment for more than 6 months (GHT). Median follow-up was 5.9 years (3.1-10.8) in GH0 group and 3.6 years (2-6.3) in GHT group. The lumbar spine Z score was -1.61 at EVAL1 and -1.32 at EVAL2 in GH0, and -1.09 at EVAL1 and -0.61 at EVAL2 in GHT ($P = 0.047$). Lumbar spine BMD was 0.90 g/cm^2 at EVAL 1 and 0.93 g/cm^2 at EVAL2 in GH0, and 0.96 g/cm^2 at EVAL1 and 1.01 g/cm^2 at EVAL2 in GHT ($P = 0.17$). The femoral neck Z score was -0.95 at EVAL1 and -0.80 at EVAL 2 in GH0, and -0.87 at EVAL1 and -0.50 at EVAL 2 in GHT ($P = 0.16$). Femoral Neck BMD was 0.81 g/cm^2 at EVAL1 and 0.79 g/cm^2 at EVAL2 in GH0, and 0.89 g/cm^2 at EVAL1 and 0.85 g/cm^2 at EVAL2 in GHT ($P = 0.76$).
Conclusion
Our study provides additional evidence supporting the benefit of GH replacement therapy in bone quality in CoGHD during transition care.

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EP738

JOINT2302

Insulin tolerance test for the diagnosis of adult GH deficiency: definition of BMI-dependent cut-offs using a clinical gold standard

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Background
The diagnosis of adult growth hormone deficiency (GHD) relies on demonstrating a reduced growth hormone (GH) response to stimulation tests. Excess body weight, a condition with increasing prevalence in the general population, is known to blunt GH secretion across all stimulation tests. Consequently, establishing BMI-specific normality cut-offs is essential to ensure accurate interpretation of somatotropic axis function. However, no validated BMI-adjusted cut-offs currently exist for the insulin tolerance test (ITT), the gold standard for GHD diagnosis. This study aimed to define BMI-dependent ITT cut-offs using a clinical criterion as the diagnostic gold standard, addressing key methodological limitations in previous research.
Subjects and Methods
We conducted a retrospective analysis of 105 patients with hypothalamic-pituitary disorders who underwent ITT at our center between January 1, 2021, and September 30, 2024. GHD was defined by the presence of at least three pituitary hormone deficiencies (MPHD), while preserved somatotropic function was established by the absence of other pituitary deficits and an IGF-I SDS ≥ 0. ITT was performed using a standardized protocol. ROC curve analysis was applied to determine optimal BMI-specific cut-off values, defined as those achieving the best sensitivity (SE) and specificity (SP).
Results
The optimal GH cut-off for diagnosing GHD was 2.8 µg/L in normal-weight and overweight subjects (normal-weight: SE 84.6%, SP 97.4%; overweight: SE 100%, SP 92.3%), while for obese individuals, the optimal threshold was lower at 2.1 µg/L (SE 88.2%, SP 87.5%). The area under the ROC curve values were 0.968, 0.957, and 0.897 for normal-weight, overweight, and obese patients, respectively, demonstrating high diagnostic accuracy across BMI categories.
Discussion
This study is the first to establish BMI-specific GH cut-offs for ITT using a clinical definition of GHD as the diagnostic gold standard. The findings reinforce the necessity of applying lower cut-offs in obese individuals to mitigate the risk of overdiagnosis and avoid unnecessary GH replacement therapy. Implementing BMI-adjusted thresholds in clinical practice could enhance diagnostic precision, ensuring that treatment is appropriately targeted to those who will benefit most.

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EP739

JOINT1903

GLP-1 receptor agonists as therapeutic approach to severe obesity in PHP/iPPSD: two case reports

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Overweight and obesity occur frequently in pseudohypoparathyroidism/iPPSD, especially in children with PHP1A/iPPSD2, who may develop severe early-onset obesity. Both impaired lipolytic response to adrenaline and decreased resting energy expenditure may contribute to weight gain, sometimes accompanied by hyperphagia. Obesity is also reported in PHP1B/iPPSD3 and acrodysostosis. There are no specific treatments for obesity in PHP/iPPSD, except for isolated cases treated with a cannabinoid receptor type 1 antagonist or gastric bypass. To now, no data are available on the use of GLP-1 receptor agonists for weight management in these patients. We aim to describe two patients with PHP/iPPSD, actively followed-up in two tertiary European centers, treated with GLP-1ra for severe obesity. The first patient was diagnosed with PHP1B/iPPSD3 at 15 years of age. He always suffered of overweight, and the mother referred hyperphagia during infancy. At 14 years his BMI was 35 kg/m^2 and dyslipidemia, liver steatosis, insulin resistance and impaired glucose tolerance were also present. At 17 years metformin therapy was introduced to improve his metabolic profile and reduce the gradual weight gain. However, weight continued to raise and at 21 years BMI was 47.6 kg/m^2, thus gastric bypass was proposed. At the same time, we started GLP-1ra therapy with subcutaneous liraglutide, that has been recently shifted to subcutaneous semaglutide. After 23 months at the last follow-up visit, he has lost 14 kg, which represents a 11% decrease in body weight, reaching a BMI of 42.6 kg/m^2. The second patient was diagnosed with PHP1A/iPPSD2 at 3 years of age. She developed early-onset obesity as soon as 4 months of age and had persistent obesity reaching a BMI of 32 kg/m^2 (2.88 SD) at the age of 13 years despite practicing sports regularly and having a healthy lifestyle. At 13 years, the liver US showed steatosis, however the blood metabolic profile was normal; she was then started on liraglutide. Her BMI dropped from 32 to 29.6 kg/m^2 in 8 months, which represents a 7.5% decrease in body weight. She described a significant improvement in satiety. Despite this good response, she stopped treatment on her own and regained weight in the following 6 months, up to a BMI of 30.5 kg/m^2 at the last visit. For both patients, GLP-1 analogs were well tolerated despite nausea and inappetence at the beginning. These two cases suggest that GLP-1ra may represent a promising therapeutic approach for the management of obesity and overweight in PHP/iPPSD patients.

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EP740

JOINT797

The effects of long-acting growth hormone therapy on serum GH and IGF-i levels and potential safety risks compared to physiological pulsatile growth hormone and daily gh injections

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Background
Long-acting growth hormone (LAGH) therapy has revolutionized treatment for growth hormone deficiency (GHD) by enhancing adherence and reducing the frequency of injections compared to daily GH therapy. However, sustained non-pulsatile GH and IGF-I levels, differing from physiological pulsatile secretion, may raise long-term safety and metabolic concerns. This review evaluates the efficacy, serum GH and IGF-I impacts, and safety risks of LAGH therapy relative to daily GH and physiological secretion patterns.
Objectives
1. To assess the clinical efficacy of LAGH in promoting growth and IGF-I regulation.
2. To explore its safety profile, particularly metabolic and proliferative risks, compared to daily GH therapy.
3. To provide quantifiable insights into the percent impact of LAGH therapy across key categories: height SDS improvement, IGF-I level changes, and safety.
Methods
A comprehensive literature review of studies published between 2006 and 2025 was conducted. Data on height SDS improvements, IGF-I level changes, and reported safety events were extracted and analyzed. Studies were categorized and impact percentages were calculated based on clinical outcomes and safety metrics.
Results
• Efficacy:
LAGH therapy demonstrated an average 12% improvement in height SDS, with efficacy comparable to daily GH therapy (Miller *et al*., 2020; Kang *et al*., 2024).
• IGF-I Monitoring:
Sustained IGF-I levels increased by 23% on average, highlighting significant metabolic activity, but requiring careful monitoring to mitigate risks of excessive exposure (Bidlingmaier & Schilbach, 2021; van Dijk *et al*., 2006).
• Safety Concerns:
Safety events, inversely scored for impact, were relatively low at 4 per 100 patients, with no severe adverse outcomes reported in recent trials (Savendahl *et al*., 2022; Bruzzi *et al*., 2023).
• Patient Adherence:
LAGH improved patient adherence and accessibility, reducing injection burden and enhancing treatment satisfaction (Steiner *et al*., 2023; Boguszewski *et al*., 2024).
• Long-Term Needs:
Personalized dosing and regular IGF-I monitoring are essential to mimic physiological GH secretion (Clemmons, 2007; Bruzzi *et al*., 2023).
Discussion
While LAGH therapy offers significant clinical benefits, sustained non-pulsatile GH and IGF-I levels deviate from natural physiology, posing potential risks such as glucose intolerance and proliferative disorders. Percent impact analysis reveals notable gains in height and IGF-I levels, with minimal safety concerns, affirming the therapy's efficacy. However, long-term safety monitoring remains essential.
Conclusion
LAGH therapy is a viable alternative to daily injections, delivering notable improvements in growth and IGF-I levels with minimal safety concerns. Optimized dosing and ongoing research are critical to aligning LAGH therapy with physiological GH dynamics.

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EP741

JOINT1648

Positive impact of healthcare professionals' interaction with a digital health platform on patient adherence to recombinant human growth hormone therapy

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Background
The Growzen® Connect digital ecosystem has been developed to support timely treatment optimisation for patients on recombinant human growth hormone (r-hGH) therapy. This ecosystem includes electronic injection devices with adherence data transmitters and a platform for healthcare professionals (HCPs) to monitor real-time patient adherence. This study aimed to investigate whether HCPs' interaction with this platform influences adherence to r-hGH therapy in patients from Spain.
Methods
Adherence data (optimal [≥85%] vs suboptimal [<85%]) at the patient level and three clinic-level metrics were extracted from the platform between July 2023 and June 2024. Patients from Spain aged <18 years were selected. The first metric for platform engagement was frequency of use, which is the number of clinic connections by number of patients, stratified by ≥1 (at least one connection/patient/-year), >0-<1 (less than one connection/patient/year), and 0 (no connection). The second metric for platform engagement was data entry, which is the number of growth data entries by the number of patients, stratified by ≥1 (at least one measurement/patient/year), >0-<1 (less than one measurement/patient/year), and 0 (no measurement). The metric for treatment engagement is defined as the number of dose changes by number of patients, stratified by ≥2 (at least two dose changes/patient/year), ≥1-<2 (less than two and greater or equal to one dose changes/patient/year), and <1 (less than one dose change/patient/year). Multi-level logistic regression analyses were performed with adherence as an outcome and metrics as input adjusted for standardised age at treatment initiation and standardised time on treatment.
Results
Adherence data were obtained from 3,980 patients in 186 clinics. In July 2023, the mean age at treatment initiation was 10.7 years and the mean time on treatment was 21 months as of July 2023, the start of the extraction period. The proportions of patients with optimal adherence were 76% (n = 883/1,161), 79% (n = 1,998/2,542; P = 0.13), and 88% (n = 245/277; P <0.001) in clinics with no (n = 92), >0-<1 (n = 65), and ≥1 (n = 29) connections/patient/year, respectively. The proportions were 78% (n = 2,551/3,270), 80% (n = 542/675; P = 0.86), and 94% (n = 33/35; P = 0.009) in clinics with no (n = 173), >0-<1 (n = 12), and ≥1 (n = 1) measurements/patient/year. Furthermore, the proportions were 71% (161/228), 78% (2,207/2,833; P = 0.62), and 82% (758/919; P = 0.25) in clinics with <1 (n = 27), ≥1-<2 (n = 111), and ≥2 (n = 48) dose changes/patient/year, respectively.
Conclusions
Our research revealed that HCPs' interaction with the digital adherence monitoring platform Growzen® Connect positively influences patient adherence to r-hGH therapy in Spain.

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EP742

JOINT1404

Results of treatment with recombinant human growth hormone (rhGH) in patients with noonan syndrome. albanian experience

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Introduction
Noonan syndrome (NS) is a relatively common disease with an incidence estimated to be from 1 in 1000 to 1 in 2500 live births. It is a genetically heterogeneous autosomal dominant malformation syndrome. Growth impairment is a common manifestation of NS. In a few studies, recombinant human GH (rhGH) treatment has been shown to increase growth and adult height (AH).
Objectives
To evaluate the effect of rhGH treatment in children with NS and to identify the best indicators of the outcome of this treatment.
Patients and Methods
This is a 24-year-long, monocentric cohort study. Children with NS were followed up from January 2000 to December 2024 in the Pediatric Endocrine Unit, Department of Pediatrics, University Hospital Centre "Mother Teresa", Albania. Patients with NS who were treated with growth hormone until near adult height (NAH) were included in the analysis of this study. We evaluated growth indicators (especially height) before treatment (at the time of starting treatment), during the treatment (evaluating these indicators for each year of treatment), and after the rhGH treatment for patients who completed treatment with rhGH. Growth indicator data were processed using Anthro-plus software, and statistical analysis was performed using SPSS.
Results
During the period mentioned above, 25 patients with NS have been treated with rhGH. There were 19 (73,08%) males and 7 (26,92%) females. The age at which rhGH treatment started was 10,08 ± 4,12 years. The Bone age was 7,38 ± 3,54 years. HAZ at the beginning of therapy was -3,65 ± 1.17 z-score. Sixteen out of 26 (61,54%) have completed the treatment after the meantime treatment duration of

5,18 ± 2.18 years with the mean dose of rhGH at 0.24 IU/week. Their height changed from -3,81 ± 0,83 z-score to -2,56 ± 1,55 z-core, gaining about 1,25 ± 1,43 z-score (p-value 0,003). Despite the late start of treatment, significant height gains were achieved, with a minority (37.5%) reaching the target height range. The NAH was found to correlate well with the adult predicted height, as well as the HAZ score at the start of treatment, the age at the beginning of treatment, the change in the HAZ score during puberty, the duration of GH treatment, and the bone age at the start of treatment.

Conclusions

Our study results provide valuable insights about the effectiveness of rhGH treatment in patients with NS, enlightening us on the factors influencing their height outcomes better.

Keywords

Noonan syndrome; recombinant human growth hormone; HAZ (Height for Age Z-score); near adult height

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EP743

JOINT224

Growh patterns and genotype-phenotype correlations in tricho-rhino-phalangeal syndrome type i: insights from a korean cohort

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Background/Objectives

Tricho-rhino-phalangeal syndrome, type I (TRPS I, OMIM#190350) is a rare autosomal dominant disorder characterized by distinctive craniofacial features, skeletal abnormality, and ectodermal dysplasia. Due to variable expressivity, TRPS I often remains undiagnosed, leading to unclear prevalence and a lack of large-scale cohort studies. This study aims to delineate the clinical features and genotypes of TRPS I patients in Korea.

Methods

We retrospectively reviewed the medical records of 20 genetically confirmed TRPS I patients (8 males, 12 females) from 20 families. Data collected included demographic information, clinical profiles (growth, craniofacial features, ectodermal dysplasia, skeletal abnormalities), radiologic findings, and treatment history. Genetic diagnoses were confirmed using Sanger sequencing, MLPA, qPCR, or gene panel sequencing.

Results

The median age at diagnosis is 9.0 years old (range: 20 months to 35.1 years). Short stature (35%) was the most common presenting symptom, followed by hypotrichosis (20%) and finger deformity (15%). Almost all patients (95%) had heights below the 50th percentile, with a median height of -1.25 SDS at diagnosis. Four patients (21%) had heights below -2.0 SDS. After 12 years of age, height SDS significantly decreased, accompanied by accelerated bone age, suggesting impaired pubertal growth spurt. Patients aged 12 years and older had significantly lower height SDS than those under 12 ($P = 0.016$). Clinical features included sparse hair (100%), sparse eyebrows (83%), and a pear-shaped nose (100%). Skeletal surveys showed cone-shaped epiphyses in all patients. Four patients (20%) had skeletal abnormalities, including hip dysplasia, with two undergoing hip surgery and one requiring femur osteotomy. Fourteen patients (70%) have been treated with Minoxidil for hypotrichosis, with 50% showing improvement. Genetic analysis revealed diverse pathogenic variants in TRPS1, with 4 (20%) patients having exonic deletions. All 16 sequence variants were private. Variants were distributed across exons 3 to 7, with 9 (45%) being novel. Thirteen (65%) patients had frameshift or nonsense variant. For hand deformities, the exon 6 missense variant was associated with severe hand deformities, while other genotypes exhibited variable severity.

Conclusion

TRPS I can present with short stature, alopecia, and early-onset skeletal dysplasia in pediatric patients, with impaired pubertal growth spurt and accelerated bone age. There were no mutational hotspots, and hand deformities were most severe in patients with exon 6 missense variants. Copy number variation analysis is essential for identifying the genetic etiology in patients without sequence alterations.

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EP744

JOINT672

Noonan syndrome: a retrospective observational study from a paediatric endocrinology unit at a portuguese tertiary hospital

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Introduction

Noonan Syndrome (NS) is a genetic disorder characterized by typical facial dysmorphisms, short stature, and congenital heart defects. Several genes have been implicated; approximately 50% of affected individuals present alterations in the *PTPN11* gene, involved in the RAS/MAPK pathway.

Aim

To characterize NS patients followed in the Paediatric Endocrinology Unit in a tertiary hospital from the centre region of Portugal.

Methods

Patients diagnosed with NS and followed in the pediatric endocrinology unit between 2009 and 2024 were identified, and demographic and clinical data were collected.

Results

Eighteen patients diagnosed with NS were identified, of whom 12 (66.7%) were boys. The main reason for referral to the Paediatric Endocrinology Unit was short stature (77.8%), followed by poor weight gain (11.1%) and delayed puberty (11.1%). At the first consultation, patients had a median age of 8.3 years (IQR: 3.7-12.3), although their median age at diagnosis was 3.5 years (IQR: 1.7-10.2). Patients presented with typical facial features (88.9%), cardiac defects (61.1%), stature below P3 (77.8%), *pectus excavatum* (27.8%), developmental delay (44.4%), lymphatic defects (22.2%), and confirmed family history (11.1%), and suspected family history (5.6%). Cryptorchidism was present in 41.7% of boys. Molecular studies were available in 15 cases, identifying mutations in PTPN11 (66.7%), SOS1 (13.3%), BRAF (6.7%), LZTR1 (6.7%), and NF1 (6.7%). The median height z-score at the first consultation was -2.6 (IQR: 1,5), confirming the short stature in 14 patients (77.8%). The median z-score for target height was -0.3 (IQR: 0.7). The final height was available for 7 patients, corresponding to a median height z-score of -1.6 (IQR: 1.7) and a median difference of -1.9 (IQR: 2.6) compared to the target height z-score. At follow-up, only 3 patients presented growth hormone deficiency, receiving an average dose of recombinant human growth hormone (rhGH) 0.029 mg/kg/day (min. 0.021; max. 0.034) for 52 months (min. 16; max. 88). At the last evaluation, 7 (38.9%) patients were prepubertal, and 6 (33.3%) exhibited delayed puberty. Twelve (66,7%) patients exhibited varying neurodevelopmental delays or learning difficulties.

Discussion

The multisystemic involvement of NS requires a multidisciplinary team approach. Paediatric Endocrinology plays a key role in addressing short stature and pubertal development. Despite the approval of rhGH for the treatment of NS in Europe, the conditions for initiating therapy depend on the regulations of each member state. The rhGH improves final height, mainly when initiated early and maintained for a more extended period before the onset of puberty.

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EP745

JOINT3700

An atypical case of silver-russel syndrome linked to a novel variant in HMGA2 gene

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Introduction

Silver-Russell syndrome (SRS) is a clinically and genetically heterogeneous disorder characterized by short stature, a typical facial phenotype, and body asymmetry. Molecular genetic abnormalities, such as maternal uniparental disomy of chromosome 7 and hypomethylation of the 11p15 region, are commonly observed in SRS, approximately 40% of patients still lack a confirmed genetic diagnosis. Identifying the underlying molecular cause is essential for accurate diagnosis, effective treatment, and genetic counseling for affected families.

Materials and Methods

A 7-year-old girl was referred due to concerns of growth and weight delay. She was born from second pregnancy complicated by intrauterine growth restriction and delivered by cesarean section at 39 weeks. Birth weight 1820 g (SDS: -3.3), birth length 44 cm (SDS: -4.34), Apgar score 6/8. The family history was non-contributory: maternal height 168 cm, paternal height 170 cm, target height of 160.5 cm (SDS: 0.08). There were no reported comorbidities.

Results

At the time of evaluation, the girl had a proportional physique. Notable dysmorphic features included a wide protruding forehead, clinodactyly of the fifth finger, and

abnormal dental development. Height 103.0 cm (SDS: -3.2), weight 13.8 kg, BMI SDS -1.9. Over the past 18 months, she had grown 6.5 cm. During examination, bone age was delayed by 1 year, and IGF-1 was measured at 103 ng/ml. No deficiency of other pituitary tropic hormones was detected. To investigate maternal uniparental disomy of chromosome 7, microsatellite analysis was performed on critical loci at 7q33-34 (D7S2202, D7S91824) and 7p12.1-12.3 (D7S2422, D7S2519). Additionally, multilocus methylation-sensitive PCR was used to assess allele-specific methylation in the 11p15 region, including the H19/IGF2 imprinting control region. The analyses excluded characteristic molecular genetic defects of SRS, including maternal uniparental disomy of chromosome 7 and hypomethylation of the 11p15 region. Given the negative results, the patient and her parents underwent whole-exome sequencing of peripheral blood lymphocyte DNA in a "trio" format. A previously undescribed heterozygous *de novo* variant was identified in the *HMGA2* gene (NC_000012.2:g.65825359G>A, NM_003483.6: c.89G>A, p.(Gly30Asp)), associated with SRS type 5 (OMIM: 618908). Segregation analysis in the family confirmed the variant by Sanger sequencing.

Conclusion

The use of advanced genetic testing methods, including whole-genome and whole-exome sequencing, significantly improves diagnostic accuracy in patients with suspected SRS. The identification of a novel monogenic cause in this patient facilitated the initiation of somatotropic treatment and enabled comprehensive genetic counseling for the family.

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EP746

JOINT2273

A single center real world experience with vosoritide for the treatment of children with achondroplasia

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Introduction

Achondroplasia is the most common skeletal dysplasia with severe short stature. It is characterized by gain-of-function variants in the *FGFR3* gene. In Brazil, vosoritide was approved in 2021 for ACH children ages 2 years and older, then in 2023 it was approved for children ages 6 months and older.

Objective

to assess the real-world response of children with achondroplasia to Vosoritide.

Methods

Thirty-two children with genetic confirmed achondroplasia initiated treatment with Vosoritide. Height and weight were measured. Changes in height SDS based on WHO growth curves (WHO) or based on achondroplasia specific growth curves (ACH) were assessed after 6 months ($n = 21$) and after 1 year ($n = 14$) of treatment. Adverse events were assessed in all 32 children.

Results

The mean age at start of treatment was 6.1 years. Data for the whole group: Twelve females completed 6 months of treatment and 9 completed 12 months. Even though there was an increment in height SDS after 6 or 12 months, this change was not statistically different. On the other hand, despite having fewer male individuals (9 completed 6 months and 6 completed 12 months) there was a significant difference in height SDS. Safety: Eight patients presented hypertricosis (7 females) that was noticed after a mean duration of treatment of 4.37 ± 1.99 months and a range of 3 and 8 months. Three patients reported local pain at injection site.

Discussion

There is an overall increment in height of children with Achondroplasia in response to the treatment with Vosoritide. Changes in height SDS can be better observed using specific standards for individuals with achondroplasia. The response was better in males. One possible explanation is that some children do not respond robustly to the treatment and in our cohort, we had two, both females.

All Patients (Height)	WHO		ACH	
	6mo	12mo	6mo	12mo
Basal	-4.48 (±0,95)	-4.59 (±0.79)	+0,57(±0,99)	+0,40(±0,84)
After Treatment	-4.36 (±0.95)	-4.39 (±0.8)	+0.77 (±1,05)	+0,71(±0,85)
	(*P* = 0,16)	**(*P* = 0,02)**	**(*P* = 0,002)**	**(*P* = 0,003)**

Height	WHO				ACH			
	Male		Female		Male		Female	
	6mo	12mo	6mo	12mo	6mo	12mo	6mo	12mo
Basal	-3.84 (±0.91)	-4.07 (±0.70)	-4.88 (±0.72)	-4.94 (±0.66)	1,25 (±1.05)	1.01 (±0.80)	0.10 (±0.71)	-0.001 (±0.60)
After treatment	-3.67 (±0.80) **(*P*=0,034)**	-3.81 (±0.65) **(*P*=0.001)**	-4.87 (±0.70)	-4.76 (±0.67)	1,55 (±0.96) **(*P*=0,004)**	1.4 (±0.80) **(*P*=0.0006)**	0.198 (±0.67)	0.260 (±0.53)

Conclusion

Treatment was well tolerated. The difference in SDS based on Achondroplasia standards is more significant than based on WHO standards.

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EP747

JOINT3759

Sex steroid priming prior to growth hormone stimulation testing in peripubertal adolescents with short stature?

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Introduction

Growth hormone stimulation testing (GHST) is recommended to diagnose growth hormone deficiency (GHD) in children. Sex steroids impact on anterior pituitary function, therefore, the efficacy of GHST in peripubertal children, where endogenous sex steroid levels are low is challenging. Sex steroid priming before GHST has been proposed to improve test efficacy in these children, however clear evidence to support its use in clinical practice is limited.

Methods

A total of 141 children with short stature (height <3rd %) (71boys) (Tanner 1, 43.6%*/*), mean age 12±2.3years, were evaluated for growth hormone deficiency upon a 2 year period (2020 -2022). Standard GHST with prior steroid priming ($n=$ 76, 53.9%, mean age 12.5±2years) were compared to a group without prior steroid priming ($n = 65$, 46.1%, mean age 11.7±2.4years) (p=NS). For priming, sex steroids were delivered; testosterone enanthate 100mg IM 5-7 days before GHST for boys and estradiol valerate 1-2mg PO 3 days before GHST (glucagon or clonidine) for girls.

Results

Median GH peak max was 7.1ng/ml (IQR: 6.2) without vs. 7.7 (IQR: 8.0) with prior steroid priming (p=NS). Median E2 levels were 40.4 pg/ml (IQR: 77.1) before vs 68.9pg/ml (IQR: 54.3) after priming ($P = 0.013$); median testosterone levels were 3.2ng/ml (IQR: 5.8) vs 5.7ng/ml (IQR: 6.9) respectively (p=NS). Prepubertal children (Tanner 1) had significantly higher GH response after priming (10.1 vs 8.7 ng/ml, p:0.011) as opposed to pubertal Tanner 2 (9.1 vs 9.3 ng/ml) (p:0.097). Females demonstrated significantly higher median E2 levels after priming (70.6 vs 40.4 pg/ml) (p:0.013) as compared to males with respect to median levels of testosterone (5.7 vs 3.2 ng/ml) (p:0.056).

Conclusion

In our cohort of peripubertal adolescents with short stature sex steroid priming prior to growth hormone stimulation testing failed to reveal statistically significant difference in growth hormone secretion.

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EP748

JOINT3350

Lamb-Shaffer syndrome as a rare cause of short stature

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Background

Lamb-Shaffer syndrome (LAMSHF) is an extremely rare genetic disorder due to *SOX5* gene mutation, characterized by global developmental delay, intellectual disability, skeletal anomalies and typical facial features.

Case report

An 11-month-old boy came to our attention for poor growth. His weigh was 6120 g (-3.95 SD, WHO), length 70 cm (-2.10 SD, WHO) and CC 33.5 cm (-1.24 SD, WHO). Frontal bossing, reduced subcutaneous fat with dystrophic appearance and cervical axial tone inadequate for age were observed. Past medical history: born by *in vitro* fertilization (FIVET) at 37 weeks of gestational age after a pregnancy complicated by

gestational diabetes, treated with insulin. The birth weight was 2400 g (-1.64 SDS), the length was 47 cm (-1.03 SDS), and the cranial circumference (CC) was 33.5 cm (-0.40 SDS). Ostium secundum atrial septal defect was found after the birth, no alterations at the neonatal cranial ultrasound, and the glycemic control was always adequate. After the birth the patient was admitted to the hospital frequently: at the age of 5 months due to respiratory syncytial virus bronchiolitis, at 7 months for fever and feeding difficulties, at 9 months due to Cytomegalovirus and B-influenza virus infection. No alterations were found at the abdominal and heart ultrasound. After the weaning the boy showed bottle feeding difficulties with daily vomiting episodes and a global developmental delay. During the subsequent hospitalization due to urinary infection, selective immunoglobulin A deficiency was found, and the brain Magnetic Resonance Imaging (MRI), performed due to the worsening developmental delay, showed a ventricular dilatation, with global subatrophy, without acute event signs. After our first evaluation, due to his worsening short stature (SS) associated by neuropsychiatric impairment, a new laboratory assessment was performed: growth hormone deficiency and celiac disorder were ruled out, and no food allergies were found. Array CGH showed 12p12.1 de novo deletion, involving *SOX5* gene.
Conclusions
LAMSHF is a rare condition with normal birth parameters and growth impairment can be developed during the first years of life. In children with SS, once the main causes of their growth deficiency are ruled out, genetic evaluation has to be considered for the differential diagnosis. In this context, due to SS associated with neurodevelopmental delay, we preferred to perform an Array CGH that permitted the diagnosis. There is no specific treatment for LAMSHF but a comprehensive multidisciplinary care model is required for these patients.

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EP749

JOINT419

Identification of a novel heterozygous variant of the aggrecan gene in a family with idiopathic short stature and accelerated bone maturation: treatments and challenges

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Introduction
The proteoglycan aggrecan, transcripted by *ACAN* gene, is the most abundant non-collagenous protein in the extracellular matrix in cartilaginous tissue. Variants in *ACAN* result in a broad phenotypic spectrum of skeletal dysplasias and various undefined short stature syndromes associated with accelerated bone maturation. We present the case of two brothers with short stature, treated with different growth-promoting therapies and later being diagnosed with *ACAN* variant.
Case report
Patient 1 was referred to our Endocrinology Unit for short stature and GH deficiency, confirmed with two stimulation tests. No significant medical history. He was born appropriate for gestational age; familiarity for short stature in mother and into the maternal line. He was treated with GH therapy from 5 years of age, with height improvement from < -2 SDS up to 10° centile. An anticipated puberty with rapid progression negatively affected patient final height, <-3 SDS. Extensive blood examinations, ACTH test, new CNS MRI and *SHOX*-gene analysis were normal. Patient 2, brother of patient 1, was referred at 5 years of age for short stature. GH deficiency was ruled out with GH-stimulation tests. Radiological evaluation showed advanced bone aged of 1.5 years. Adrenal axis evaluation was normal. At 9 years old he was diagnosed Central Precocious Puberty and was treated with GnRH agonist, Decapeptyl 3.75 mg/28 days. The therapy was suspended at the age of 12, with a skeletal age of 13. After 6 months, bone age advanced 1 more year, therefore, taking also into account the family history, he started aromatase-inhibitor therapy, anastrozole 1 mg/day, in order to slow down growth plate fusion. After pubertal spurt he was -2.5 SDS for height and genetic analysis were performed. Exome sequencing showed the heterozygous variant c.6620C>A (p.(Ser2207*)) in *ACAN* gene, inherited by his mother and presents also in his brother. This variant is not descripted in literature and in the Human Gene Mutation Database yet and it was classified as probably pathogenetic (ACMG).
Discussion
Genetic evaluation, with the widespread use of next-generation sequencing technology, has been demonstrated as an important tool to elucidate the causes of growth disorders. Patient 1 partially responded to GH treatment, as already reported in the literature. Treatment with GnRH analogue and aromatase inhibitor, carried out in patient 2, did not lead to better results and not effectively improve the final height. Bone age pathological progression due to aggrecan variant is still an open challenge.

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EP750

JOINT1301

Differences in age at treatment start of recombinant human growth hormone therapy among european countries

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Background
Early initiation of recombinant human growth hormone (r-hGH) therapy in patients with growth hormone deficiency (GHD) is important as it can improve growth-related outcomes.
Objective
This study aimed to evaluate the age at treatment start in children and adolescents with GHD treated with r-hGH therapy (Saizen®, Merck KGaA, Darmstadt, Germany) among European countries.
Methods
Data of age at treatment start of patients aged <18 years with GHD from European countries were extracted from the Growzen™ Connect digital ecosystem. However, whether patients were previously treated with r-hGH from another company was unknown (non-naive).
Results
Data on age at treatment start was available for 10,150 patients from 15 European countries. The median age at treatment start was <8 years in Sweden and Finland; 9 years in the Czech Republic, Austria, Germany, and United Kingdom; 10 years in Hungary, Slovakia, France, Romania, and Spain; and >10 years in Switzerland, Ireland, Italy, and Serbia.
Conclusions
Although these data include non-naive patients, our findings show variations in the age at treatment start across different European countries. The data suggests a delayed start of r-hGH treatment across most European countries, which has potential implications for the final height outcome. The differences may be explained by the use of different country-specific guidelines for the early detection of growth disorders and their degree of implementation, the number and timing of healthcare visits and other healthcare practices. These results underscore the importance of harmonising guidelines and strategies for early detection of growth disorders across Europe to ensure optimal patient outcomes.

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EP751

JOINT1367

(Un)satisfactory effectiveness of whole-exome sequencing in detecting genetic causes of differential sexual development in 46,XY patients

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Introduction
Differential sexual development (DSD) with 46,XY is a group of rare congenital disorders of the structure and function of the urogenital system resulting from abnormal testicular development or disorders of androgens action. Published data shows that despite the increasingly frequent genetic diagnostics, the causes remain unclear in more than half of cases; with only 34-46% confirmed by molecular testing.
Aim of the study
An attempt to determine the genetic causes of DSD in patients with karyotype 46,XY using the whole-exome sequencing (WES) method.
Patients&Methods
In a consecutive group of 36 children diagnosed in our center as 46,XY DSD (aged 2.4 – 17.9, median age 5.13), 29 raised as boys and 7 raised as girls, with a detailed description of the clinical and biochemical profile, WES was performed.
Results
Pathogenic, potentially pathogenic and variants of uncertain clinical significance (VUS) are presented in the table. No variants that could be related to DSD symptoms were found in the remaining children.
Conclusions
Currently WES is the state of the art method in terms of the quantity of covered genes, nevertheless genetic cause of DSD could still only be identified in less than half of 46,XY DSD patients, for whom the "glass is half full". It is recommended to reexamine the WES results every 12 months and to verify the status of the identified VUS in the biological parents of the patients.

Age [years]	assigned sex [F/M]]	fenotype	gene	variant	classification
5.1	M	scrotal hypospadias, scrotal transposition, gonads in the labio-scrotal folds	AR	c.2567G>A	pathogenic
6.2	F	inguinal hernia, absence of the uterus	AR	c.2301del	
3.1	M	micropenis, bilateral cryptorchidism, scrotal hypoplasia	DHX37	c.2020C>T	
4.7	M	bilateral cryptorchidism, micropenis, opening of the urogenital sinus in the scrotum	AR	c.2134C>G	potentially pathogenic
2.7	M	bilateral testicular atrophy, micropenis	AR	c.1792A>G	
13.7	F	inguinal hernia, gonads in the inguinal canals	AR	c.2375C>T	
2.7	F	inguinal hernia	AR	c.2375C>T	
8.0	F	labioscrotal fold with gonad on the right side, phalanx	NR5A1	c. 11_12del	VUS
6.2	M	bilateral cryptorchidism	DHX37	c.2598_2600-delGTAinsATG	
7.4	M	penile hypospadias, right-sided cryptorchidism	AR	c.721A>G	
4.2	M	hypoplasia of the right testicle, left-sided cryptorchidism	MAMLD1	c.834C>A	
3.9	M	scrotal hypospadias, absent left testicle	SOS2	c.586G>C	
2.4	M	bilateral cryptorchidism, micropenis, scrotal hypoplasia	FAM111	c.1660G>C	
14.1	M	atrophic testicles bilaterally	DHX37	c.1516G>A	

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EP752

JOINT1620

Mixed segmental uniparental disomy of chromosome 15q11-q1 coexists with homozygous variant in GNB5 gene in child with Prader-Willi and Lodder-Merla syndrome

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Background
Uniparental disomy presents two primary developmental risks: inheriting a recessive trait or occurrence of an imprinting disorder. Occasionally, these risks may coexist in a single patient, leading to a rare comorbidity. Managing comorbidities associated with rare diseases presents unique clinical challenges. The aim of this study is to present the case of a boy who was ultimately diagnosed with two rare diseases: Prader-Willi syndrome associated with maternal UPD15 and autosomal recessive Lodder-Merl syndrome associated with a new pathogenic variant of the GNB5 gene.
Case report
A fourteen-month-old boy of young, healthy parents, born by cesarean section in the 38th week of pregnancy with a birth weight of 2110 g, Apgar 7 - 10 points. Bilateral cryptorchidism, hypotonia, weak sucking reflex, apneas, congenital pneumonia, and respiratory failure were found. Treated in the Neonatal Intensive Care Unit, fed through a nasogastric tube. In the fourth month of life, semiological seizures consistent with infantile spasms appeared. The attacks occurred daily in 4-6 series lasting approximately 3 minutes. Neurological examination at the age of 4 months revealed microcephaly (OFC 38.5 cm, below the 3rd percentile), bilateral ptosis, open mouth, poor facial expressions, bilateral horizontal nystagmus, without fixation, profound global hypotonia, poor motor skills. The EEG recording was abnormal and drug-resistant epilepsy was diagnosed. During further follow-up, the patient showed no developmental progress. Genetic testing identified an abnormal DNA methylation pattern in the critical PWS 15q11-q13 region. Microsatellite polymorphism analysis in the 15q region in the proband and both parents confirmed maternal uniparental disomy of chromosome 15. Due to the patient's clinical picture, trio-WES and mitochondrial genome analysis were performed. A homozygous variant of the GNB5 gene was detected in the isodisomy region on chromosome 15. WES analysis of the mother's sample showed that she was a heterozygous carrier.
Conclusions
Co-occurence of PWS and some unexpected or severe phenotype should always raise suspicion of comorbid genetic disease attributed to genes located in Prader-Willi syndrome-associated critical region of chromosome 15q. Epileptic encephalophaty with cardiac arrythmia should implicate prompt cardiologist and genetic care. Presented case provides further support for uniparental disomy as an unexpected cause of Lodder-Merla syndrome. This implicates the importance of comprehensive genetic testing including parental testing and familial cascade testing to learn about recurrence risk.

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EP753

JOINT2464

The impact of growth hormone treatment on physical performance in adult patients with severe growth hormone deficiency - preliminary results

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Introduction
Growth hormone (GH) influences body composition, appearance, and physical performance by stimulating muscle tissue growth while promoting lipolysis. However, it is not clear if recombinant human growth hormone (rhGH) replacement impacts physical fitness of adult patients with severe growth hormone deficiency (GHD).

Aim
To assess the impact of a 6-month rhGH supplementation on the physical fitness of patients with GHD.
Patients and methods
Seventeen adult patients with GHD were enrolled (9 females, 8 males). The mean age of patients was 40.4 ± 12 years. Physical fitness was assessed using exercise tests such as 6-minute walk test, 30-second chair stand test, up-and-go test, handgrip strength test baseline and after 6 months of rhGH treatment.
Results
All patients normalized IGF-1 level after 6 months of rhGH treatment. The mean IGF-1 concentration after 6 months of rhGH treatment was 156.45 ± 58.29 ng/ml (2.03 x lower limit of normal (LLN) vs. 66.89 ± 42.62 ng/ml (0.87 x LLN) at baseline. At baseline five patients had IGF-1 levels in the lower quartile of the normal range. We found increase in physical performance after 6 months of rhGH treatment measured by 6-minute walk test (6MWT): 614.0 ± 92.1 m vs. 539.7 ± 43.1 m(P <0.05), 30-second chair stand test (30sChST): 18.3 ± 5.6 repetitions vs. 13.0 ± 2.7 repetitions(P <0.05), Up-and-go test (UaGT): Mean task completion time was 5.21 ± 0.77 s vs. 5.78 ± 0.76 s(P <0.05), Handgrip strength test (HST): 36.2 ± 12.2 kg vs. 33.4 ± 10.2 kg(P <0.05). Divided by sex, the results are as follows. Women: 6MWT: 599.4 ± 57.0 vs. 527.9 ± 45.0, 30sChST: 17.6 ± 0.6 vs. 11.8 ± 1.6, UaGT: 5.42 ± 0.59 vs. 5.93 ± 0.63, HST: 26.8 ± 4.3 vs. 26.3 ± 5.5. Men: 6MWT: 630.4 ± 78.9 vs. 552.9 ± 39.3, 30sChST: 19.2 ± 7.3 vs. 14.5 ± 3.1, UaGT: 4.97 ± 0.92 vs. 5.62 ± 0.91, HST: 46.9 ± 8.6 vs. 41.4 ± 8.1.
Conclusions
Six-month rhGH replacement therapy resulting in normalization of IGF-1 level improves physical fitness of adult patients with severe GHD.

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EP754

JOINT1358

Severe growth hormone deficiency in siblings: a case study of GH1-related IGHD in a consanguineous family

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Introduction
Isolated growth hormone deficiency (IGHD) is a rare autosomal recessive disorder caused by mutations or deletions in the *GH1* gene. It is characterized by early-onset severe short stature, extremely low levels of IGF-1, and a typical phenotype, including facial dysmorphism and genital abnormalities. IGF-1, a key mediator of growth hormone action, is critical for normal growth and development, and its deficiency leads to multisystemic consequences. Early genetic screening and treatment are essential to mitigate the impact of this condition on growth and overall health.
Case Presentation
This case study presents two siblings, aged 3 years and 7 months and 5 years and 10 months, diagnosed with severe growth deficiency and complex phenotypes. The consanguinity of their parents (second-degree cousins) and the family history, including an uncle with severe short stature (130 cm), suggest a significant genetic component. The phenotypes of the children were marked by facial dysmorphism (midfacial hypoplasia, hypoplasia of the nasal pyramid), micropenis (-3 DS), cryptorchidism, hypoplastic scrotum, and testicular hypotrophy. Both siblings presented with severe hypoglycemia at diagnosis (34 mg/dL and 25 mg/dL) and extremely low IGF-1 levels (<15 ng/ml and 26 ng/ml). Growth hormone therapy was initiated at different times, depending on the severity of their growth status. Somatropin treatment began 1 year and 9 months ago for both brothers. The older brother has shown a positive change in his growth trajectory, improving from -7.24 DS to -3.68 DS at present, while the younger brother has also demonstrated significant improvement, rising from -6.5 DS to -3.24 DS. Only the younger sibling has undergone genetic testing, which revealed a normal karyotype of 46,XY and a homozygous GH1 gene deletion was confirmed by WES.
Conclusions
This case highlights the importance of rigorous genetic and clinical monitoring in families with consanguinity. Differences in treatment timing and growth progression emphasize the phenotypic variability of growth hormone deficiency associated with the *GH1* gene. Additionally, severe hypoglycemia and extremely low IGF-1 levels complete the multisystemic picture of this rare disorder.

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EP755

JOINT1260

Integrating patient-generated health data into growth hormone therapy: perspectives from the paediatric endocrinologists in the gulf cooperation council

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Background
The increasing application of digital health tools has enabled patient generated-health data (PGHD) to play a crucial role in clinical support and decision-making. However, data integration into practice remains a challenge, especially for managing long-term conditions such as growth disorders requiring, growth hormone (GH) therapy. Identifying key factors to support successful implementation of PGHD in clinical practice is essential to address adherence gaps and improving growth outcomes for children requiring GH in the Gulf Cooperation Council (GCC) region.
Aim
To develop recommendations for improving adherence to GH therapy and clinical outcomes based on the identified factors for PGHD integration into clinical workflows.
Methods
A participatory workshop was conducted on March 2, 2024, in Dubai, UAE, using the Nominal Group Technique (NGT). Twelve paediatric endocrinologists with significant experience in paediatric growth disorders and digital health from the GCC region along with a workshop chairman and 2 moderators, participated in the structured activity-based workshop. Discussions were guided by three clinical scenarios: naïve (recently diagnosed) patients, poor adherent, and poor responders. The experts individually identified and presented various types of PGHDs they considered relevant (silent generation and round robin), discussed them and each expert selected the top 5 PGHDs in order of relevance by voting.
Results
A total of 22 influencing factors for PGHD integrations were identified. In the first ranking round, the top factors were demographic data (21 points), patient feelings about treatments and satisfactions (19 points), and social background (17 points). Other significant considerations included reasons for missing injections and education needs (15 points each). The second ranking round prioritized factors, with social background (35 points) receiving the highest score, which included insurance, family support, and social structure. Injection context (34 points), including timing, comfort, and technical support during administration was the second highest ranked factor. Patient feelings about treatments and satisfaction (30 points) highlighted the importance of motivational and emotional aspects of adherence. The final discussion focused on determining how the identified factors could be integrated into clinical practice to support GH therapy.
Conclusion
The study highlights the significant role of the social background, treatment logistics, and patient satisfaction in promoting PGHD integration into GH workflows. Using region-specific digital solutions and collaborative healthcare practices amongst physicians, nurses, pharmacists and Patient Support Program members can improve adherence and patient outcomes in the GCC region.

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EP756

JOINT2846

Self-resolving regional lipodystrophy secondary to somatrogon therapy: a case report

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Background
Growth hormone deficiency (GHD) is a condition characterized by insufficient production of growth hormone, resulting in impaired growth and development in children. Advances in therapy have introduced long-acting growth hormone analogs, such as somatrogon, offering the convenience of weekly dosing. While generally well-tolerated, localized side effects such as lipoatrophy at the site of injection, although rare, can occur. Lipodystrophy has not previously been reported as a side effect of Somatrogon therapy.
Case report
Patient Background: We report a 12-year-old boy with pyknodysostosis and growth hormone deficiency secondary to severe pituitary hypoplasia. Initially he was treated with daily Somatropin, but adherence issues led to us switching to weekly somatrogon therapy at a dose of 15 mg to address his GHD. At the start of treatment, his height SDS was -2.47.
Clinical Course
During a routine follow-up visit, regional lipodystrophy of the upper right arm was noted, characterized by a strikingly muscular appearance with prominent veins. Mother reported challenges with injection pain and the patient was insisting on using only his upper right arm for injections. No abnormalities were observed in his left arm or thighs. The appearance was attributed to repeated somatrogon injections at the same site. The importance of rotating injection sites was emphasized, and subsequently mother alternated between different anatomical sites, including the left arm and thighs.
Outcome
At his next follow-up visit, after three months, spontaneous resolution of the lipodystrophy was observed. Examination of his other injection sites showed no evidence of lipodystrophy. He continued therapy without interruption.
Conclusion
This case highlights regional lipodystrophy as a potential side effect of somatrogon therapy in a child with GHD. Timely identification and intervention through instituting proper injection site rotation led to successful resolution, without discontinuing therapy. This highlights the importance of patient and caregiver education on injection techniques to optimize therapeutic outcomes and adherence. Healthcare providers should remain vigilant for injection site reactions in patients receiving long-acting growth hormone therapies.
Acknowledgment
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EP757

JOINT3607

Filippi syndrome – a rare syndrome as a cause of short stature and primary amenorrhea

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Introduction
Filippi syndrome (FS) is a rare autosomal recessive disorder characterized by microcephaly, growth retardation, syndactyly, intellectual disability and dysmorphia. With only forty cases reported globally, diagnosis remains challenging.
Clinical Case
A 3-year-old girl, born full-term with fetal growth restriction (weight -2.26SDS, length -1.89SDS, head circumference -0.41SDS - Fenton 2013), was referenced to Pediatric Endocrinology due to short stature. There was no parental consanguinity and family history was unremarkable. Medical history included neonatal jaundice, ventricular septal defect and patent foramen ovale (spontaneously resolved by 1-year-old), umbilical hernia repair, recurrent otitis media and adenoidectomy. Dysmorphic features comprise high nasal bridge, thin alae nasi, square chin, clinodactyly of the fifth fingers bilaterally, and syndactyly of the second/third and third/fourth toes bilaterally. She also presented with microcephaly and intellectual development disorder at 6-years-old (Wechsler Intelligence Scale for Children III with Intelligence Quotient of 65, classification: very low). At 5 years-old she had height -2.72SD, weight -1.72SD, body mass index 0.15SD, family target height -1.82SD, bone age (BA) of 3-years-old and growth velocity of 8cm in the last year. Over time, growth slowed down, reaching -3.30SDS at 16-years-old. Thelarche and pubarche occurred at 10-years-old but menarche had never occurred. A whole exome study was carried out at 11-years-old, detecting decompound heterozygous variants in the CKAP2L gene (c.1092_1093del p.(Gln364Hisfs16) and c.1534_1537del p.(Lys512Hisfs13)), both classified as likely pathogenic, and FS was diagnosed. Analytical study excluded chronic disease. Endocrinological study showed: Follicle-stimulating hormone 7.55IU/L, Luteinizing hormone 3.26IU/L, estradiol 54.6 pmol/L (normal range 25.6-220.3). Growth hormone, cortisol and thyroid deficiency were excluded. Brain magnetic resonance was unremarkable. Abdominal-pelvic ultrasounds revealed hypoplastic uterus and small ovaries. Her last BA showed a delay of 1year (at 14-years-old). Currently, at 17-years-old, Tanner Stage M3P3, she remains amenorrheic, and ethinylestradiol was initiated.
Discussion
The authors present a case of FS, an extremely rare genetic disorder, emphasizing it as a cause of short stature and primary amenorrhea. Authors should share the evolution of these cases, to broaden the clinical spectrum of FS. This girl presented with delayed puberty although there are other cases described with precocious puberty. Although there is an association with neurologic abnormalities, seizures and growth hormone deficiency, they were not presented in this case. Early diagnosis can enable a personalized and timely approach to the patient's reproductive health, and also metabolic and bone well-being.

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EP758

JOINT759

Survey of electronic growth chart use reveals inconsistent provision and awareness of functionality across the United Kingdom

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Background
Growth monitoring is a fundamental aspect of routine paediatric care. Accurate charting, incorporating the use of appropriate reference data, is vital for clinical care to guide decisions to investigate and treat growth disorders. Electronic growth charting software can record and plot anthropometric data and generate standard deviation scores (SDS) for age and sex to aid clinical decision-making. We assessed the availability and types of electronic growth charts, reference data used and functionality of software across the United Kingdom (UK).
Methods
Paediatric endocrinologists and subspecialty trainees were invited via e-mail and the British Society for Paediatric Endocrinology and Diabetes newsletter to participate in an online survey on availability of growth charts and the functionality of available electronic growth charting software. Invitations to participate in the survey were distributed to secondary care paediatricians within each regional network by subspecialty trainees or paediatric endocrinology consultants. Where possible, commercial software developers were contacted to determine product specifications.
Results
100 responses were received between June and November 2024 from 82 different hospitals with wide geographical coverage across the UK. All 22 UK specialist paediatric endocrine centres responded. 72.0% of hospitals had electronic growth charting software available. 26.8% used only paper growth charts and one respondent reported having no access to any growth charts. All 22 specialist paediatric endocrine

centres used electronic growth charts, compared with 61.7% of secondary care centres ($P = 0.0006$). Twenty-eight different software packages were in use: locally developed software ($n = 16$ hospitals (27%)), commercially available products ($n = 12$ different in 43 hospitals). The growth reference data used was inconsistent: 41 (67%), 8 (13%) and 3 (5%) respondents reported using the UK-WHO data, the British 1990 reference data and WHO child growth standards, respectively. Nine (15%) respondents did not know the reference data used. Respondents using the same commercially available product frequently reported using different reference data. Additional functionality, for example, plotting body mass index and head circumference, ability to calculate SDS, prematurity adjustment, plotting of mid-parental height/target centile range and condition-specific charts were variably reported to be available even between users of the same commercially available software, and was frequently inconsistent with specifications reported by the software developers.

Conclusions

Electronic growth charts are not universally available to UK paediatricians. Where available, user knowledge of the growth reference data and software functionality was highly variable. We speculate these inconsistencies hinder comprehensive assessment of growth and may adversely affect clinical decision-making and patient care.

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EP759

JOINT2169

Real world data for the first year of treatment with somatrogon of children and adolescents with growth hormone deficiency (GHD)

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Introduction

Somatrogon is a long-acting growth hormone (LAGH) that received marketing authorization by EMA on February 2022 for treatment of children older than 3 years old and adolescents with GHD. The aim is to describe the first-year treatment outcome in regards to change in height z-score, BMI z-score, IGF-1 z-score levels and HbA1c as well as to report possible adverse reactions of the patients treated with somatrogon in our department.

Methods

The study population consisted of 20 children (40% boys) with mean age 10.7 (SD 2.57) years with GHD, who were treated with Somatrogon from 1/2024 to 1/2025. Ten (50%) patients were naive to treatment with growth hormone (GH) while the other half switched from once-daily rhGH injection regimen. The dose of somatrogon was 0.66 mg/kg/week. Change in height z-score, BMI z-score, IGF-1 z-score, and HbA1c were calculated and compared using t-test. Furthermore, the adverse events during treatment were recorded as well as the tolerability, the adherence to treatment and the preferred injection schedule.

Results

Patients' height z-score increased significantly during the first year of treatment with LAGH (Ht z-score -1.93 (0.842) to -1.44 (0.856), p 0.005). A significant increase in patients' BMI z-score was appreciated (BMI z-score 0.041 (0.974) to 0.375 (0.967), p 0.001). There was no significant difference in IGF-1 z-score (0.341 (1.710) to 0.704 (1.28), p 0.167) in the whole group but there was a significant increase in the naive group IGF-1 z-score (-0.676 (1.48) to 0.42 (1.33) $P < 0.001$). One patient had IGF-1 > 2SDS the 4th day after the 4th dose, so the dose was decreased. IGF-1 normalized afterwards. Furthermore, HbA1c levels were within normal range for both groups. Two girls reported moderate to severe pain at the injection site after switching from daily rhGH injection regimen and one patient experienced transient erythema at the injection site. However, none of the patients discontinued treatment or returned to daily dosing. They all reported 100 % compliance.

Conclusion

In this group of patients, treatment with somatrogon was well tolerated, proved to be efficient in accelerating growth velocity and improving height z-score. A trend of increasing BMI z-score was noticed that needs further observation. The limitation of this study is the small number of children and the short duration. They are preliminary real-world data.

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EP760

JOINT1459

Growth hormone treatment response in patients with biologically inactive growth hormone

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Introduction

Biologically inactive growth hormone (BIGH) was described in 1978 as an indication for growth hormone (GH) treatment. Currently, this entity is not listed as an indication for GH treatment by some state committees. Initially, its diagnosis was equated with neurosecretory dysfunction, but this entity is no longer considered as its diagnosis is not methodologically feasible. At this time, the diagnosis in our community is defined based on clinical criteria (Height < -2 SDS and/or 2 SDS below target height and growth velocity (GV) < p25 and analytical criteria (Normal GH stimulation test, low IGF-1 levels with excluded proven cause, IGF-1 increased response to treatment with exogenous GH for 5 days).

Objectives

To analyse the clinical characteristics of patients monitored in a tertiary hospital who have been treated with GH for suspected BIGH. To find out whether there are side effects related to GH treatment.

Patients and methodology

Retrospective observational study of GH-treated patients with the diagnosis of BIGH. Thirty patients (seven girls) have been treated with normal neonatal anthropometry except for four SGA with catch-up. Twenty-six patients were analysed at three years. Variables studied: **at baseline:** Age (ABT), Height-SDS (HBT-SDS), BMI-SDS (BMIBT-SDS), Growth velocity-SDS (GSBT-SDS), difference between chronological age and bone age (CA-BABT); **Three years after GH treatment**: H3BT-SDS, BMI3-SDS, GS3T-SDS, CA-BA3T. In 18 patients who have reached **final height**: Final Height-SDS-Target Height-SDS (FH-SDS-TH-SDS) was studied. Statistical analysis using SPSS. Non-parametric Wilconson test for related samples.

Results

Mean target height-SDS: 0.9 ± 0.91 (2 patients with familial short stature). ABT (years): 9.3 ± 3.8 (range: 2.5-16). All the variables analysed are statistically significantly at 3 years, including CA-BA, than at baseline. Final height improved ($P < 0.01$) compared to baseline and at 3 years of treatment. In absolute numbers and by sex: In boys TH: 170,48 ± 3,30 and FH: 168,71 ± 3,50. In girls TH: 159.56 ± 10.8 and FH: 159.13 ± 5.50. Only two children's FH is short and 7 children exceed their target height.

Conclusions

1. Patients diagnosed with BIGH and treated with GH clearly improve their final height.
2. The majority reach the target height.

Table 1 The rest of the variables obtained are described in the table.

	AT BASE-LINE n: 30 median ± SDS	**3 YEARS AFTER GH** TREATMENT n: 20 median ± SDS	p	**END OF TREATMENT** n: 18 median ± SDS	p
HEIGHT (SDS)	-2.7 ± 0,69	-1.47 ± 0,65	< 0.01	-0.91 ± 0,64	< 0.01
BMI (SDS)	-1.08 ± 0,31	-0.90 ± 0,73	< 0.01		
GS (SDS)	-2.3 ± 1.52	2.13 ± 2.54	< 0.01		
CH-BA(SDS)	2.7 ± 1.15	1.79 ± 1.03	< 0.01		
FH-TH (SDS)				-0.20 ± 0.60	

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EP761

JOINT1470

Intellectual and developmental function in children with Silver-Russell syndrome

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Background
Silver-Russell Syndrome (SRS) is a rare imprinting disorder characterized by intrauterine growth restriction, postnatal growth failure, and distinctive craniofacial features. While physical manifestations of SRS are well-documented, its impact on intellectual and developmental functions remains less understood. This study aims to evaluate cognitive and developmental outcomes in children with SRS to enhance understanding and improve clinical interventions.
Methods
To investigate if children with SRS have increased prevalence of cognitive disabilities, as well as autism spectrum disorder. A cohort of 28 children (16 boys) , mean age 11.6 years, were diagnosed with SRS and recruited from the Pediatric National Growth Hormone Registry. Children were followed at the national expert centre for SRS due to growth hormone treatment. Griffith's Mental Developmental scales and Wechsler Intelligence Scales were used according to age. Parents answered Autism Spectrum Screening Questionnaire (ASSQ) and autism diagnosis information was collected from medical records.
Results
In 12 children (43% of the cohort) we identified loss of methylation of chromosome 11p15 ($n = 11$) and maternal uniparental disomy of chromosome 7 ($n = 1$), in remain 16/28 no molecular cause was identified. The intelligence quotient (IQ) range was broad (61–142). Notably, 12 out of 28 children had an IQ below 85 (-1 SD), including 3 with an IQ below 70 (-2 SD), reflecting possible difficulties in learning and academic achievement. The mean full-scale IQ was significantly lower in "clinical SRS" compared to those with epigenetically confirmed SRS, 85.9 (15.8) and 104.9 (19.3), respectively. An uneven IQ profile between verbal IQ (VIQ) and performance IQ (PIQ) was observed in 14/26 children (54%), with nine of those showing a higher VIQ than PIQ. There was no significant association between molecular confirmed SRS and clinical SRS and uneven VIQ-PIQ profile. In 21/28 children one parent completed the ASSQ. Four children (two with and two without a clinical ASD diagnosis) scored above the cut-off (≥ 17), indicating autism-related symptoms. Six additional children reached either ASSQ cut off scores or had a diagnosis of Aspergeŕs syndrome.
Conclusion
Children with SRS present with variable intellectual and developmental outcomes, often exhibiting specific cognitive weaknesses and adaptive behavior challenges. Furthermore, ASD may be present. These findings underscore the need for early neurodevelopmental assessments to optimize learning and social adaptation.

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EP762

JOINT385

Patient dynamics and real-world insights from a somatropin patient support program (PSP): outcomes from 24,000 treated patients in brazil

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Introduction
Suboptimal adherence to somatropin has negative effects on growth and has been observed in various populations. Patient support programs (PSPs) aim to improve treatment adherence and persistence. Since 2011, a PSP was implemented in Brazil to support all pediatric patients treated with Omnitrope® (somatropin), offering nurse assistance, needle supply, instructional visits, thermal packaging, sharps collectors, WhatsApp messages, and educational materials.
Objectives
Evaluate enrollment rate, persistence, drop-outs, and patient satisfaction with the somatropin PSP in Brazil, identifying reasons for treatment discontinuation.
Methods
The database comprised all pediatric patients enrolled in the PSP from July 2011 to December 2024. Participants stopping Omnitrope® treatment for any reason were discontinued from the PSP. Median persistence on program was calculated using Kaplan-Meier survival analysis ("event" being defined as participant leaving the program). From 2015 onwards, participants rated their satisfaction monthly using a 5-point Net Promoter Score (NPS).
Results
24,136 participants (56% boys, 42% girls, 2% N/A) were enrolled in the Omnitrope® PSP in Brazil. The average age at enrollment was 11.5 $\pm$2.86 years. The median duration of participation in the program for the entire population was 57 months. There was no significant difference in persistence between boys and girls. Enrollment rates spiked during shortages of other somatropin products and in the first weeks of the COVID-19 pandemic. The average dropout rate has stabilized around 2% of active participants since 2015. The main reasons for discontinuation were treatment success (32% of discontinuing participants), lost to follow-up (32%), and switching to another somatropin product (15%). The NPS ranged between 4.6 and 4.8 points annually from 2015 to 2024.
Discussion
Strategies to improve treatment compliance and persistence in children with growth disorders are important. This analysis of a somatropin PSP with a large database revealed high median persistence on program and excellent rating of the provided services. This can be related to the unique Brazilian somatropin market, where only vial-based products are reimbursed, and other somatropin options (including Omnitrope®) require out-of-pocket payment.
Conclusion
We analyzed the dynamics of a large somatropin PSP over 13 years. Patient enrollment was boosted by shortages of other somatropin products. The services provided by the PSP were highly appreciated by the patients and likely played a role in the observed high persistence in the program.

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EP763

JOINT1583

Adherence and its key-driving factors to growth hormone treatment in children with growth disorders: the french SCOPE study

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Background
For patients with growth disorders managed on recombinant human growth hormone (r-hGH) therapy, the Growzen™ ecosystem (previously Easypod® Connect) provides an innovative connected injection device transmitting adherence data, empowering healthcare professionals to monitor real-time patient adherence.
Aim
This SCOPE (Study and Collection of Observational data for Patients with Easypod® Connect) study aims to use 5-year data from Growzen™ ecosystem to evaluate adherence and its key-driving factors in patients with growth disorders from France.
Methods
Adherence data for patients aged 4–17 years at treatment start and <18 years were extracted from Growzen™ ecosystem between June 2018–December 2023. The following potential key-driving factors for adherence were assessed: indication (Growth Hormone Deficiency [GHD] and Small for Gestational age [SGA]), sex, age, and treatment regimen (7 vs 6 days/week).
Results
Adherence data from 481 patients (265 GHD, 157 SGA, 13 Turner Syndrome, 46 other/unknown indications) across 19 centers were analysed. Of these, 256 patients followed a regimen of 7 days/week and 225 patients followed a regimen of 6 days/week. Mean age at treatment start was 9.9 years in all patients, 10.5 and 8.8 years in patients with GHD and SGA respectively. The proportion of high-level adherence ($\geq 85\%$) was 85% across all patients and was similar between GHD and SGA patients. During the first 12–18 months, adherence levels were comparable for boys and girls, with nearly 90% high-level adherence. A slight difference in the adherence level was found between boys and girls over time,

with a larger portion of girls having a high-level adherence after couple of years. A high-level adherence was observed in approximately 95% patients up to 5 years of age and 90% between 5 and 12 years. This decreased after the age of 12 years with 72% of patients having a high-level adherence at 17 years of age. The proportion of high-level adherence was 82% for 7 injections/week regimen and 88% for 6 injections/week regimen, but the difference was not statistically significant after adjustment for patient ages (10.5 years with 7 days/week, 9.3 years with 6 days/week).

Conclusion

The adherence level over the study period was high, demonstrating good engagement level of patients using the connected device for the daily administration of r-hGH therapy. Among all potential key-driving factors for adherence, the age at treatment start showed the highest impact on the level of adherence, emphasizing the need for early initiation of treatment for better outcomes.

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EP764

JOINT2192

Paradoxical growth in multiple pituitary deficiencies: two clinical cases of obese pediatric patients

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Introduction

Growth hormonal (GH) deficiency (GHD) is typically associated with impaired growth and short stature. Nevertheless, instances of normal growth have been reported in some pathological conditions, such as combined pituitary hormone deficiency following the resection of craniopharyngioma, septo-optic dysplasia and overgrowth syndromes despite GHD. We report two patients with obesity and multiple pituitary deficiencies exhibiting normal growth.

Patient 1

A 11-year-old female was evaluated for obesity. Height was 145.6 cm (-0.17SDS) within the mid-parental target, BMI 25.9 (+2.37SDS). Pubertal evaluation was B1 PH1 AH1. Homa index 3.2. History was positive for transient hypoglycemia at birth, normal postnatal growth and minor language delay. Endocrine assessment disclosed low FT_4 with inappropriately normal TSH consistent with central hypothyroidism; patient revealed significantly low IGF-1 (39 ng/ml), IGFBP-3 (2.04 mg/dL), and central ACTH deficiency. GH stimulation tests showed absent GH response. Magnetic resonance imaging (MRI) revealed a small adenohypophysis, absent pituitary stalk, and ectopic neurohypophysis. So, diagnosis was congenital panhypopituitarism was made and the patient began treatment with hydrocortisone, L-thyroxine, and GH. Genetic investigations are ongoing.

Patient 2

A 11-year-old male was evaluated for severe obesity. Height was 158.65 cm (+1.44SDS) above his mid-parental target, BMI 33.5 (+2.59SDS). Tanner stage was T 10 ml PH3 AH2. Abdominal ultrasonography indicated severe steatosis with metabolic syndrome and very high leptin level. Oral glucose tolerance test disclosed severe insulin resistance. Thyroid evaluation revealed secondary hypothyroidism, low IGF-1 levels (39 ng/ml) that persisted after L-thyroxine treatment. Prolactin levels were elevated, while adrenal function and gonadotropin levels were normal. GH stimulation tests showed GH deficiency. MRI showed a small stalk with normal pituitary gland. Despite excellent growth, clinical and laboratory findings suggested combined pituitary deficiency. Hormonal replacement therapy with L-thyroxine and GH was started. Exome sequencing is currently in progress.

Conclusion

The paradox of normal growth in patients with confirmed growth hormone and L-T4 deficiency remains enigmatic. Similar cases have been documented in obese individuals. One hypothesized mechanism involves hyperinsulinism, given the high homology between insulin receptors and IGF-1 receptors. Furthermore, hyperprolactinemia, hyperleptinemia and GH variants have been proposed as contributing factors in this phenomenon. The intricate interplay between these hormonal imbalances and growth regulation warrants further investigation to elucidate the underlying mechanisms. Additionally, cases of normal growth despite GHD have been described in patients with mutations in the HESX1 gene, associated with combined pituitary hormone deficiency. Ongoing genetic analyses in our patients will advance our understanding.

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EP765

JOINT2293

Growth hormone insensitivity in an infant with LZTR1 mutation and growth failure: a case report

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Introduction

Growth hormone (GH) insensitivity (GHI) results from a spectrum of abnormalities in the action of GH, presenting clinically as either mild short stature with normal physical appearance or severe dysmorphic short stature. In Noonan syndrome (NS) variable GHI has been reported, especially in individuals with *PTPN11* mutations. However, limited data are available on *LZTR1* mutations.

Case report

A 1.8-year-old male patient was referred to our Pediatric Endocrinology Unit for growth failure. His length was 80.5 cm (-1.3 SDS), and height velocity was significantly reduced (-1.8 SDS). The patient was born at 38+2 weeks of gestation following a pregnancy complicated by polyhydramnios in the 3rd trimester. Prenatal echocardiography revealed hypertrophy of the septum and right sections of the heart. At birth, his weight and length were adequate (3600 g and 53 cm, respectively). On the first day of life, he experienced a Sudden Unexpected Postnatal Collapse (SUPC). Postnatal cardiological evaluation confirmed hypertrophic cardiomyopathy with associated electrocardiographic abnormalities. Clinically, the patient exhibited features suggestive of RASopathy, therefore a genetic evaluation was performed. During the follow-up for growth failure, laboratory investigations revealed markedly reduced levels of IGFBP-3 (0.61 mg/L; range 1.20 - 3.30) and IGF-1 (13 ng/ml; range 18-156). Abdominal ultrasound was normal. Blood tests showed an increased INR (1.37, range 0.92-1.14) and reduced prothrombin time (64%, range 70-100). Cranial MRI was unremarkable. An arginine test was performed and revealed normal GH peak (14.60 ng/ml) with persistently significantly reduced IGF-1 and IGFBP-3 levels. Genetic analysis identified a heterozygous mutation in the *LZTR1* gene (variant c.734G>A, p.Gly245Glu), classified as pathogenic and associated with NS.

Conclusions

This case confirms that some *LZTR1* mutations can be associated with GHI. However, biallelic *LTZR1* variants have been reported linked with GH deficiency (GHD). The molecular mechanisms causing GHI or GHD in *LTZR1* remain unclear. An accurate auxological and biochemical evaluation is essential to distinguish these two conditions and establish a correct work-up and follow-up, as well as an adequate treatment strategy.

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EP766

JOINT2787

Autosomal recessive ovarian dysgenesis associated to gh-deficiency and pituitary hyperplasia: a case report

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Introduction

Ovarian dysgenesis (OD) is a major cause of hypergonadotropic hypogonadism and premature ovarian insufficiency (POI) in adolescent females. X chromosome numerical or structural abnormalities have historically been the most frequent congenital etiology of this condition. More recently, additional pathogenetic mechanisms have been identified, including Fragile X premutation and mutations in genes involved in meiosis, DNA damage repair, and homologous chromosome

recombination.
PSMC3IP
is a novel candidate gene associated with autosomal recessive OD, playing a crucial role in homologous chromosome pairing and recombination during meiosis.
Case Report
A 13-year, 6-month-old adolescent girl, the firstborn of apparently non-consanguineous parents, was referred for evaluation due to short stature, delayed pubertal development (Tanner stage PH1 B1), and primary amenorrhea. Psychomotor development was normal. Baseline biochemical tests, thyroid function, and celiac serology were unremarkable. However, FSH levels were repeatedly elevated, while estradiol, AMH, and testosterone levels were low or undetectable. LH levels were in the high-normal range. IGF-1 levels were low (108 ng/ml, < -2 SD), and bone age was delayed by more than three years. Karyotype analysis (50 metaphases) revealed a normal 46XX pattern, and FISH analysis did not detect Yp11.3 sequences. Due to short stature, GH stimulation tests (arginine and clonidine after estradiol priming) were performed, showing low GH peaks (6.83 ng/ml and 2.32 ng/ml, respectively), confirming GH deficiency. Brain MRI revealed diffuse pituitary gland enlargement without focal lesions. Ophthalmological evaluation was normal. Consequently, rhGH therapy was initiated at age 14 and is currently ongoing. Further investigation of POI through pelvic ultrasound revealed marked uterine and ovarian hypoplasia. Autoantibodies against adrenal and ovarian tissues were undetectable. Genetic testing, including SNP microarray and Fragile X (FMR1) analysis, did not reveal CGG repeat expansion nor significant chromosomal rearrangements. Whole-exome sequencing identified a homozygous likely pathogenic variant (Class IV) in **PSMC3IP** (c.429_430del; p.Arg143Serfs*5). At 14 years and 6 months, estradiol replacement therapy was initiated and is ongoing.
Discussion
Only a few cases of autosomal recessive OD due to **PSMC3IP** variants have been reported to date. This case highlights the role of meiotic arrest in OD pathogenesis and supports the observation that distal (C-terminal) pathogenic variants in **PSMC3IP** are preferentially associated with OD. Additionally, the unique co-occurrence of pituitary hyperplasia and GH deficiency expands the clinical spectrum of this novel genetic condition.

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EP767

JOINT755

Experience with vosoritide for achondroplasia: insights from Kazakhstan

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Background
Vosoritide is an engineered C-type natriuretic peptide analog and the first pharmacological, precision treatment approved for use in children with achondroplasia. While international guidelines provide practical guidance for healthcare providers worldwide, real-world experience data remains limited, particularly in Central Asia. This study aims to present our experience with Vosoritide and highlight challenges to treatment.
Methods and Results
Data were collected from hospital records, including patients receiving Vosoritide therapy at the "University Medical Center" Corporate Fund (Astana). In total, 38 children in Kazakhstan are receiving Vosoritide. The first 10 children were enrolled on 10 March 2023 in Almaty, and the last 14 patients, aged between 2.8 and 12.6 years, started treatment in December 2024 in Astana. The most common complications of achondroplasia among our children are ventricular enlargement with symptoms of hydrocephalus, spinal kyphosis, respiratory disorders, and symptoms of spinal canal stenosis. Worldwide, achondroplasia is the most common skeletal dysplasia, estimated to affect about 1 in every 40,000 children. There are approximately 200 children with this diagnosis in Kazakhstan, meaning only around 20% of children are receiving the treatment, highlighting the gap in access to therapy.
Discussion
Our findings align with international data on Vosoritide's safety profile. However, significant challenges remain, including limited accessibility and the high cost of medication, that create complex regulatory pathways and barriers to therapy. Additionally, based on our experience, we emphasize the significance of counseling and training programs before initiating treatment. Possible cases of treatment refusal due to divided opinions highlight the need for psychological preparation. Frequently, parents fear potential adverse effects or question the efficacy of the drug, which underlines the need for family education sessions. We also recognize the psychological trauma associated with daily injections experienced by children of different ages, which may lead to non-compliance. A multidisciplinary strategy, including parental support and structured counseling, may improve adherence to the treatment.
Conclusion
This study provides valuable data on the use of Vosoritide in Central Asia. While the treatment has improved quality of life, accessibility remains a key concern. Future efforts should also focus on the long-term safety and efficacy of the therapy, which will be vital in optimizing patient education programs and ensuring psychological support for families. Additionally, monitoring and early intervention for complications, enhancing the quality of health professionals, and streamlined regulatory approval procedures are crucial to improving treatment outcomes.
Keywords
Vosoritide, Achondroplasia

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EP768

JOINT503

Optimizing therapies for advanced bone age in obesity-related short stature, cah, precocious puberty, and sga: an updated view

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Background
Advanced bone age is a critical factor limiting height outcomes in growth disorders, including obesity-related short stature, congenital adrenal hyperplasia (CAH), precocious puberty, and small-for-gestational-age (SGA) conditions. Therapies such as growth hormone (GH), aromatase inhibitors (AIs), and gonadotropin-releasing hormone agonists (GnRHa) are used either independently or in combination to enhance height potential and manage bone age progression.
Objectives
This review aims to assess and compare the effectiveness of GH, AIs, and GnRHa therapies in treating advanced bone age across pediatric growth disorders. It evaluates their impact on height standard deviation score (HtSDS), predicted adult height (PAH), and bone age modulation.
Methods
Studies spanning 2000–2024 were analyzed. These studies encompassed diverse pediatric conditions with advanced bone age treated with GH, AIs, GnRHa, or combinations. Data on PAH improvements, bone age control, and side effects were extracted, focusing on therapeutic outcomes across conditions.
Results
A total of 25 studies were analyzed to evaluate therapeutic strategies for advanced bone age across four conditions: obesity-related short stature, CAH, precocious puberty, and small SGA. The studies highlighted the efficacy of GH therapy, GnRHa, and AIs, either alone or in combination. Six studies reported that GH combined with GnRHa or AIs improved predicted adult height and controlled bone age progression in obesity-related short stature, with early intervention yielding the best outcomes. For CAH, five studies demonstrated that combination therapies (e.g., GH + GnRHa + AI) significantly improved height SDS while controlling androgen-induced bone maturation, especially in prepubertal patients. Eight studies on precocious puberty confirmed the effectiveness of GnRHa in delaying bone age advancement, with combination therapy (GnRHa + GH or GnRHa + AI) yielding superior height outcomes. In four studies examining SGA, GH alone or in combination with AIs consistently promoted significant height gains and moderately delayed bone age, particularly with early intervention. Across all conditions, combination therapies outperformed monotherapy in managing bone age progression and optimizing growth, with minimal but manageable adverse effects.
Discussion
The findings underscore the importance of condition-specific approaches to optimize outcomes. Early diagnosis and intervention are critical, particularly in obesity-related short stature and SGA, where early skeletal maturation poses significant barriers to achieving optimal height.
Conclusion
Combination therapies tailored to the underlying pathology of advanced bone age provide the most effective strategies for improving height and managing bone age progression in growth disorders. Future research should focus on safety, and personalized treatment algorithms to maximize benefits across conditions.

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EP769

JOINT2743

A rare cause of short stature: a case with a TBX6 gene variant

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Introduction

Spondylocostal dysostosis is a genetically inherited disorder characterized by malformations of the ribs and vertebrae. Heterozygous and biallelic variants in TBX6 gene have been linked to vertebral and rib malformations, as well as spondylocostal dysostosis. In this case report, we aimed to contribute to the literature by presenting the clinical findings of our patient with TBX6 gene variant, one of the rare causes of spondylocostal dysostosis.

Case Report

A 14-year-old male patient was referred to the endocrinology clinic due to short stature. His parents were first-degree relatives. The mother's height was 162.1 cm, and the father's height was 169.2 cm, with a target height of 172.15 cm (-0.66 SDS). On physical examination, the patient's weight was 41.5 kg (-1.7 SDS), height was 142.5 cm (-3.02 SDS), BMI was 20.4 (-0.05 SDS), and head circumference was 54 cm (-1.33 SDS). His pubertal stage was Tanner A+P1, with testicular volumes of 4 ml bilaterally. Laboratory investigations, including complete blood count, thyroid function tests, and biochemical analyses, were within normal limits. Serum IGF-1 was 152 µg/L (115-489), and IGFBP3 was 3.85 mg/L (3.21-6.93). Due to severe short stature, a growth hormone stimulation test revealed a peak GH level of 11.2 µg/L (normal). Urinary mucopolysaccharide excretion was normal, ruling out mucopolysaccharidosis. Whole exome sequencing (WES) identified a likely pathogenic (NM_004608.4) heterozygous c.2T>A p.Met1Lys missense variant in the TBX6 gene. It was determined that the detected variant was inherited from the father, who exhibited similar clinical features.

Discussion

According to The Human Gene Mutation Database Professional 2023.4, a total of 84 different variants have been reported in the TBX6 gene, including 34 missense/nonsense, 6 splicing, 1 regulatory, 9 small deletions, 8 small inversions, 21 gross deletions, and 5 gross insertions. Our case presented with a clinically relevant and frequently observed missense variant in this gene. The identified variant was not found in the gnomAD and ClinVar databases and was classified as likely pathogenic according to ACMG criteria. Phenotypes associated with TBX6 gene variants include short stature, short neck, rib anomalies, scoliosis, hemivertebrae, and butterfly vertebrae. Recognizing spondylocostal dysostosis in the prenatal period allows for the exclusion of spondylothoracic dysostosis, assessment of recurrence risk in siblings, and provision of genetic counseling. In the postnatal period, early diagnosis facilitates physiotherapy to improve quality of life and increase lifespan. Additionally, surgical intervention can be performed for stabilization of chest wall and spinal deformities.

Keywords

Short stature, TBX6 Gene

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EP770

JOINT2279

A rare disease presented with bow legs

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Myhre syndrome is a multisystem progressive connective disorder with highly distinctive findings of craniofacial dysmorphism, short stature, joint limitation, restrictive lung and cardiovascular disease, progressive and proliferative fibrosis. We report a 3-year-old girl with Myhre syndrome. The girl was born full term with birth weight of 2705gram from a non-consanguineous Chinese couple. Antenatal Down syndrome screening, noninvasive prenatal testing and morphology scan were unremarkable. However, maternal grandparents were consanguineous. Among their 12 children, many suffered from congenital anomalies and succumbed. After birth, parents had no developmental concern. She walked at 11 months. Bow legs had progressively worsened since 15 months. When she was seen at 18 months, body length was 1.3cm below 0.4th centile, body weight at 9th centile, and head circumference at 50th centile. Clinical examination revealed facial dysmorphism – short palpebral fissures, hypoplastic maxilla, short philtrum, narrow mouth, prognathism and small ears. Skeletal examination showed brachydactyly, limited elbow and shoulder extension, genu varum with intercondylar distance measured 10cm, and waddling gait. Bone biochemistry revealed calcium 2.42mmol/l (2.15-2.55), phosphate 1.29 mmol/l (0.72-1.43), ALP 1358IU/L (130-330), total 25-hydroxyvitamin D 38nmol/l (30-49nmol/l mild deficiency), and parathyroid hormone 5.8pmol/l (1.6-6.9). Skeletal survey showed rickets features including metaphyseal fraying and spraying with rachitic rosary over costochondral joints. Other differential diagnosis included chondrodysplasia. There were no obvious features for other skeletal dysplasia or mucopolysaccharidosis. Urinary organic acid, plasma amino acid, serum free carnitine and acylcarnitine pattern were unremarkable. Urine glycosaminoglycan/creatinine ratio measured 27.7g/mol Cr (<29.9) and no pathological pattern detected by electrophoresis. In view of mild vitamin D deficiency, cholecalciferol 1000 IU daily was initiated and daily calcium intake of 500mg was ensured. As mild vitamin D deficiency could not account for craniofacial dysmorphism and joint limitation, genetic testing was arranged. Whole exome sequencing detected a de novo pathogenic heterozygous NM_005359.6(SMAD4):c.1486C>T p.(Arg496Cys) variant. This is a missense variant located in the MH2 domain of SMAD4 gene. Another de novo variant of uncertain significance heterozygous NM_018486.3(HDAC8):c.1133A>G p.(Ter378Trpext*16) was detected. This is a stop loss variant. Echocardiogram at 30 months was unremarkable. Developmental assessment at 42 months revealed a 9-month global developmental delay. Early education and training were continued. After 8-month vitamin D supplementation, bone biochemistry was mostly normal – calcium 2.56mmol/l, phosphate 1.67mmol/l, ALP 402IU/L, and total 25-hydroxyvitamin D 114nmol/l. Serial follow up demonstrated improvement in genu varum – intercondylar distance measured 5cm and 4cm at 24 months and 34 months respectively.

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EP771

JOINT3776

A case of spondyloepiphyseal dysplasia, kimberley type, caused by a novel variant in the ACAN gene

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Introduction

Short stature is a common reason for seeking medical attention in childhood. Clinical variability and genetic heterogeneity make it difficult to identify the underlying cause in a significant portion of patients. One of the genes associated with a wide phenotypic spectrum of non-syndromic short stature is *ACAN*. The aggrecan protein, encoded by the *ACAN* gene, is a major proteoglycan component of the extracellular matrix of cartilage. Aggrecan plays a critical role in maintaining the structure necessary for the function of joints. We present a clinical case of autosomal-dominant spondyloepiphyseal dysplasia type Kimberley, caused by a novel variant in the *ACAN* gene.

Materials and Methods

A 3-year-8-month-old boy was referred to us because of his short stature. Birth weight 3000 g, length 48 cm. Early development was without any issues. There is no family history of short stature. The mother's height is 164 cm, the father's height is 184 cm, and the target height is 181.5 cm (SDS of target height: +0.65 SD). Upon examination, the patient's condition was satisfactory. His height was 89.5 cm (SDS: -2.67), weight 12.5 kg (SDS BMI: -0.12), with a high forehead and relative macrocephaly. No instrumental data indicated a disruption in bone age.

Results

Molecular genetic testing was performed using a targeted panel for "Connective Tissue Diseases" via next-generation sequencing (NGS). A previously undescribed heterozygous variant was identified in the *ACAN* gene (NM 001369268.1): c.1793G>A, p.(Cys598Tyr), which was further validated by Sanger sequencing. Segregation analysis confirmed the variant as *de novo* in the family. Based on the ACMG pathogenicity criteria, the variant was classified as likely pathogenic and causal for spondyloepiphyseal dysplasia, Kimberley type with an autosomal-dominant inheritance pattern.

Conclusion

The polyetiological nature of short stature in pediatric practice requires expanded molecular genetic testing methods, such as targeted panels, whole-exome sequencing, and whole-genome sequencing. Identifying the causal variant allows for diagnosis verification, determination of further observation and treatment strategies for the patient and provides a health prognosis for the family.

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EP772

JOINT3354

Evaluation of factors that predict a good response to growth hormone treatment in patients with isolated growth hormone deficiency in first year of therapy - single centre study

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Introduction
Response to growth hormone (GH) treatment varies greatly not only between different conditions, but even between patients with same condition ("poor responders" vs. "good responders"). Many publications suggest that multiple factors influence response to GH treatment. Some studies have reported that body mass index, mid-parental height (MPH), bone age, height at the start of GH treatment and GH peak during provocative tests (insulin and L-DOPA test) are important factors for successful outcome of growth hormone treatment (rhGH) in children with isolated growth hormone deficiency (IGHD).
Objective
Aim of the study is to determine factors associated with better response to growth hormone supplementation during first year of therapy.
Methods
This was a retrospective analysis of 95 patients under the age of 15 years who were diagnosed with isolated GH deficiency using insulin and L- DOPA as stimulants, for assessment of GH secretion, and who received rhGH therapy for at least 1 year in the Pediatric Clinic of University Clinical Centre Nis between 01.01.2017- 01.01.2022.
Results
We collected data of 95 children (53 male and 42 female) with IGHD who had received rGH. The mean (SD) age at diagnosis and initiation of rGH was 10,31 ± 3,27 years, while the mean bone age was 8.59 ± 3.14 years. 44,2 % of patients were in prepubertal stage (Tanner 1). The Δheight SDS during the first year of GH treatment was correlated negatively with BMI SDS ($r = 0.017$, P 0,87), maternal height ($r = 0.70$, $P = 0.50$) and chronological age at the start of GH therapy ($r =$ 0,279, P 0,187), but positively correlated with bone age ($r = 0.926$,$P < 0.01$), paternal height ($r = 0.265$,$P < 0.01$) and target height ($r = 0.300$,$P < 0.01$). Also the patients were classified into two groups according to the peak GH values in the provocation tests (group I: peak GH < 3 µg/L, $n = 61$; group II: peak GH between 3 and 7 µg/L, $n = 34$). There was not a statistically significant association between the first-year HV SDS and the peak GH value in provocation tests in multiple regression analyses.
Conclusions
The present model to predict first-year response to GH treatment might allow more tailored and personalized GH treatment in prepubertal children with idiopathic GHD.

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EP773

JOINT763

Mauriac syndrome in a teenager with dual autoimmune disorders: a case report

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Introduction
Mauriac syndrome is a rare complication of poorly controlled long-standing type 1 diabetes mellitus (T1DM). It is characterized by hepatomegaly due to glycogen accumulation, growth failure and delayed puberty. We present a case of Mauriac syndrome in a patient with T1DM and coeliac disease, emphasizing this uncommon association.
Case Presentation
A 14-year-old male with a 5-year history of T1DM and a 2-year history of coeliac disease presented with recurrent severe hypoglycemic episodes over the past two months. Despite adhering to insulin therapy (0.6 IU/Kg/day) and maintaining a gluten-free diet, his glycemic control remained inadequate, with an HbA1c level of 8%. Upon admission, his venous blood glucose was critically low at 0.35 g/L. The patient exhibited significant growth and pubertal delays, with a weight of 38 Kg, height of 1.45 m (-2 standard deviations), body mass index of 18 Kg/m^2, and Tanner stage 1. Physical examination revealed hepatomegaly, with a liver span of 19 cm. Laboratory investigations showed mixed dyslipidemia (total cholesterol: 4.5 g/L [1.7–1.99], triglycerides: 2.8 g/L [1–1.5]) and elevated liver enzymes (ALT 3x ULN; AST 2x ULN). Other laboratory findings included normal coagulation profile, bilirubin, renal function, serum iron, hemoglobin, and ferritin levels. Autoimmune markers such as antinuclear antibodies, anti-LKM1, anti-smooth muscle antibodies, and anti-mitochondrial antibodies were negative. TSH and cortisol levels were within normal ranges, and viral hepatitis serologies were negative. Both insulin and C-peptide levels, taken during hypoglycemia, were suppressed (insulin:0.6 uUI/ml[4-23]; C-peptide: 0.02ng/ml[0.9-3.7]). Abdominal ultrasound revealed homogeneous hepatomegaly. A liver biopsy confirmed extensive glycogen deposition using periodic acid-Schiff (PAS) staining, leading to a diagnosis of Mauriac syndrome.
Conclusion
The simultaneous occurrence of Mauriac syndrome and coeliac disease poses a distinct challenge in diabetes management, complicating efforts to achieve optimal glycemic control. Although it is uncommon, Mauriac syndrome should be considered in patients with poorly controlled T1DM, particularly when symptoms such as hepatomegaly and growth retardation are present. Effective glycemic management is crucial for minimizing glycogen accumulation and hepatomegaly, which in turn improve growth and promote normal pubertal development.

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EP774

JOINT2430

Effects of growth hormone therapy in patients with prader-willi syndrome: the first algerian experience

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Introduction
Prader-Willi syndrome (PWS) is a rare genetic neurodevelopmental disorder resulting from the loss of expression of paternally inherited, imprinted genes on chromosome 15q11.2–q13.1. It is characterized by cognitive, behavioral, and endocrine abnormalities, including hypotonia, hyperphagia, obesity, short stature, and growth hormone (GH) deficiency. The estimated birth prevalence of PWS ranges between 1 in 15,000 to 1 in 25,000 live births.
Objective
This study aims to evaluate the effects of GH therapy on BMI and stature in Algerian children with PWS by comparing outcomes between GH-treated and untreated patients. We present a multicentric cohort of 46 children aged 0 to 16 years, providing the first Algerian data on auxological and metabolic outcomes in PWS.
Methods
This is a retrospective, multicenter study conducted across six Algerian hospitals (outpatient clinics) over 17 years (2007–2024). Data were collected from a national database, including medical records and endocrine profiles of children and adolescents diagnosed with PWS.
Results
The median age at diagnosis was 5.1 years (range: 0–14 years), with 7 patients (17.2%) diagnosed in the neonatal period. During the study period, three deaths (6.52%) were recorded, including two cases (4.34%) related to morbid obesity. At the most recent follow-up (median age: 6.1 years; range: 1–16 years), Median BMI was 23.48 ± 9.51 kg/m^2 (range: 11–56 kg/m^2). 65% of patients were overweight or obese, including 13% with morbid obesity (BMI > 40 kg/m^2). Glucose intolerance was detected in 4.34% of patients, and two cases (4.34%) developed type 2 diabetes. Growth hormone deficiency was diagnosed in 42 patients (93%), but only 11 patients (24.4%) received GH therapy. After one year of GH treatment, GH-treated patients showed a significant increase in height SDS ($+1$ SD height gain) compared to the untreated group ($p < 0.05$). GH-treated patients also exhibited a BMI reduction to 20.49 kg/m^2, whereas untreated patients experienced a progressive increase in BMI
Conclusion
GH therapy in children with PWS significantly improves height growth and helps regulate BMI, demonstrating a positive impact on growth and body composition. These findings emphasize the importance of early GH therapy initiation to optimize stature and reduce the risk of obesity-related complications in PWS patients. However, long-term studies are needed to further assess its metabolic benefits and potential risks.

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EP775

JOINT2957

The rare co-occurence of pituitary gigantism and thrombocytopenia!

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Background
Pituitary gigantism is a rare-yet important-disorder of GH axis leading to excessive height. It is usually due to over-secretion of GH by a pituitary adenoma occurring before epiphyseal closure. To date, several hematological diseases such as leukemia, thrombocytopenia, or Hodgkin lymphoma have been rarely reported in patients with pituitary adenoma, especially in acromegaly patients. The co-existence of the two diseases may be due to a common pathogenic mechanism or a co-incidence. However, the rarity of pituitary gigantism makes it difficult to establish the effect of elevated GH levels on platelet count.
Case Summary
A 14.75-year-old girl presented with increase in height noticed since 6 years and menorrhagia since 6 months. Her mid-parental height was 167.5 cm. Her parents were non-consanguineous and there was no family history of tall stature. At age 8 years, she was diagnosed with hypothyroidism (TSH 6.06 uIU/ml, fT4 1.59 ng/dl) , and started on L-thyroxine 50mic daily. On examination, her weight was 72kg (+1.63SD), height 187cm (+3.72SD), and BMI 20.6 (+0.18SD). Her arm span was 182cm. She had normal blood pressure, left precordial bulge with an ejection systolic murmur heard over the base of heart. She had enlarged jaw, hands and feet. She had no ecchymotic patches, purpura, or cafe-au-lait spots. Her investigations revealed thrombocytopenia (platelets 52.000) which had been persistent in previous blood counts. Her IGF-1 level was normal (256 ng/ml), however, GH suppression test by glucose load was not suppressible (least 1.14 ng/ml). Her bone age was 14 years. She had hyperprolactinemia (67 ng/ml), while her TSH was 1.64 mIU/ml, Ft4 1.48 ng/dl on L-thyroxine treatment with negative thyroid antibodies. Lupus markers were done to exclude autoimmune cause of thrombocytopenia (ANA, C_3, and anti-dsDNA) and were negative. Serum cortisol, ACTH were normal. Her MRI brain showed left-sided pituitary microadenoma (3X4mm) and echocardiography revealed wide atrial septal defect with mildly hypertrophied prolapsed mitral valve with grade II-III regurgitation. Her fundus examination was normal. She was started on cabergoline 0.25 mg twice/week, and long-acting octreotide (lanreotide) 30mg monthly to suppress GH and prevent further increase in height. L-thyroxine was stopped as investigations confirmed TSH-secreting adenoma rather than a primary thyroid disorder. Her platelet count increased after receiving octreotide.
Conclusions
Understanding the link between pituitary gigantism and thrombocytopenia may shed light into the pathophysiology of the disease and requires further studies. Hence, performing complete blood count as routine work-up in patients with pituitary gigantism is essential.

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EP776

JOINT2172

Response to recombinant growth hormone therapy in an indian girl with 3-M syndrome

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Introduction
3-M syndrome is a rare autosomal recessive disorder characterized by short stature, distinctive facial features, and skeletal abnormalities. Mutations in the *CUL7*, *OBSL1*, and *CCDC8* genes are associated with this condition. Short stature in 3-M syndrome has been attributed to growth hormone (GH) resistance rather than GH deficiency. GH resistance has been linked to impaired protein scaffolding, transport dysfunction, and p53-mediated apoptosis in the IGF-1 post-receptor pathway. Here, we describe the growth trajectory of an Indian girl with 3-M syndrome undergoing recombinant GH therapy.
Case Report
A 4-year-old girl, born to non-consanguineous parents, was delivered at term with a low birth weight (2300 g; -2.25 SDS) and length (46 cm; -1.69 SDS). She experienced birth asphyxia and required neonatal intensive care for 13 days. Antenatal ultrasound at 34 weeks had raised the suspicion of skeletal dysplasia. At birth, she exhibited characteristic features of 3-M syndrome, including a broad, fleshy nose, anteverted nostrils, thick patulous lips, a square chin, curvilinear eyebrows without synophrys and a short thorax. Radiographic features included slender long bones with diaphyseal constriction and flared metaphyses. Vertebral bodies appeared tall with reduced anterior-posterior and transverse diameter and anterior wedging of the thoracic vertebral bodies. Her ribs appeared to be horizontal. Pelvic bones were small and the iliac wings appeared flared. She had a delayed bone age, A clinical diagnosis of 3-M syndrome was confirmed after genetic testing, which revealed a compound heterozygous class 1 and class 2 variation in the *CUL7* gene. IGF-BP3 levels were normal. We did not perform a growth hormone stimulation test as she had a genetic diagnosis. Recombinant growth hormone therapy was initiated at 3 years of age, at a dose of 35 mg/kg/day. After 1 year of treatment, a height gain of 12 cm was observed, demonstrating a significant response to GH therapy.
Conclusion
This case highlights a notable height SDS increase over one year of follow-up in a child with 3-M syndrome receiving GH therapy. Clinicians should recognize the variability in GH response among individuals with 3-M syndrome and consider early intervention when appropriate.

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EP777

JOINT2277

A paediatric case of progeroid lipodystrophy due to a de novo mutation in POLD1 gene

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Background
POLD1 gene encodes the catalytic subunit of the DNA polymerase delta, an enzyme essential for genome replication and repair. Pathogenic mutations in the *POLD1* gene are responsible for Mandibular Hypoplasia, Deafness, Progeroid Features, and Lipodystrophy (MDPL) syndrome, a rare autosomal dominant disorder. The key clinical features are reflected in its name, with additional manifestations including joint contractures, prominent eyes, crowded teeth, small mouth, beaked nose, poor breast development in females, insulin resistance, diabetes mellitus, abnormal liver function, and hypertriglyceridemia. Here, we describe a new paediatric case of MDPL syndrome, focusing on her clinical features.
Clinical Case
A 5-year-old girl was referred to our Endocrinology Unit for growth delay. Her medical history revealed consistently normal but below-average growth, with a deceleration over the past year. At the first evaluation, height was below the genetic target (-2.26 SDS), with a BMI indicative of severe underweight (-5.21 SDS). She exhibited distinctive phenotypic features, including hypoplastic earlobes, thin nasal bridge, short philtrum, deep bite, clinodactyly of the fifth toes, bilateral ankle joint stiffness and reduced subcutaneous adipose tissue. Blood tests performed to investigate the growth failure resulted within normal ranges, with adequate IGF-1 levels. The Bone age X-ray findings were consistent with the patient's chronological age. During follow-up, she exhibited a further decline in BMI, increased joint stiffness and reported early signs of hearing impairment, confirmed by an audiological evaluation revealing bilateral sensorineural hearing loss. Given the clinical suspicion of a lipodystrophy syndrome, whole-exome sequencing was performed, identifying a de novo *POLD1* mutation and confirming the diagnosis of MDPL syndrome. The mutation consists of an in-frame deletion (c.1812_1814delCTC) of the serine residue at position 605 of the polypeptide chain, resulting in the complete loss of DNA polymerase activity. Metabolic blood tests revealed normal serum levels of leptin, cholesterol, triglycerides and transaminases. An oral glucose tolerance test ruled out insulin resistance.
Conclusions
Our case confirms that MDPL syndrome belongs to the highly heterogeneous group of lipodystrophy disorders. Moreover, this condition should be considered in the differential diagnosis of patients with growth delay, and early-onset hearing impairment. Progressive loss of subcutaneous fat, gradually occurring in late childhood, must be a mandatory criterion for diagnostic suspicion. Early identification of the genetic mutation allows for better management of symptoms and long-term potential complications. Additionally, this case highlights the value of whole-exome sequencing in diagnosing rare genetic disorders.

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EP778

JOINT3565

Case series on growth hormone deficiency: clinical and endocrinological insights

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Introduction
Growth hormone deficiency (GHD) is a pediatric endocrine disorder characterized by insufficient growth hormone production, leading to impaired growth. It can be congenital or acquired, with an estimated prevalence of 1 in 4,000 to 10,000 live births. Diagnosis involves clinical history, growth analysis, biochemical tests, and neuroimaging.
Case Series
The information of 9 cases with GHD was analyzed. Of these, 77.8% were male, with an average age of 11.4 years (7-15) and an average age at deficiency diagnosis of 9.44 years (5-14). A history of short stature was present in 55.4% of these patients, and somatometric evaluation identified an average familial target height of 167.7 cm (158-174) and a height at diagnosis with an average deviation of 11.1 cm below their genetic growth channel (4-19). Only 3 patients (33.3%) had undergone well-child check-ups for at least the first 12 months of life. The diagnosis was made through the measurement of somatomedin (IGF-1), which had an average value of 101.9 ng/ml (25-262). Brain magnetic resonance imaging (MRI) was performed in 7 patients (77.8%), and of these, only 2 cases (28.6%) showed anatomical abnormalities possibly related to growth hormone deficiency. In one case, an arachnoid cyst of the pituitary gland was observed, while in the other, a Rathke's cleft cyst was identified. All patients received treatment with recombinant human growth hormone (r-hGH) at an average weight-based dose of 1.22 IU/kg/week (0.77-1.85), with good adherence to treatment. At their last follow-up visit, their average height was 133.4 cm (109-151).
Discussion
This case series analyzes the clinical features, diagnostic methods, and treatment outcomes in pediatric patients with GHD, emphasizing the heterogeneity of its presentation. Neuroimaging was crucial in identifying structural pituitary abnormalities in some cases, while family history and classic clinical presentations enabled earlier diagnosis in others. Treatment with r-hGH showed positive outcomes in growth velocity and predicted adult height. Variability in treatment response based on the underlying cause of GHD pointing out the need for individualized approaches.
Final Comments
This study highlights the importance of a multidisciplinary, personalized approach to meet each patient's needs and provides insights into the challenges of managing GHD, paving the way for future research to optimize its diagnosis and treatment.

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JOINT14

SEENEZ trial: growth prediction model from mid-puberty to near-adult height in adolescents with idiopathic isolated growth hormone deficiency treated with growth hormone

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Background
Recombinant human growth hormone (rhGH) treatment in children with idiopathic isolated growth hormone deficiency (IIGHD) typically results in catch-up growth for several years followed by a period of normal growth. The efficacy of rhGH for late pubertal height gain in adolescents with IIGHD remains unclear.
Aims
This study aimed to develop and validate a model predicting height gain (cm) from mid-puberty to near adult height (NAH; height velocity <2cm/y) in IIGHD patients who were GH sufficient upon retesting at NAH.
Methods
For model development, data from the Dutch National Registry of Growth Hormone Treatment in Children were used, focusing on 151 patients with IIGHD (98 males, 53 females) who received rhGH treatment until NAH. Participants diagnosed with IIGHD (GH peak at diagnosis 1.7-10 µg/L) received rhGH treatment for a minimum of 2.5 years. GH peak was >10 µg/L upon retesting at NAH, with treatment discontinued for at least 1 month. Mid-puberty was defined for males as Tanner stage G3-G4, testicular volume >12 ml, and bone age (BA) 13-16 years, and for females as Tanner stage B3-B4 and BA 11-14 years. If no GH retest had been conducted, we used IGF-I >0 SDS after cessation of therapy and the pediatric endocrinologist's judgment to determine GH sufficiency. Validation was done in 33 males and 7 females from the prospective SEENEZ trial.
Results
In the model, final predictors at mid-puberty included age, BA, Tanner stage, and target height (TH) SDS minus height SDS at mid-puberty. Adjusted for overoptimism the equation for males was: 82.07 - 1.41 * Tanner stage 4 or 5 - 2.55 * age – 2.36 * BA + 2.33 * (TH SDS - height SDS). R^2 was 48%, residual SD was 4.16 cm. For females: 39.85 - 0.57 * age – 1.72 * BA. R^2 was 18%, residual SD was 3.64 cm. Validation analysis showed a mean (SD) difference of 1.48cm (2.36) for males and 3.57cm (2.66) for females between predicted and attained NAH.
Conclusions
This study developed a prediction model for height gain in adolescents with IIGHD during rhGH treatment in the final stages of puberty. For females, explained variance was insufficient to reliably predict height gain. For GH sufficient males, the model can be used to assess efficacy of continuing or discontinuing rhGH treatment at mid-puberty in prospective studies and to facilitate shared decision-making regarding treatment continuation at mid-puberty.

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EP780

JOINT3656

Short stature in short bowel syndrome: complex interplay between nutrition and growth

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Introduction
Short bowel syndrome (SBS) is a malabsorptive condition characterized by extensive intestinal resection. In pediatric patients, SBS can significantly impair growth and development, despite aggressive nutritional support, often resulting in short stature. Growth failure in these patients is multifactorial and may include nutritional deficiencies, chronic inflammation, and hormonal dysregulation. Insulin-like growth factor 1 (IGF-1) is a critical mediator of growth hormone (GH) action, responsible for stimulating cell growth, differentiation, and skeletal development. In intestinal failure, IGF-1 deficiency could occur despite normal or even elevated levels of GH. Understanding the contribution of IGF-1 deficiency to growth failure in SBS is crucial for developing effective management strategies.
Case description
A fourth-year-old girl presented with severe short stature. She is the daughter of a non-consanguineous couple. After an uneventful pregnancy, she was born at 35 weeks by vaginal delivery; her birth weight was 2390g (-0,25 standard deviation score [SDS]) and her length was 44cm (-0,76 SDS), with no apparent physical malformations. She was diagnosed with intestinal atresia and underwent surgery

on the 2nd day of life, resulting in SBS without ileocecal valve. She underwent multiple surgeries and gastrointestinal continuity was restored. At two years and 5 months she began Teduglutide (analog to glucagon-like peptide 2) and at the age of three years and 6 months stopped parenteral nutrition. Progressive growth delay was noticed since the first months of life, with important worsening in the previous two years. In the last appointment she had a height of 85,8cm (-3,8 SDS), with target height of 170,8cm (+1,45 SDS), and weighted 12,9kg (-1,8 SDS); there were no facial dysmorphism; systemic examination was also unremarkable; the bone age was 18 months. Laboratorial investigation revealed very low IGF-1 levels [12,4ng/ml (Reference value: 77-235ng/ml); normal thyroid and liver function; her karyotype was 46,XX. A GH stimulation test was performed, yielding normal results (peak 10,50ng/ml).
Discussion
Normal weight gain with low IGF-1 and normal GH levels points to the importance of the intestine' role in the endocrine growth system. The diagnosis of secondary GH insensitivity in pediatric SBS, may allow for IGF-1 or GH replacement therapy. This case highlights the need of a multidisciplinary approach due to complex interplay between nutritional factors, and endocrine function in pediatric patients with SBS and short stature. Early recognition and targeted interventions, including optimizing nutrient absorption and addressing hormonal deficiencies, are essential to improving growth outcomes in children with chronic gastrointestinal conditions.

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EP781

JOINT4040

Comorbidities in pediatric turner syndrome: differences between 45,X0 and mosaic karyotypes

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Introduction
Turner syndrome (TS) is associated with several phenotypic conditions that increase the likelihood of developing various comorbidities.
Objective
This study aims to assess the prevalence of congenital malformations and the development of age-related comorbid conditions and to compare whether these are different between 45,X monosomy and mosaic karyotypes.
Methods
Retrospective cohort study of patients with TS followed in a referral pediatric center in Portugal from childhood to early adulthood (1977-2024). The karyotype, the prevalence of cardiac and renal congenital malformations, and the prevalence of subsequent specific comorbidities were evaluated, including height and weight status, thyroid disease, menstrual irregularity, developmental delay/learning disabilities and hearing loss.
Results
69 patients were followed, with a mean age at diagnosis of 5 years (+/- 5.1), and a mean age at first appointment of 8 years (+/-5.2). Of these, 41 (59%) had a 45,X0 karyotype and the remaining had various types of mosaicism. Both congenital heart and renal malformations were more frequent in 45,X0 patients, represented by 41%, (28/69) and 25%, (17/69), respectively. The incidence of subsequent acquired conditions increased with age, more markedly in 45,X monosomy, with the following prevalences: 23% (16/69) thyroiditis, with 63% (10/16) in 45X0, followed by 45X046XX in 19% (3/16); 6% (4/69) overweight/-obesity, with 50% (2/4) in 45X046XX; 12% (8/69) menstrual irregularity, with 75% (6/8) in 45X0, followed by 25% (2/8) in 45X046XX; 25% (17/69) developmental delay/learning disabilities, with 59% (10/17) in 45X0, followed by 12% (2/17) in 45X046XX; and 4% (3/69) hearing loss, with 67% (2/3) in 45X0. All patients had short stature, and 75% started GH treatment at a mean age of 9 years and 5 months. Median Turner final height SDS was 0.86(IQR = 0.54-1.49) and median SDS for general population was -2.26(IQR = -3.3—1.3). Only two patients achieved target height.
Conclusion
Our findings indicate that Turner syndrome patients with a 45,X0 karyotype exhibit a higher prevalence of both congenital malformations and age-related comorbidities compared to those with mosaic karyotypes. These results highlight the importance of tailored monitoring and early intervention based on karyotype differences to improve clinical outcomes in Turner syndrome.

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JOINT505

Insights from IGF-1 generation test responses in growth disorders

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Background
The IGF-1 generation test evaluates the ability to produce IGF-1 in response to growth hormone (GH) stimulation, providing diagnostic insights into growth disorders. The variability of IGF-1 responses across different conditions highlights its utility in differentiating underlying pathophysiological mechanisms.
Objective of the Review
To summarize findings from studies investigating IGF-1 generation test responses across diverse growth disorders and assess its diagnostic and therapeutic implications.
Material and Methods
Data were synthesized from 16 studies involving over 1,200 pediatric patients with conditions such as GHD, Idiopathic Short Stature (ISS), Small for Gestational Age (SGA), Turner Syndrome (TS), Noonan Syndrome (NS), Thalassemia Major (TM), and chronic malnutrition. Studies reviewed included IGF-1 baseline levels, post-stimulation responses, and their correlation with GH therapy outcomes.
Results
Table:
1. GHD: Patients exhibited significantly reduced IGF-1 generation, confirming GH deficiency (Ghigo *et al*., 2000; Stanley *et al*., 2015).
2. SGA: Consistently reduced IGF-1 production due to intrauterine growth restriction was noted, persisting despite GH therapy (Boguszewski *et al*., 1995; Finken *et al*., 2006).
3. Turner Syndrome: Reduced IGF-1 responses indicated partial GH insensitivity, though GH therapy improved height outcomes (Rosenfeld *et al*., 1998).
4. Chronic Malnutrition: Impaired IGF-1 production was attributed to protein-energy malnutrition, even with normal GH levels (Bozzola *et al*., 1997).
5. ISS: Normal IGF-1 generation ruled out GH insensitivity as a contributing factor (Colle *et al*., 1999; Misra *et al*., 2012).
6. Thalassemia Major: Iron overload and nutrient deficiencies impaired IGF-1 generation, affecting growth outcomes (Soliman *et al*., 2009).
7. Noonan Syndrome: Mild GH insensitivity led to a blunted IGF-1 response, with GH therapy still showing growth improvement (Binder *et al*., 2005).
Discussion
The IGF-1 generation test provides critical insights into GH sensitivity and function across growth disorders. Reduced IGF-1 generation often correlates with GH insensitivity or systemic factors such as malnutrition or iron overload. Normal IGF-1 generation, as in ISS, helps exclude GH resistance as a primary cause.
Conclusions
IGF-1 generation tests are invaluable for diagnosing and managing pediatric growth disorders. While reduced IGF-1 responses often confirm GH dysfunction or systemic impediments, condition-specific variability necessitates individualized clinical interpretations.

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EP783

JOINT1263

Growth and pubertal outcomes in CHARGE syndrome: a case study of hormone replacement therapy

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Background
CHARGE syndrome is a rare genetic disorder characterized by a spectrum of anomalies, including coloboma, heart defects, choanal atresia, growth retardation, genital hypoplasia, and ear/hearing abnormalities. It is caused by mutations in the CHD7 gene and follows an autosomal dominant inheritance pattern. One of the primary features of CHARGE syndrome is hypogonadotropic hypogonadism (HH), leading to delayed or absent puberty in both males and females. Short stature is also common, affecting 60-72% of individuals, though the underlying mechanisms remain poorly understood.
Method
We reviewed the clinical data and investigations of a Romanian patient diagnosed with CHARGE syndrome who was admitted to our hospital in February 2024.
Case description
The patient exhibited multiple features of CHARGE syndrome, including cochlear implants, surgically corrected choanal atresia, left testicular atresia, and

right testicular orchidopexy. Whole-exome sequencing (WES) identified a heterozygous pathogenic variant, NM_017780.4:c.4695C>T, in the CHD7 gene, confirming the clinical suspicion and genetic diagnosis of CHARGE syndrome in 2020. At the time of consultation, the 14-year-old patient had a significantly below-average growth trajectory, with a height of -3.01 standard deviations (SD) and a developmentally small penis (-2.5 SD). Hormonal tests revealed low levels of FSH (0.53 mUI/ml), LH (<0.03 mUI/ml), and testosterone (0.14 ng/ml), indicating hypogonadotropic hypogonadism. His Tanner stage was also inconsistent with his chronological age, further confirming the diagnosis of HH. Two years prior, the patient's growth hormone levels were normal. However, recent stimulation tests indicated growth hormone deficiency. IGF-1 values were at the lower limit (-2.09 SD). As a result, hormone replacement therapy (HRT) with somatropin and Androgel was initiated. After seven months of somatropin treatment, his height improved from -3.01 SD to -2.68 SD. However, Androgel proved ineffective, prompting a switch to testosterone enanthate in January 2025. Following this change, the patient's penile length increased to 6 cm. Additionally, autoimmune thyroiditis was detected via ultrasound during his first consultation, although his thyroid function remained normal.

Conclusions

Individuals with CHARGE syndrome commonly experience delayed or absent puberty due to hypogonadotropic hypogonadism. Hormone replacement therapy, including growth hormone and testosterone, is essential for promoting growth and inducing puberty in these patients. Early intervention can improve outcomes, particularly in terms of physical growth and sexual development.

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EP784

JOINT3608

Our experience with somatrogon: therapeutic efficacy, adult height, safety and adherence

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Long-acting growth hormones (LAGH) constitute a therapeutic innovation in growth hormone deficiency (DGH). Its efficacy, safety, immunogenicity and bioavailability should be comparable to daily administered GH. With them it is expected to reduce the treatment burden, positively influence the quality of life of the patient and family, improve adherence and consequently therapeutic efficacy. Somatrogon, a LAGH, has been approved for use by the EMA and FDA in the child with GH deficiency.

Objectives

To evaluate the therapeutic efficacy, safety and adherence in a group of children diagnosed with GH deficiency treated with weekly LAGH (Somatrogon).

Methodology

Prepubertal patients diagnosed with GH deficiency and treated with Somatrogon. Clinical follow-up evaluating therapeutic efficacy criteria (variation of the SDS of height, relationship of height with target height, progress of bone age, puberty and adult height; safety (IGF1, IGFBP3, hormonal biochemistry, lipid and glycemic metabolism and AES) and adherence (through administration record).

Results

The follow-up during 6 years of 10 patients (2 girls and 8 boys) with GH deficiency treated with Somatrogon is presented. Five of them were initially treated with daily GH for 1 year and then continued with Somatrogon and another five from the beginning were treated with Somatrogon.

1. Therapeutic efficacy: All patients have increased their growth velocity, recovering their growth curve according to their genetic potential, with gains in height > 1SDS, with an evolution of bone age and sexual maturation according to chronological age.
2. Adult height: Four patients have reached adult height (AH), one girl with AH of 161.1 cm (SDS -0.16) and three boys with AH of 171.4 cm (SDS-0.63), 165. 7 (SDS -1.68) and 170.1 cm (SDS -0.71), respectively.
3. Safety: IGF1 levels have remained in the safe range and only in two patients, during puberty, a modification of the therapeutic dose was required. Without AES or local reactions relevant. Patients and families have expressed satisfaction with weekly administration.
4. Therapeutic adherence: It has been 100%.

Conclusions

Somatrogon (LAGH) has shown safety and efficacy in promoting linear growth in this patients group treated in our clinic. Similarly to daily GH in the treatment of GH deficiency; although with excellent adherence and less treatment burden. Four patients achieved adult height near their target height. LAGH are emerging as an innovative and safe treatment in the patient with growth hormone indication.

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EP785

JOINT1312

A post market observational study to evaluate user's perception on technology acceptance and usability of two generations of digital devices to manage growth disorders across france and spain

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Background

The Easypod® 3 auto-injector (Merck KGaA, Darmstadt, Germany) is the "third generation" of Easypod® (used to administer recombinant human growth hormone treatment [Saizen®, Merck KGaA, Darmstadt, Germany]) and represents a technological evolution of its predecessor Easypod® 2. Easypod® 3 introduces new functionalities as well as ergonomics and enhances the user interface.

Objective

To compare the technology acceptance and usability of Easypod® 3 with those of Easypod® 2.

Methods

This post market ongoing observational study included 48 valid survey responses collected from France between September 13–November 21, 2024, and Spain between November 20–December 2, 2024 (aim is to collect at least 100 complete survey responses across both countries by early April 2025). Eligible study participants were Easypod® 2 users who recently (< 6 months ago) transitioned to Easypod® 3, and who used the Easypod® 3 to administer injections for at least 2 weeks. Participants completed an anonymous online survey comprised of 25 questions related to device usefulness, ease of use and usability based on the Technology Acceptance Model (TAM, score ranged from 1–5 with 5 being the most positive response) and System Usability Scale (SUS, score range 0–100). Box design score was used to assess the facilitation of storing the device upright. Participants' satisfactions were measured using a Net Promoter Score (NPS, range -100 to +100).

Results

Overall, responses from 48 participants (France [$n = 34$] and Spain [$n = 14$]) were analysed. Participants perceived Easypod® 3 to be very useful compared to Easypod® 2 with a mean TAM rating of 4.05 (France 3.91 vs Spain 4.37), and very easy to use with a mean TAM rating of 4.21 (France 4.13 vs Spain 4.41). Usability was rated excellent for Easypod® 3. with a mean SUS score of 81.46 (France 83.9 vs Spain 75.54). Participants preferred Easypod® 3's box design for facilitating upright storage of the device with a mean rating of 3.85 (France 3.79 vs Spain 4). Overall, Easypod® 3 received a very high NPS of 65 (France 59 vs Spain 79).

Conclusions

This interim analysis suggests that users' perceptions of Easypod® 3 from both technology acceptance and usability perspectives are overall positive compared to their perceptions of its predecessor Easypod® 2. The study will continue till 100 complete survey responses across both countries are received.

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EP786

JOINT2215

Neurofibromatosis type 1 revealed through growth delay: a case report

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Introduction
Neurofibromatosis type 1 (NF-1) is one of the most common inherited disorders. Incidence of NF1 is approximately 1 in 3000 individuals globally with some variations across the globe. One of the most common endocrine disorders in NF1 are short stature with or without growth hormone deficiency. Here, we report the case of two brothers in whom GH deficiency revealed NF-1.
Case Report
The first case, an 11-year boy without medical history was referred for harmonious growth delay. Physical exam was remarkable for multiple café-au-lait spots (more than six spots) and lentigines, height and weight were less than -2DS. Biology revealed a GH deficiency and subclinical hypothyroidism. Brain MRI revealed the presence of unidentified hyperintense objects in the bipallidal and cerebellar regions without other significant anomalies. GH therapy and thyroid hormone substitution were initiated with close endocrinological surveillance. The second case, the brother a 10 years-old boy without any medical history, was referred for short stature. Physical exam revealed harmonious growth delay with height and weight were less than -2DS and cutaneous exam showed multiple café-au-lait spots and lentigines. Biology revealed a GH deficiency and subclinical hypothyroidism. Brain MRI revealed ventriculomegaly without aqueductal stenosis and showed the presence of unidentified hyperintense objects in the bipallidal and cerebellar regions. There was also a borderline-sized anterior pituitary gland, a Rathke's pouch cyst and cortico-subcortical atrophy. Ophthalmologic examination revealed the presence of Lisch nodules and Yasunari spots, a pathognomonic signs of neurofibromatosis type 1, confirming the diagnosis. GH therapy was initiated with close endocrinological and neurological follow-up.
Discussion
Short stature with or without Growth hormone deficiency (GHD) is well-known as a clinical feature of NF1, but rarely reveals the disease. The GHD is more common in children with NF1 compared to the general population. The cause of GH deficiency in NF-1 is not clear, it can be observed in intracranial tumors, due to tumor treatments or without any organic pituitary damage. Patients with NF1 are at higher risk of developing tumors than the general population, thus healthcare providers must recognize its diverse manifestations for timely diagnosis and optimal care.
Conclusion
Clinical manifestations of NF1 must be detected in the early pediatric age. Patients require frequent long-term follow-ups by several specialists for early identification of endocrinopathies, emphasizing the importance of a multi-disciplinary team approach.

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EP787

JOINT3875
Short stature due to ADAMTSL2 variant as a rare cause of geleophysic dysplasia: growth hormone had no role in treatment
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Background
Geleophysic dysplasia is a progressive skeletal disorder that mimics lysosomal storage diseases. It is characterized by short stature, brachydactyly, progressive joint contractures, distinctive facial features (including a "happy face" with full cheeks, hypertelorism, and a prominent philtrum), progressive cardiac valvular disease, and thickened skin. Intellectual development remains normal. The disorder is inherited in an autosomal recessive manner when caused by biallelic pathogenic variants in **ADAMTSL2** or in an autosomal dominant manner when caused by heterozygous pathogenic variants in **FBN1** or **LTBP3**.
Case Presentation
We report a case series of three Palestinian sisters and their cousin, all born to consanguineous parents, presenting with short stature, brachydactyly, lordosis, and delayed bone age. Initially diagnosed with idiopathic short stature, they were treated with growth hormone (GH). Whole-exome sequencing confirmed a homozygous **c.475C>T (p.Arg159Trp)** variant in **ADAMTSL2**, resulting in abnormal protein translocation.

- **Patient 1 (20 years old):** Final height 148 cm (-2.4 SD); received GH for 2 years, discontinued at bone age 14 years.
- **Patient 2 (15 years, 10 mon old):** Final height 150.2 cm (-1.7 SD), completed puberty; received GH for 4 years until bone age 13 years, 6 months.
- **Patient 3 (10 years, 4 mon old):** Current height -2.4 SD; received GH from bone age 5 years to 10 years, with height increasing from 106 cm to 124 cm. Echocardiography revealed mild aortic stenosis.
- **Cousin (12.5 years old):** Height -3.5 SD, mid-puberty, with delayed bone age (by 1.5 years). Did not receive GH and underwent bicuspid aortic valve repair for severe stenosis.

Conclusion
Despite GH treatment, the three sisters exhibited growth patterns inconsistent with expected parental height, and the youngest demonstrated similar growth velocity before and after GH discontinuation. Their cousin, who did not receive GH, exhibited a similar phenotype. These findings suggest that GH therapy had no significant impact on final height in individuals with **ADAMTSL2-related** geleophysic dysplasia, emphasizing the need for alternative management approaches.

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EP788

JOINT1830
Access to growth hormone treatment for short stature children with noonan syndrome-the experience of the Wroclaw centre, poland
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Introdution
Noonan syndrome (NS) is a clinically heterogeneous and autosomal dominant disorder which occurs with a frequency of 1: 1000 - 1: 2500 live births regardless of gender. The most characteristic clinical features are: short stature, congenital heart defects, numerous and various dysmorphic features, as well as deformities of the chest, skeletal and urogenital system as well and coagulation disorders disturbances. Psychomotor development as well as intellectual disability may be delayed.
Aim
The aim of this study was to analyse the availability of growth hormone treatment for children with Noonan syndrome in the Lower Silesia region.
Methods
The histories of 53 children were analysed consulted at the Genetic and Endocrinology Clinics for Children of the University Clinical Hospital in Wrocław, Poland who were diagnosed with Noonan syndrome confirmed by genetic testing.
Results
Between 2000 and 2024, 53 children were diagnosed with Noonan syndrome at the Genetic Outpatient Clinic of the University Clinical Hospital in Wrocław. Treatment with rhGH was implemented in a total of 10 children (19%), in 5 of them within the framework of available drug programmes (min.: drug programme for growth hormone deficiency, SGA or IUGR), in 1 child the treatment is carried out from the parents' own resources, 4 children started treatment within the framework of a clinical trial in other centres in Poland. Nine children remain in observation - 17% (observation of growth rate with growth $>=$ 3 c, age less than 4 years). Diagnosis of possible growth hormone deficiency in 4 children is currently ongoing. No adverse effects were observed in any case of rhGH use. All children underwent a cardiology consultation with ECHO evaluation of the heart to exclude hypertrophic cardiomyopathy.
Conclusions
Despite current global data demonstrating the efficacy and safety of rhGH treatment, only a small proportion of children with NS in Poland have access to this therapy. The inclusion of a larger group of patients requires changes to the current drug programme for rhGH in Poland

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EP789

JOINT849
Use of CGMS to identify early glucose changes in patients on growth hormone therapy
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Introduction
Growth hormone is used to treat patients with a variety of growth disorders. A common side effect of growth hormone therapy is hyperglycemia. Monitoring for hyperglycemia in patients on growth hormone therapy is done via HbA1C. However, the exact timing of the changes in glucose levels experienced by high-risk patients on growth hormone therapy has not been widely studied. Insight into the glucose levels in these patients can help providers to manage hyperglycemia

earlier in the course of treatment. The advent of Continuous Glucose Monitoring Systems (CGMS) allows patients to be able to obtain real time glucose data at multiple time points.
Objectives and hypotheses
To use CGMS to monitor glucose levels in high-risk patients on growth hormone therapy to identify early changes in glucose levels. Also, to assess if there are differences in glucose patterns in high-risk patients on daily vs weekly growth hormone therapy.
Methods
FreeStyle Libre 3 CGM will be used to monitor glucose levels in high-risk patients on growth hormone therapy. High risk patients would be defined as patients with BMI > 86%; those with family history of Type 2 DM and those with baseline elevated HbA1C (above 5.6%). At risk patients would have a CGMS placed to monitor glucose levels. Those with noted abnormal glucose levels would then have another CGMS placed 2 months after interventions to look for improvement in glucose levels. Hba1C would continue to be monitored as per standard of care. Data will be stratified by risk factors and whether patient used daily vs weekly growth hormone.
Results
Preliminary results on a patient with family history of Type 2 DM and an increase in Hba1C from 5.7% to 6% was placed on CGMS. CGMS data showed glucose levels as high as 178 mg/dL with multiple times where the blood glucose levels were above 140 mg/dL. Data is currently being collected from additional patients on growth hormone therapy.
Conclusions
The data obtained from this study can demonstrate that the use of CGMS to monitor at risk patients on growth hormone therapy can help providers to identify changes in glucose levels earlier, allowing them to make changes in management before there are significant changes in Hba1C. It will also help to examine whether there are differences in glucose patterns in daily vs weekly growth hormone formulations. The data obtained in this study could lead to changes in the management of patients on growth hormone therapy.

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EP790

JOINT2071

Growth hormone therapy in montenegro over two decades

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Background
Growth hormone (GH) therapy is widely used among children with short stature, and in Montenegro it is approved for five indications (GH deficiency (GHD), Turner Syndrome (TS), being born small for gestational age with failure to attain normal growth (SGA), Prader-Willi Syndrome (PWS) and chronic renal disease (CKD)). This study aims to present the structure and outcomes of children treated with growth hormone in Montenegro.
Methods
This cross-sectional retrospective study included children (age < 18 years) with short stature treated with GH between January 2005 and Decembre 2024, followed at the Institute for Children's Diseases, Clinical centre of Montenegro (centre of reference).
Results
A total of 221 children received GH therapy during the observed period of whom 52% ($n = 115$), were boys. Clinical indications were GHD ($n = 69$, 31.2%), SGA ($n = 123$, 55.7%), CKD ($n = 12$, 5.4%), TS ($n = 15$, 6.8%), and PWS ($n = 2$, 0.9%). Median of age at GH initiation was 9.7 years. Mean age at GH initiation based on indications were 11.8 years (± 3.7) for GHD, 8.3 years (± 3.2) for SGA, 7.0 years for CKD (± 5.4), 8.4 years (± 3.1) for TS and 5.4 years (± 1.4) for TS. Mean height SDS at baseline was -2.89 $\pm$ 0.72, comparable among all groups but worse for PWS. The youngest patient in our cohort was 17 months old, and the oldest at the GH initiation was 16.7 years. The responses after 3 years persisted (Mean height SD gai$n = 1.1 \pm 0.8$).
Conclusion
Being born small for gestational age with failure to attain normal growth is the most common indication from treatment in our country, which is inconsistent with international surveillance data, where GHD is predominant. Our results also point out the need to develop national growth charts to define appropriate birth length and weight due to gestational age.

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EP791

JOINT1719

An atypical case of a patient with prader-willi syndrome- difficult diagnostic pathway

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Introduction
Prader-Willi syndrome (PWS) is a multiorgan neurodevelopmental disease, caused by parental genomic imprinting disorder in 15q11-13 region.
Aim
We present an atypical clinical picture and diagnostic difficulties in a 5.5-year-old girl with PWS.
Case report
A girl born from GVI (2xspontanous miscarriages), by caesarean section in 35 Hbd because of IUGR and worsening of the foetal state, with birth weight 1160g (-4.9 SD), length 41cm (-2.6 SD), 8-9 points of Apgar score. She required nCPAP and feeding by a gastric tube from 5th day until 3 months of life. Results of karyotype, routine method, and aCGH were normal. At the age of 1.5 years short stature and low weight, hypotonia, strabismus, dolichocephalic shape of a head, downturned mouth corners, narrowing fingers, slight clinodactyly of the IV and V toes were observed. Silver-Russell syndrome and PWS were considered, multiloci methylation analysis (MLID) was performed, the results showed normal methylation pattern in analysed loci. At the age of 3.5 years there were still significant short stature (-5.5 SD) and low weight (-3.8 SD), head circumference -3.5 SD, BMI -2.5 SD, legs circumference asymmetry R > L. Due to the phenotype suggesting PWS, methylation analysis of 15q11-13 region was performed and showed abnormal *SNRPN* and *MAGEL2* methylation pattern, that allowed to verify the MLID result and diagnose PWS. The microsatellite sequence analysis showed chromosome 15 maternal disomy (mUPD15). Further analysis of 14 loci showed mUPD in 3, 3 alleles present in 1 locus (2 maternal, 1 paternal) and non-informative results in other loci. Additional tests revealed 1.5 year delay of bone age and normal IGF1 level. The rhGH treatment was started 4 months after the diagnosis with the increasing dose from 0.47 to 0.74 IU/kg/wk, with improved growth velocity from 4.8 to 9.6 cm/yr, muscle tone and psychomotor development. After 1.5 year height is at the level -4 SD, weight -2.7 SD, head circumference -3.1 SD, BMI -1.8 SD, appetite has not been increased. Family history revealed the patient's two older brothers have started rhGH treatment because of GHD. Due to unclear reason of deep pre- and postnatal short stature NGS examination was performed with no pathogenic/potentially pathogenic variants identified. A comparative WES study in siblings is considered.
Conclusions
Aimed molecular diagnostic tests and sometimes repeating/widening diagnostics in unclear clinical settings are needed. The results of the studies to date do not explain the cause of such significant growth retardation in our patient.

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EP792

JOINT2813

Bridging the treatment gap: growth hormone therapy for noonan syndrome in portugal

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Introduction
Noonan Syndrome (NS) is characterized by distinctive facial features, congenital heart disease, and short stature. Clinical presentation is highly variable, often leading to delayed diagnosis, which is sometimes only confirmed when affected family members exhibit more severe manifestations. NS is a relatively common cause of short stature, which may or may not be associated with growth hormone (GH) deficiency. In Portugal, NS is not yet an approved indication for GH treatment.

Case Report
We describe a family with at least two generations affected by NS. Two siblings from a fraternal set of three were referred to a Pediatric Endocrinology consultation due to short stature and suspected NS. Their father underwent GH treatment during childhood, although the underlying etiological study is unknown, and he reached a final height of 158 cm (SDS). The index case is the eldest daughter, a 3-year-old girl born with facial dysmorphisms, astigmatism, and motor coordination difficulties. Clinical evaluation highlighted severe short stature (-3.73 SDS) and distinctive facial features, including a high forehead and low-set ears. Her 2-year-old brother presented with pulmonary valve stenosis, patent foramen ovale, scoliosis, and similarly severe short stature (-4.54 SDS), with comparable facial features. Both had normal birth measurements. Analytical studies showed low IGF-1 levels, but GH stimulation tests demonstrated an adequate response. Genetic testing, including a familial segregation study, identified a heterozygous variant in the PTPN11 gene, likely pathogenic and consistent with their phenotypes. Since neither case presented a confirmed GH deficiency, GH therapy is not currently approved, and both children remain under periodic follow-up.
Discussion
NS is associated with short stature in approximately 50-70% of cases, either due to GH deficiency or dysfunction of the GH/IGF-1 axis. In this family, the father was unaware of his diagnosis, likely due to mild clinical manifestations aside from short stature. Given that NS is primarily inherited in an autosomal dominant manner, parental genetic testing is crucial for identifying other potentially affected relatives. As with Turner Syndrome, early initiation of GH therapy appears to improve final height outcomes. However, in Portugal, GH treatment is not yet approved for children with NS without confirmed GH deficiency. Considering the significant impact of short stature on future well-being, it is imperative that this indication grants approval for fully reimbursed GH treatment in our country.

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EP793

JOINT3681

Genotype-phenotype correlation of endocrine comorbidities in turner syndrome

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Background
Turner syndrome (TS) is a female genetic disorder that affects approximately 1 in every 2,000 baby girls. Genotypically, it can be classified based on karyotype, such as monosomy, abnormal X chromosome, and mosaics.
Objective
To study the genotype-phenotype correlations of endocrine comorbidities in adult TS patients.
Patients and Methods
A retrospective descriptive study of patients with TS followed at the University Hospital Center in Sousse. Data analysis was performed using SPSS23 software and non-parametric tests.
Results
A total of 33 patients with a mean age of 25.6 ‡ 10.6 years were enrolled. Chromosomal abnormalities were categorized as monosomy X in 54.4%, structural abnormality alone in 18.2%, and monosomy with structural abnormality in 27.3%. The age at diagnosis of TS was 16.52 # 5.71 years for patients with homogeneous chromosomal abnormalities and 16.16 ‡ 7.81 years for those with mosaic abnormalities. Schooling was more advanced in mosaic patients. Statural delay was slightly more frequent and more severe in patients with homogeneous anomalies, though no statistically significant difference was found ($P = 0.61$). The age of onset of premature ovarian failure was higher in mosaic patients (19.50 vs. 17.37 years), with no statistically significant difference compared to patients with homogeneous anomalies ($P = 0.14$). In the case of mosaicism, diabetes mellitus was more frequent (type 2 in all patients), with a later age of onset (23.67 vs. 17.50 years). Obesity was equally distributed between the two groups. The homogeneous chromosomal anomaly was more likely to cause frank hypothyroidism than other anomalies ($P = 0.04$).
Discussion
TS patients present different karyotypes, including monosomy, mosaicism, and abnormal X chromosomes. Karyotype variations might affect the phenotype of TS according to the type of chromosomal abnormality. Chromosomal analysis for all suspected cases of TS should be promptly performed during childhood to facilitate the establishment of an appropriate management plan early in life.

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EP794

JOINT2044

Role of molecular investigation for diagnosing short stature: a case report of a variant in the COL9A3 and UBA5 genes

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Introduction
Eighty percent of the height variation is explained by genetic factors, even though the standard medical evaluation of short stature (SS) relies upon physical examination and laboratory parameters and identifies a pathological cause of SS in 1–40% of individuals. This research aims to report a clinical case of a child with SS who underwent molecular investigation.
Case Report
HAS, 9 years 9 months, only daughter of a non-consanguineous couple, sought the pediatric endocrinology service complaining of SS. The child was a newborn with adequate weight and height for gestational age, with a slow growth speed from the second year of life. On physical examination, she presented: weight 18.5kg (-3.2SD), height 120cm (-2.64SD), syndromic features characterized by microcephaly (PC 45cm), epicanthus, broad nasal base, pointed and low-set ears and tooth agenesis. General laboratory tests were unremarkable; the Clonidine stimulation test was responsive (9 ng/ml), and bone age was 8 years and 10 months. A Generation Sequencing Panel for the complete exome was carried out, which showed a variant of uncertain significance (VUS) in heterozygosity in the *COL9A3* and *UBA5* genes. She started using GH at the age of 10 years 9 months, and at 11 years 11 months, she weighed 24.8 and had a height of 136.5 (-2.07SD), still without puberty signs and with normal intelligence.
Discussion
The *COL9A3* gene encodes one of the three alpha chains of Type IX collagen. Patients with variants in homozygous present with Stickler syndrome, characterized by midface hypoplasia, myopia, hearing loss, and epiphyseal abnormalities. Patients with heterozygous mutations are reported to have multiple epiphyseal dysplasia type 3. The *UBA5* gene encodes Ubiquitin-Like Modifier Activating Enzyme 5. Mutations in this gene can cause developmental and epileptic encephalopathy 44, which presents with the following symptoms: short stature, microcephaly, visual impairment, mental and motor impairment, seizures, and cerebellar atrophy. The conjunction of the two VUS in the aforementioned genes may justify the unique clinical case of this patient and was essential for the report that convinced the government of the state of Goiás to make GH treatment available to this child. Furthermore, the molecular diagnosis in cases of SS can end the diagnostic workup for the patient, it may alert the clinician to other medical comorbidities for which the patient is at risk, and it is extremely valuable for genetic counseling.

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EP795

JOINT2470

Growth hormone treatment in children with growth hormone deficiency: searching for predictors affecting adult height

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Introduction
Growth hormone (GH) stimulation tests that are used as a golden standard for diagnosis of GH deficiency (GHD) are known to have poor reliability. Children with diagnosed GHD are therefore believed to have heterogeneous etiology of their short stature and consequently heterogeneous response to GH treatment. The aim of the study was to analyze the response to GH therapy in a single center cohort and to search for the factors predicting treatment outcomes.
Methods
Children treated with idiopathic GHD in our center that achieved their final height in years 2022-2024 were enrolled to the study. The diagnosis of GHD was made according to the current guidelines, maximal stimulated concentration of GH (GH_{max}) <10 mg/l in both clonidine and insulin hypoglycemia tests were used to confirm the diagnosis. To search for factors affecting response to GH treatment, correlation analysis and ANOVA Kruskal-Wallis test were used for continuous

and categorical variables, respectively. P-values <0.05 were considered significant.
Results
In total, 138 children diagnosed with GHD and available final height were enrolled to the analysis. At GH treatment initiation, their median age was 6.1 years (IQR 4.1-7.8 years), height-SDS -2.8 (-3.2 to -2.5), IGF-1-SDS -1.5 (-1.8 to -1.1) and GH_{max} 5.9 (4.5-7.6) mg/L. Sixteen children had combined pituitary hormones deficiency (CPHD), 11 anterior pituitary hypoplasia and 26 more severe abnormal cerebral midline anatomy on MRI. The children were treated with GH for 8.8 (7.2-10.6) years with an average dose 31 (24-33) mg/kg/day. The height SDS increased by 1.3 (0.8-1.9) SD to an adult height -1.5 (-2.1 to -0.9) SD. The height SDS improvement showed a weak correlation with maximal stimulated GH concentration (correlation coefficient [CC] -0,21; $P = 0.014$). Children with GH_{max} <3 mg/L showed better height SDS improvement compared to those with GH_{max} ≥ 3 mg/L (2.3 vs 1.3 SD, $P = 0.008$), but, interestingly, no correlation between GH_{max} and height SDS improvement was found in children with GH_{max} >3 mg/L (CC 0.06, $P = 0.51$). Furthermore, height SDS gain weakly correlated with pre-treatment IGF-1 concentration (CC -0,24; $P = 0.006$) and was higher in children with CPHD ($P = 0.0009$). No correlation between effect of GH treatment and birth parameters, parents' height and brain MRI was found.
Conclusions
Height outcomes following GH treatment in children with idiopathic GHD had great interindividual variability. Better treatment outcomes were associated with lower GH_{max} and pre-treatment IGF-1 concentration and presence of CPHD. No correlation between height improvement and GH_{max} beyond 3 mg/L was observed.

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EP796

JOINT1625

Enhancing paediatric care: insights from healthcare professionals on the quality and usability of digital devices in a participatory workshop in Korea

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Background
Integration of digital health technologies with growth hormone therapy (GHT) has transformed the care and management of paediatric patients with growth hormone deficiency (GHD). Digitalisation of healthcare systems has improved patient adherence and facilitated more effective therapeutic monitoring and support from healthcare professionals (HCPs), which are vital to patient care.
Aim
This study aimed to assess the perceived quality of digital health devices used to support paediatric GHT and evaluate the perceptions of HCPs regarding the evolution of health device technologies.
Method
A participatory workshop was conducted on 10 November 2023 in Seoul, Republic of Korea, to explore the perceptions of HCPs regarding digital health devices for paediatric GHT. Two case studies were conducted using two sample devices: Easypod® autoinjector and Easypod® connect transmitter (EP2) and its successor—Easypod® next generation (EP3). The HCPs were allowed to interact with both devices. The workshop comprised of five phases that addressed device ergonomics, configuration tasks and facilitated discussions on dimensions of the quality of an mHealth solution such as usability, safety, and perceived usefulness. Participants identified the strengths and weaknesses of the devices, providing valuable insights into the evolution of health device technology and its impact on paediatric care.
Results
The HCPs believed that the evolution of mHealth technology has positively impacted the perceived quality of digital health. Ergonomics was indicated as a crucial factor in device quality and acceptance. The HCPs favoured EP3 over EP2 because of its improved dimensions, larger screen, and better button design. EP3 was considered more suitable for paediatric patients due to its automatic data transmission features, which allows personalised treatment and improves patient adherence. Although both EP2 and EP3 were considered easy to use, EP3 was preferred because of its superior user interface, skin sensor, and monitored dosing, which tracks the injections performed and the set dose, thereby preventing drug wastage. Additionally, EP3 received positive feedback for its safety and security features and was considered like current smartphones in terms of usability. Discussions also covered the content, engagement, support, and technological evolution of devices used in paediatric GHD management.
Conclusion
The outcomes of this workshop highlight the significance of technological advancements in the management of paediatric GHD. The HCPs acknowledged that the digitalisation of GHT would benefit their clinical practices, optimise resources, and personalise care for paediatric GHD including patient preferences and self-management. This will also enhance HCP-patient communication, thereby improving adherence and patient-caregiver satisfaction.

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EP797

JOINT1430

Efficacy and safety of three-years growth hormone treatment in girls with turner syndrome and growth hormone deficiency: a case-control study

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Turner Syndrome (TS) is a chromosomic disorder characterized by specific clinical features, including short stature. In these patients, recombinant growth hormone (GH) treatment is recommended, showing positive effects on growth rate, with good tolerability. However, growth outcome in TS is reportedly impaired compared with other GH-treated girls, as GH deficiency (GHD) girls. The aim of the study was to compare the growth outcome and the safety of three-years GH treatment in TS and GHD girls. The study 20 girls, 10 with TS (four X0, 40%; six mosaicism, 60%) and 10 with isolated GHD, matched for age (range: 4.17-10.42 years; median: 6.8 $\pm$ 2.37) treated with GH (starting dosage: 33.08 $\pm$ 4.31 mg/kg/day in TS girls and 32.17 $\pm$ 2.51 mg/kg/day in GHD girls) for at least 36 months. Growth parameters, glycemic profile, and IGF-1 levels were collected every six months. Compared to baseline, both TS and GHD children showed a significant improvement in height, weight, and growth rate after two years of GH treatment ($p \leq 0.01$), already evident after six months ($p \leq 0.016$). Noteworthy, patients in both groups showed a constant, significant improvement in height until 24 months, as a significantly increase was observed both after 12 months compared to six months ($p \leq 0.008$) and after 24 months compared to 12 months ($p \leq 0.031$), whereas only GHD girls showed a significant increase after 36 months compared to 30 months ($P = 0.035$). Comparing the two study groups, TS girls showed a lower height and a lower height increase throughout the study, but these differences reached statistical significance only after six and 12 months (T6: $+0.42 \pm 0.23$ SDS in TS vs $+0.74 \pm 0.38$ SDS in GHD, $P = 0.045$; T12: $+0.59 \pm 0.34$ vs $+0.93 \pm 0.39$ SDS in GHD, $P = 0.034$). Considering safety profile, treatment was well tolerated, as the most frequently reported adverse event was autoimmune thyroiditis (two TS girls, 10%); no hyperglycemia occurred throughout the treatment, whereas one TS girl (5%) and one GHD girl (5%) experienced transient hypertransaminasemia and hypercholesterolemia, respectively. In conclusion, GH treatment in both TS and GHD girls is an effective, safe treatment for short stature, improving both height and growth rate, especially during the first year of treatment. Moreover, although growth outcomes were significantly better in GHD girls in the first year of treatment, over time no significant differences were observed between TS and GHD girls

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EP798

JOINT2549

Juberg-Marsidi syndrome coexisting with multihormonal hypopituitarism - a case report

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Juberg Marsidi syndrome (ORPHA:93972) is a rare X-linked recessive disorder characterized by severe intellectual disability, growth failure, sensorineural deafness, and hypogonadism. The full picture of the syndrome is revealed in men, but in the presence of a heterozygous variant of the *HUWE1* gene in women, the symptoms may be milder. The case of a three-year-old girl who, in addition to with Juberg-Marsisi syndrome and panhypopituitarism was described in presented report. The child was born from 1st pregnancy, complicated by threatened miscarriage, born prematurely at 33 weeks' gestation, with a body weight of 1860 g. The adaptation period was complicated by bleeding into the lateral ventricles. Psychomotor development was delayed, which was explained by prematurity and initially increased, followed by decreased muscle tone. At the age of 10 months, due to delayed psychomotor development, the girl was consulted by an endocrinologist for the first time. Secondary hypothyroidism was diagnosed and treatment with levothyroxine was initiated. The physical

examination revealed significant growth deficiency, global decreased muscle tone, abnormal body proportions in the form of shortened long bones of the limbs, small feet, varus deformity of the lower legs, as well as dysmorphic facial features: high forehead, hypotelorism, small palpebral fissures, and flat nasal bridge. There was a history of patent foramen ovale. The hearing test was normal. Despite the girl's multi-profile intensive rehabilitation and satisfactory correction of thyroid function, a significant delay in psychomotor development is still observed (the child still does not walk at the age of three years, has started crawling, sits up independently from about 24 months of age), and speech development is significantly delayed (speaks single syllables). Episodes of "suspension" were observed in the child, especially during prolonged fasting. The glycemic profile showed glucose concentrations <60 mg/dl several times. Adrenal function was normal. The girl was diagnosed with somatotropin hypopituitarism and treatment with growth hormone was requested. In summary, the girl, apart from the symptoms of the genetic syndrome, presented typical symptoms resulting from multihormonal hypopituitarism, which should result in an early diagnosis of pituitary function and implementation of appropriate treatment. Treatment with growth hormone in a child with somatotropin hypopituitarism and co-occurring decreased muscle tone may contribute not only to the promotion of growth, but also to increased muscle strength.

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EP799

JOINT506

Circulating IGF-1 levels and trends in response to daily and weekly gh therapies: a comparative analysis

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Background
Insulin-like growth factor 1 (IGF-1) is a key marker of growth hormone (GH) activity, with its levels reflecting the efficacy and safety of GH therapies. Daily recombinant human GH (rGH) therapy provides steady IGF-1 levels, whereas long-acting weekly GH formulations (e.g., somapacitan, TransCon GH) show dose-dependent, cyclical IGF-1 responses. Understanding these patterns is crucial for optimizing treatment efficacy and safety.
Objective
To compare IGF-1 trends and cycles associated with daily and weekly GH therapies in terms of their patterns, peaks, and overall exposure (AUC).
Methods
Data were synthesized from eight studies analyzing IGF-1 response to various GH therapies, including daily rGH and weekly long-acting formulations such as somapacitan, PEG-rhGH, TransCon GH, and Nutropin Depot. Key metrics included IGF-1 levels before and after treatment, trends in weekly cycles, and AUC comparisons.
Results
• Weekly GH Therapies: Studies on somapacitan, TransCon GH, and PEG-rhGH demonstrated dose-dependent increases in IGF-1 levels, with a distinct cyclic pattern characterized by peaks around day 3-4 post-injection and gradual declines by day 7. These therapies maintained IGF-1 levels within the normal range and were associated with sustained efficacy and safety over long-term use-(Sävendahl *et al*., 2020; Chatelain *et al*., 2017).
• Daily GH Therapies: Daily rGH therapy (e.g., Genotropin, Norditropin) resulted in more consistent IGF-1 levels with minor daily fluctuations, providing a steady profile throughout the week-(Lundberg *et al*., 2018).
• Comparison of AUC: Weekly GH therapies exhibited a higher IGF-1 AUC due to pronounced peaks, while daily GH therapy maintained lower but more consistent IGF-1 levels. The higher AUC in weekly therapies indicates greater overall IGF-1 exposure, potentially enhancing efficacy but requiring careful monitoring to prevent side effects.
Discussion
Weekly GH therapies offer convenience and adherence benefits through reduced injection frequency while maintaining effective IGF-1 levels. However, the cyclic IGF-1 patterns and higher AUC necessitate careful patient monitoring to minimize risks associated with IGF-1 peaks. Daily rGH provides a stable IGF-1 profile, facilitating better fine-tuning, but at the cost of daily injections.
Conclusion

Table 1. IGF-1 Trends and Patterns Between Daily Vs Long-Acting-GH Therapies

GH Therapy Type	Key IGF-1 Trends	IGF-1 Patterns	IGF-1 Response Consistency
Daily GH	Variable-Timing, Stable Long-Term	Fluctuates-Daily	Higher consistency across days
Long-Acting GH	Dose-Dependent, Sustained Weekly	Weekly-Peaks and Troughs	Higher overall AUC due to peaks

Both weekly and daily GH therapies effectively elevate IGF-1 levels, with distinct advantages and limitations. Weekly formulations optimize patient adherence and long-term exposure, whereas daily rGH ensures consistent IGF-1 profiles.

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EP800

JOINT1015

Myhre syndrome – it is never too late

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We present the case of a rare genetic disorder in a male patient that developed over a span of 10 years. The patient was a child of a pathological pregnancy due to intrauterine growth restriction, born small for gestational age at the 35th gestation week (1970 g, 41 cm). He underwent cardiac surgery for aortic coarctation at 5 months of age, and orchiopexy at 20 months. He was transiently treated for subclinical hypothyroidism. Subsequently, a euthyroid state was achieved without the need for further medication. He is still under regular follow-up with a neurologist, urologist, ophthalmologist, and cardiologist. Due to joint contractures in the lower limbs, botulinum toxin injections were administered. Genetic counseling was first performed in early infancy (1.5 years old), confirming a normal male karyotype and exclusion of SHOX gene defects, as well as genomic imbalances. The diagnostic process was paused for several years, during which he was referred to a pediatric endocrinologist at our center, at the age of 8.5 years. Physical examination revealed significant growth retardation (height SDS -2.7), facial dysmorphism, shortened limbs and digits, skin stiffness with gross motor limitations, normal cognitive and speech development, no pubarche and adrenarche, and bilateral testicular volume of 5 mL. The criteria for growth hormone therapy as a small for gestational age (SGA) child without catch-up growth were met, and recombinant growth hormone (rGH) treatment was initiated (dose of rGH 0.035 mg/kg/day). Given the pronounced phenotype, re-evaluation of genetic counseling was conducted. Subsequent analysis identified a de novo heterozygous mutation in the SMAD4 gene (c.1499T>C; p.Ile500Thr), which is pathogenic and causal for Myhre syndrome. SMAD4 is recognized as a tumor suppressor gene, and its mutations which are presumed to result in a gain of function are associated with Myhre syndrome. To date, no systematic studies have assessed the use of supraphysiological doses of growth hormone (SGA indication) in this specific group, moreover there is a lack of evidence that there is a consistent increase in height velocity by using rGH. Based on current knowledge, we considered rGH therapy inappropriate due to its potential anabolic effects, which may interact with SMAD4's function, and thus, treatment was immediately discontinued. Myhre syndrome is a rare, multisystemic connective tissue disorder with no specific treatment. We emphasize the importance of ongoing genetic counseling in cases of clustering pathological signs and the need for re-evaluating therapeutic approaches based on the latest evidence and interdisciplinary collaboration.

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EP801

JOINT3585

Short stature and treatment in KBG syndrome: a case report

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Introduction
KBG syndrome is a rare autosomal dominant disorder characterized by specific craniofacial features (triangular face, macrodontia, a single upper central incisor), short stature, and skeletal abnormalities. The condition is caused by heterozygous mutations or deletions in the ANKRD11 gene. Herewe present a case of a patient diagnosed with KBG syndrome, monitored in our clinic due to short stature.
Case Report
A 9-year-9-month-old male patient presented to our clinic with short stature. His history revealed a birth weight of 2450 grams at 35 weeks of gestation. Short stature was noticed from six months of age. He had been followed by pediatric gastroenterology due to recurrent vomiting, which resolved after a diagnosis of

cholelithiasis and subsequent cholecystectomy. Parental consanguinity was noted. The mother's height was 150.9 cm, and the father's height was 168 cm (mid-parental height: 165.9 cm). The patient's physical examination showed a weight of 21 kg (-2.59 SD), height of 120 cm (-2.79 SD), and BMI of 14.5 (-1.29 SD). He exhibited atypical facial features (triangular face, long philtrum), macrodontia and Tanner stage 1 puberty. Laboratory findings included IGF-1 at 140 ng/ml (0/+1 SD), IGFBP-3 at 3817 ng/ml (+1/+2 SD), normal thyroid function tests, negative celiac antibodies and a bone age of 6 years and 6 months. The patient was monitored for growth velocity. At 10 years and 8 months of age, he entered puberty, with a pubertal growth velocity of 5.2 cm/year. A growth hormone stimulation test revealed a peak response of 11.2 ng/ml. Genetic testing confirmed KBG syndrome by identifying a heterozygous c.5273_5274dup variant in the ANKRD11 gene, consistent with the patient's atypical facial features, macrodontia, and short stature. Due to inadequate pubertal growth and short stature, somatropin therapy was initiated. Growth velocity improved to 7.7 cm/year with treatment. At his last follow-up (15 years and 9 months), his chronological age was 15 years and 9 months, height age was 12 years and 8 months, bone age was 15 years, weight was 47.1 kg (-2.14 SD), height was 156.9 cm (-2.36 SD), and his pubertal examination corresponded to Tanner stage 4.

Discussion/Conclusion

Short stature is a common feature of KBG syndrome, and achieving target height is rare in affected individuals. Growth hormone therapy may be effective in patients with KBG syndrome presenting with significant prepubertal short stature, even in the absence of growth hormone deficiency. However, larger-scale studies are needed to evaluate treatment efficacy and safety comprehensively.

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EP802

JOINT1755

Serum levels of intact and total IGFBP-4, and stanniocalcin-2 in congenital isolated gh deficiency

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The Itabaianinha cohort is composed of subjects with a homozygous *GHRH-R* c.57 + 1G →A mutation, causing congenital isolated GH deficiency (IGHD). These subjects exhibit severe short stature, central obesity, hypercholesterolemia, but no premature atherosclerosis, and normal lifespan. They have marked reductions in serum IGF-I, IGFBP-3 and ALS, but normal IGFBP-1 and IGFBP-2 levels. Stanniocalcin-2 (STC2), plasma pregnancy-associated protein A (PAPP-A) and IGFBP-4 are functionally related proteins that in concert regulate IGF-I action, and hence body growth. PAPP-A cleaves IGFBP-4 enzymatically, and liberates bound IGF-I, whereas stanniocalcin-2 inhibits PAPP-A. These proteins have not previously been characterized in GH deficiency, Here, we present data on total and intact IGFBP-4 and Stanniocalcin-2. Table 1 shows that levels of intact IGFBP4 are 4-times higher in IGHD ($P < 0.0001$), with a very large effect size (Mann Whitney Eta-squared = 0.539 and a Cohen's d = 2.165), whereas total IGFBP-4 (intact plus fragments) and STC2 are similar to age- and BMI-matched controls. The higher levels of intact IGFBP-4 suggest a role of PAPP-A in mediating IGFBP-4 cleavage, which contributes to the growth reduction in this cohort

Table 1. Clinical and biochemical data in 23 IGHD individuals and 11 controls. Data are expressed as mean (standard deviation), except for glucose, insulin, triglycerides, IGF-1, IGFBP3, and intact IGFBP4 expressed as median (interquartile range)

Parameters	IGHD	Controls	95% CI	P
Age (years)	50.8 (13.7)	44.9 (15.6)	-4.8 to 16.6	0.273
Female sex, n (%)	10 (43.5)	6 (54.5)	-0.5 to 0.3	0.717
Weight (kg)	42.8 (7.0)	72.6 (11.78)	-36.2 to -23.2	<0.0001
Height (m)	1.29 (0.10)	1.65 (0.08)	-0.4 to -0.3	<0.0001
BMI (kg/m^2)	25.9 (3.9)	26.1 (5.4)	-3.6 to 3.1	0.879
Glucose (mg/dl)	87.0 (15.0)	89.5 (12.3)	-13.6 to 4.8	0.186
Insulin (μU/ml)	4.2 (1.8)	6.7 (3.9)	-5.0 to -1.1	0.004
HOMA-IR	0.88 (0.44)	1.63 (0.86)	-1.3 to -0.1	0.018
Total cholesterol (mg/dl)	222 (41)	185.4 (42.1)	-6.4.0 to 45.6	0.134
LDL cholesterol (mg/dl)	119.1 (36.3)	102.3 (25.7	-8.0 to 41.8	0.178
HDL cholesterol (mg/dl)	49.7 (8.1)	51.7 (14.1)	-9.7 to 5.7	0.603
Tryglicerides (mg/dl)	139.0 (178.0	77.0 (96)	-44.9 to 106.0	0.424
IGF1 (ng/ml)	11.0 (6.0)	180.5 (76.8)	-163 to -128	< 0.0001
IGFBP-3 (ng/ml)	579 (222)	3458 (1476)	-3258 to -2272	<0.0001
Stanniocalcin-2 (ng/ml)	43.4 (7.4)	47.8 (10.1)	-11.1 to 3.1.	0.191
Total IGFBP-4 (ng/ml)	101.6 (28.1)	96.6 (30.9)	-19.7 to 29.8	0.678
Intact IGFB-4 (ng/ml)	83.9 (22.2)	21.2 (34.2)	39.7 to 64.2	<0.0001

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EP803

JOINT1976

The significance of cardiac MRI in transition care for Turner Syndrome: a prospective study

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Background

Turner Syndrome (TS) is associated with cardiovascular abnormalities, including bicuspid aortic valve (BAV), coarctation of the aorta (CoA), and aortic dilatation, increasing the risk of life-threatening complications such as aortic dissection. Continuous cardiac monitoring is essential, particularly during the transition to adult care. While transthoracic echocardiography (ECHO) is widely used, it has limitations in assessing aortic valve morphology. Current guidelines recommend cardiac MRI for comprehensive evaluation when general anesthesia is unnecessary.

Objective

This study evaluates the role of cardiac MRI in detecting cardiovascular abnormalities in TS patients before transition to adult care, identifying undiagnosed defects, and aiding risk stratification.

Methods

This prospective study (Sep/2020 – Jan/2025) recruited TS patients from southeastern Poland. Inclusion criteria were confirmed TS diagnosis, ability to undergo MRI without anesthesia, and informed consent. Exclusion criteria included contraindications to MRI or lack of consent. Cardiac MRI (1.5T scanner with contrast) assessed aortic dimensions, left heart parameters, and congenital heart defects. Aortic dilation was evaluated using the aortic height index (AHI), aortic size index (ASI), and TS-specific Z-scores.

Results

A total of 40 TS patients with mean (min-max) age 16.2 ± 1.4 (11.7-18.0) years were included. Among them, 9 (22.5%) had a 45,X karyotype, and 31 (77.5%) non-45,X variations, 6 (15%) were overweight, 10 (25%) had obesity. Medical history revealed BAV in 6 (15%) patients, one (2.5%) with CoA. Other singular cases included persistent left superior vena cava, mitral insufficiency, aortic stenosis, and left subclavian artery widening. 10 (25%) had arterial hypertension. MRI detected BAV in 13 (32.5%), patients post-CoA in 1 (2.5%), great vessel anomalies in 4 (10%), and partial anomalous pulmonary venous return (PAPVR) in 3 (7.5%). Additional single cases included a right coronary artery aneurysm, persistent left superior vena cava, mitral annular disjunction, atrial septal defect, mitral insufficiency, and left subclavian artery widening. Aortic dilatation was found in 5 (12.5%) patients, BAV was diagnosed in 4 of them. None of them had aortic hypertension. Differences in AHI, ASI, and TS-specific Z-scores for ascending aorta dimension between BAV and non-BAV patients were not statistically significant ($P = 0.054$, 0.12, 0.07, respectively). No significant differences in congenital defect prevalence were found between 45,X and other karyotypes ($p > 0.05$).

Conclusion

The high rate of (un)diagnosed CV-pathies supports integrating MRI with routine ECHO for early detection and intervention. Strengthening transition protocols and increasing awareness of cardiovascular risks in TS could improve outcomes.

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EP804

JOINT2007

Effects of gonadotropin-releasing hormone analog, alone and in combination with recombinant human growth hormone, on height in girls with early puberty across age groups

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Background
Central precocious puberty (CPP) is the early activation of the hypothalamic-pituitary-gonadal axis, resulting in the onset of puberty in girls before 8 years of age. GnRH analog therapy is commonly used to delay puberty, but it often leads to height suppression and metabolic changes. Growth hormone (GH) supplementation is sometimes added to improve final adult height, but its effect on weight and body mass index (BMI) is not well understood. This study aims to evaluate the impact of GnRH analog therapy vs GnRH analog therapy combined with GH on final height, weight, and BMI in girls with CPP.
Methods
This retrospective cohort study was conducted at Ramallah Governmental Hospital, Palestine, from 2020 to 2023, including 56 girls diagnosed with CPP before the age of 8. The patients were divided into two groups: one group received GnRH analogs only ($n = 29$), and the other received GnRH analogs with GH therapy ($n = 27$). They were further categorized into prepubertal (0–8 years), early pubertal (8.1–11 years), and mid-pubertal (11.1–14 years) subgroups. Data on height, weight, BMI, Tanner stage, and hormone levels were collected. Statistical analysis was performed using SPSS version 20, and the independent samples t-test was used for comparison, with statistical significance set at $P < 0.05$.
Results
Both groups experienced significant increases in height after treatment. The mean height in the GnRH analog group increased from 122.31 $\pm$ 10.45 cm to 145.84 $\pm$ 12.24 cm, while the combination therapy group increased from 111.81 $\pm$ 10.37 cm to 136.96 $\pm$ 11.67 cm. Weight gain occurred in both groups, but it was more pronounced in the GnRH analog-only group (from 26.12 $\pm$ 5.44 kg to 39.36 $\pm$ 6.04 kg) compared to the combination therapy group (from 19.84 $\pm$ 6.05 kg to 34.94 $\pm$ 8.27 kg). Changes in BMI were not significantly different between groups, although the combination therapy group had a lower increase in BMI, particularly in mid-pubertal patients ($P = 0.024$).
Conclusions
Adding GH to GnRH analog therapy improves final height outcomes in girls with CPP without significantly affecting BMI. GH supplementation may also reduce weight gain commonly observed with GnRH analog therapy. These findings emphasize the importance of a personalized approach based on pubertal stage and metabolic risk. Further studies are needed to confirm long-term outcomes and refine treatment strategies.

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EP805

JOINT359

ZTTK syndrome with growth hormone deficiency: a case report and literature review

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Growth hormone deficiency (GHD) is a disorder of growth hormone secretion from the pituitary gland. Its clinical presentation can include neonatal hypoglycemia, prolonged jaundice, and midfacial defects. However, in children, it sometimes presents only as short stature and/or growth deceleration. GHD is diagnosed when children with short stature (<2 standard deviation score [SDS] relative to the general population) show delayed bone age and peak growth hormone levels of less than 10 ng/ml in at least two growth hormone stimulation tests. For patients who show growth faltering and/or a suboptimal response even when treated with recombinant human growth hormone, additional phenotypes, such as severe short stature and body disproportion, should be assessed, and additional diagnoses should be considered. A 5-year-old girl visited the Department of Pediatrics because of short stature and low weight. She had previously undergone karyotyping and single nucleotide polymorphism (SNP) array testing because of developmental delay, intellectual disability, short stature, and distinctive facial dysmorphisms, including frontal bossing, deep-set eyes, low-set ears, depressed nasal bridge, and short philtrum after birth. The results at the time showed no abnormal finding, but GHD was diagnosed in growth hormone stimulation tests. She was being treated with a high dose of growth hormone (50 μg/kg/day) for GHD in children born SGA, and showed a poor rate of growth even after 5 years of treatment, with a height SDS of -3.98 (formerly -4.05). However, following next-generation sequencing (NGS)-based whole exome sequencing (WES), the patient was diagnosed with Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome (OMIM: 617140), due to a heterozygous mutation in SON. She is currently continuing growth hormone treatment, as well as receiving pediatric rehabilitation and orthopedic care. Recently, following advances in molecular genetic techniques, genetic causes for many endocrinological diseases have been discovered; hence, genetic testing is commonly used in the diagnosis and genetic counseling of endocrinological diseases. Guidelines for the genetic testing of children with short-stature have also been established. Generally, this disease is unrelated to GHD; however, in 2020, a case of ZTTK syndrome accompanied by GHD with a unique presentation was reported. We believe that this case may be useful references for expanding the genotype-phenotype map. Here, we report the case of ZTTK syndrome with GHD diagnosed by WES in a patient with GHD who did not respond well to GH treatment.

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EP806

JOINT1004

Whole exome sequencing uncovers the genetic diagnoses and new candidate genes for growth disorders in a cohort from the brazilian amazon

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Introduction
Growth disorders are one of the main challenges in pediatric endocrinology, significantly affecting the quality of life of children and adolescents. The use of next-generation sequencing technologies, such as whole-exome, has revolutionized the investigation of genetic disorders.
Objective
This study aimed to identify new genetic-molecular alterations in patients with growth disorders and characterize the phenotype of rare genetic causes of monogenic growth disorders in the Amazon region.
Methods
Twenty-two patients (15 males; 7 females) clinically diagnosed with idiopathic short stature with or without syndromic features, treated in Santarem, Brazil were selected for exome sequencing.
Results
The average age of the participants at their first presentation to the clinic was 6.7 $\pm$3.7 years. Bone age minus chronological age showed a mean delay of -1.0 $\pm$ 1.7 years in relation to chronological age. The participants Z-score for height was -3.0 $\pm$1.0. Three patients were born small for gestational age. Of the seven syndromic children, one was found with heterozygous deletion of Xp22.33 confirmed by MLPA and another child had homozygous deletion involving the *CLCNKB* gene which confirmed Bartter syndrome type 3. Two other children harbored heterozygous likely pathogenic and VUS variants in *LZTR. LZTR* germline mutations have been known to cause dominant and recessive forms of Noonan syndrome. Another child harbored heterozygous pathogenic variant in *CDK13,* and this is clinically associated with congenital heart defects, dysmorphic facial features, and intellectual developmental disorder. One syndromic child had a negative result in exome sequencing. There were fifteen non-syndromic cases. Ten of the non-syndromic children had negative results in exome sequencing however two of these children had secondary findings: Lynch syndrome and malignant hyperthermia. One child harbored heterozygous deletion of Xp22.33 which confirmed SHOX deficiency disorder. The other four children harbored candidate genes including *IBR4*, *IHH*, *RARA* and *MAU* genes.

Conclusions
This research enabled patients from the Brazilian Amazon to benefit from the use of exome sequencing in the investigation of idiopathic short stature, allowing the identification of new genes that may be involved in growth disorders and the detection of monogenetic diseases, such as SHOX deficiency disorder, Bartter syndrome type 3 and secondary findings having significant implications in the clinical segment, therapeutic decision and genetic counseling. This made it possible to rationally and viable apply genomic medicine in clinical and research practice.

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EP807

JOINT1551

Rare TXNRD2-related familial glucocorticoid deficiency in a chinese patient: a case report

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Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disorder that is primarily characterized by isolated glucocorticoid deficiency. Mutations of *MC2R*, *MRAP*, *STAR*, *NNT*, and *TXNRD2* have been shown to cause FGD. There have been 2 cases reported of mutations in the *TXNRD2* gene causing familial glucocorticoid deficiency-5 (FGD5) in the world. We report a patient who had clinical features consistent with FGD5, increasing the total number of reported cases. This patient is the third case in the world. The details of this case confirm the importance of the *TXNRD2* gene in adrenal cortex redox homeostasis and provide further insights into the nature of FGD5. Further experiments demonstrate that the newly identified variant causes a decrease of TXNRD2 protein levels when expressed in a heterologous expression system. The *TXNRD2* compound heterozygote variant can cause FGD5. The *TXNRD2* compound heterozygote variant of FGD5 may be associated with abnormal findings on electrocardiography. Our case expands on this genetic variation and provides new evidence for the clinical diagnosis of FGD5.

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EP808

JOINT1385

GH therapy and its short-term effectiveness in hong kong (the growth study)

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Background
To understand the use of recombinant human growth hormone (GH) therapy (rhGH) in Hong Kong, six paediatric centres in Hong Kong have used the GloBE-Reg platform to systematically collect data on rhGH in children and adolescents.
Methods
A descriptive and comparative analysis of retrospective data of local patients treated with rhGH on GloBE-Reg (https://globe-reg.net/). Anthropometric measurements were converted into standard deviation scores (SDS) using local reference data. Baseline height SDS (HtSDS) and first-year response to rhGH, including delta HtSDS, were calculated.
Results
Of the 294 cases in the registry, baseline and first-year data were available for 261(89%) (M:F, 126:135). All cases received daily rhGH. Among these 261, 107 (41%) had GH deficiency (GHD), with rhGH initiated at a median age of 10.9yrs (10^{th}, 90^{th} centiles, 5.9, 14.3). The median HtSDS increased from -3.2 (-4.2, 1.9) at baseline to -2.7 (-3.8, 1.4) after one year, with a median delta HtSDS of 0.4(-0.1, 1.1). A total of 47 (18%) cases received rhGH for idiopathic short stature, with therapy initiated at a median age of 11.0yrs (5.6, 13.9). Over the first year, the median HtSDS increased from -2.9 (-4.1, -2) to -2.4 (-3.5, -1.8), with a median delta HtSDS of 0.5 (0.2, 1.1). Among the 46 (18%) patients with Turner syndrome, rhGH was initiated at a median age of 10.6yrs (4.4, 14.7). The median baseline HtSDS was -3.5 (-4.5, -2.6), increasing to -3.0 (-4.2, -2) after one year, with a median delta HtSDS of 0.5 (0.03, 0.9). In the 15 (6%) patients with Prader-Willi syndrome, rhGH commenced at a median age of 3.8yrs (1.1, 13.1). The median baseline HtSDS was -1.8 (-3.5, -0.4), improving to -1.4 (-2.4, 0.3) after one year, with a median deltaHtSDS of 0.8 (-0.2, 1.3). In the 19 (7%) cases classified as "Other Disorders" who did not have a clear rhGH indication, rhGH was initiated at a median age of 9.6yrs (4.4, 10.7). The median baseline HtSDS reduced from -0.3 (-3.7, 2.5) to -0.7 (-3.1, 2.2) over the first year, with a median delta HtSDS of -0.3 (-0.6, 0.8). Compared to the GHD group, the median first-year delta HtSDS was significantly lower in the "Other Disorders" group ($P < 0.0001$).
Conclusion
This is the first study to characterize the local treatment landscape of rhGH in children and adolescents. The observed heterogeneity in treatment response in Hong Kong requires further analysis so that clinical effectiveness can be optimised.

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EP809

JOINT690

Identification of a novel IGF1R mutation in a family with short stature: a case report

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Background
Insulin-like growth factor 1 receptor (IGF1R) mutations are rare genetic variants associated with growth failure due to impaired IGF1 signaling. We report a family with a novel likely pathogenic IGF1R mutation presenting with short stature, elevated IGF1 levels, and suboptimal growth response to growth hormone (GH) therapy.
Case Presentation
A 4-year-old boy born at 37 + 1 weeks by cesarean section with a birth weight of 2210 g (SGA) presented with short stature below the 3rd percentile. GH stimulation testing revealed a peak GH level of 13.7 ng/ml, indicating normal GH secretion. Initial IGF1 levels were significantly elevated at 202 ng/ml (reference range: 26.8–134 ng/ml for 4-year-old boys). Genetic analysis using a short stature NGS panel identified a heterozygous likely pathogenic IGF1R mutation (c.16G > A, p.Glu56Lys). Despite starting GH therapy (0.23 mg/kg/week), the patient showed a poor growth velocity, and his height percentile remained below the 10th percentile. The proband's 8-year-old sister, who had been treated for idiopathic short stature (ISS) with GH therapy since the age of 5, exhibited persistently elevated IGF1 levels (576 ng/ml) without achieving height above the 10th percentile. Genetic testing confirmed the same IGF1R mutation. Their mother, with a height of 148 cm, was also found to carry the heterozygous mutation.
Conclusion
This family highlights the clinical characteristics of a novel IGF1R mutation, including short stature, elevated IGF1 levels, and suboptimal response to GH therapy. These findings underscore the importance of genetic evaluation in patients with short stature and poor response to GH treatment. Further functional studies of the c.16G > A, p.Glu56Lys variant are needed to understand its impact on IGF1 signaling and growth

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EP810

JOINT618

The impact of puberty on IGF-1: factors influencing growth and development

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Background
Insulin-like growth factor 1 (IGF-1) plays a pivotal role in pubertal growth and development. Its levels peak during puberty, driven by growth hormone (GH) secretion, and are influenced by factors such as sexual dimorphism, nutritional

Table 1. Key Factors Influencing IGF-1 Levels During Puberty

Factor Addressed	Main Findings
Peak Levels During Mid-Puberty	GH and IGF-1 peak during puberty, driving skeletal growth and bone density.
Sexual Dimorphism	IGF-1 levels differ by sex, influenced by androgen and estrogen modulation.
Interdependence with Nutritional Status	Nutritional status strongly impacts IGF-1 levels; malnutrition blunts growth effects.
Variability in Onset and Duration	Delayed or precocious puberty alters IGF-1 timing, affecting growth trajectories.

status, and the timing of puberty onset. These interactions highlight IGF-1's critical role in skeletal growth, sexual maturation, and overall development.
Objective
To explore the effects of puberty on IGF-1 levels and identify the factors—peak levels, sexual dimorphism, nutritional status, and timing variability—that influence its patterns during this
Methods
A comprehensive review of 10 studies was conducted, spanning various subjects, including adolescents, animal models, and *in vitro* research. The studies address IGF-1 dynamics during mid-puberty, sexual dimorphism, the influence of nutrition, and the variability in IGF-1 timing due to delayed or precocious puberty.
Results: Table
1. Peak Levels During Mid-Puberty: GH and IGF-1 levels reach their highest during mid-puberty, essential for skeletal growth and bone density (Locatelli & Bianchi, 2014; Dixit *et al*., 2020).
2. Sexual Dimorphism: IGF-1 levels differ by sex, influenced by androgen and estrogen modulation, with higher levels noted during central precocious puberty in girls (Juul & Skakkebæk, 2019; Sørensen *et al*., 2012; Venken *et al*., 2006).
3. Interdependence with Nutritional Status: Malnutrition and chronic illness blunt IGF-1 levels, limiting growth, while well-nourished adolescents maintain higher IGF-1 levels (Mohan *et al*., 2003; Acerini *et al*., 2001; Turchyna *et al*., 2022).
4. Variability in Onset and Duration: Delayed or precocious puberty alters the timing and variability of IGF-1 levels, impacting growth trajectories (Dees *et al*., 2021).
Discussion
Puberty-induced IGF-1 changes are driven by GH secretion and influenced by multiple factors. Sexual dimorphism highlights hormonal modulation, while nutritional status underpins the IGF-1 response. Variability in timing emphasizes the dynamic nature of IGF-1, reflecting broader growth and developmental processes.
Conclusion
IGF-1 levels during puberty and the interplay of peak levels, sex differences, nutritional factors, and timing variability underscores its multifaceted role, necessitating a tailored approach to understanding IGF-1 dynamics.

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EP811

JOINT794

Safety profile of large IGF-1 fluctuations: long-acting growth hormone therapy vs. daily growth hormone therapy

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Background
Long-acting growth hormone (GH) therapy offers improved adherence and convenience compared to daily GH therapy, but it is associated with periodic IGF-1 fluctuations due to its extended release profile. The clinical safety of these fluctuations and their potential impact on adverse events remain important considerations in choosing therapy for GH deficiency (GHD).
Objective
To evaluate the safety profile of long-acting GH therapy compared to daily GH therapy, focusing on the implications of IGF-1 fluctuations and potential adverse outcomes.
Material and Methods
A comprehensive review of studies was conducted comparing safety profiles between long-acting GH therapies (e.g., somapacitan, TransCon GH) and daily GH therapies (e.g., Genotropin). Data were extracted on IGF-1 fluctuations, IGF-1 SDS excursions, and adverse events. The results are summarized in a comparison table.
Results
Key Findings:
1. Long-Acting GH Therapy:
• **Fluctuations:** Large IGF-1 peaks were observed post-injection, typically on days 3–4, with troughs approaching baseline by day 7.
• **Safety:** Minimal adverse events were reported despite IGF-1 SDS excursions > 2.0 in some patients, particularly at higher doses.
• **Specific Studies:**
• Kildemoes *et al*. (2023): Weekly somapacitan showed transient IGF-1 SDS excursions >2.0 but was well-tolerated.
• Chatelain *et al*. (2017): IGF-1 SDS >2.0 occurred in 4/14 patients at the highest dose of TransCon GH, with no clinical adverse events or dose modifications.
• **Adverse Events:** Rare occurrences of injection-site reactions and mild transient hyperglycemia.
2. **Daily GH Therapy:**
• **Fluctuations:** Daily administration resulted in smaller, more consistent IGF-1 fluctuations, typically maintaining IGF-1 SDS <1.0.
• **Safety:** Well-tolerated with no IGF-1 SDS excursions above therapeutic thresholds.
• **Specific Studies:** Garner *et al*. (2023): No significant adverse events were observed, with stable IGF-1 levels within the therapeutic range.
Discussion
The larger IGF-1 fluctuations observed with long-acting GH therapies are generally transient and dose-dependent, with no significant safety concerns reported in short-term studies. Daily GH therapy exhibits a more stable IGF-1 profile, minimizing the risk of IGF-1 excursions but requiring frequent dosing. Long-term monitoring is necessary to assess the clinical implications of sustained IGF-1 peaks with long-acting therapies.
Conclusion
Long-acting GH therapy is a safe and effective alternative to daily GH therapy, despite larger IGF-1 fluctuations. Careful dose titration and regular monitoring are essential to minimize transient IGF-1 SDS excursions and maintain a favorable safety profile.

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EP812

JOINT948

Diagnostic utility of IGF-1 levels in growth and puberty-related disorders: a comprehensive review

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Background
Insulin-like growth factor 1 (IGF-1) serves as a key biomarker in assessing growth and puberty-related conditions. Variations in IGF-1 levels reflect underlying pathophysiological changes, helping to differentiate between normal growth and growth-related disorders such as Growth Hormone Deficiency (GHD), Turner Syndrome, and Constitutional Delay of Puberty (CDP). However, standardizing IGF-1 cut-offs across different conditions remains challenging.
Objective of the Review
This review consolidates data from multiple studies to summarize the diagnostic IGF-1 cut-offs across various growth and puberty-related conditions and highlights its utility and limitations as a diagnostic tool.
Material and Methods
A comprehensive analysis was performed by synthesizing findings from studies published in peer-reviewed journals. Data on IGF-1 levels in conditions such as CDP, Small for Gestational Age (SGA), Chronic Malnutrition, GHD, Turner Syndrome, and rare genetic mutations were extracted and compared.
Results
1. **IGF-1 cut-off for normal growth**: Typically ranged between 150-200 ng/ml across conditions.
2. **GHD**: Consistently indicated by IGF-1 levels < 100 ng/ml in multiple studies.
3. **SGA**: IGF-1 levels < 100 ng/ml or 110 ng/ml in various studies supported its role as a disease marker.
4. **Turner Syndrome**: IGF-1 < 120 ng/ml was associated with disease states, with larger studies reinforcing this threshold.
5. **Chronic Malnutrition and Thalassemia Major**: IGF-1 levels < 90 ng/ml and < 70 ng/ml, respectively, indicated growth disturbances.
6. **Rare conditions**: IGF1R mutations presented variable or fluctuating IGF-1 levels, reflecting unique pathophysiology.
Discussion
IGF-1 levels provide a reliable diagnostic indicator for many growth-related disorders, with thresholds helping clinicians differentiate between normal and pathological growth states. Larger studies, particularly on conditions like Turner Syndrome, provide robust diagnostic thresholds, while rare cases emphasize the variability due to genetic and environmental factors.
Conclusions
IGF-1 is a critical diagnostic marker for growth and puberty-related conditions. While general thresholds like IGF-1 < 100 ng/ml for GHD and SGA are well-

Table: IGF-1 cut Levels by Condition

Condition	IGF-1 Cut-Off (Normal)	IGF-1 Cut-Off (Abnormal)
(CDP)	> 150 ng/mL	< 150 ng/mL
(SGA)	> 200 ng/mL	< 100â£″110 ng/mL
Chronic Malnutrition	> 180 ng/mL	< 90 ng/mL
Turner Syndrome	> 170â£″200 ng/mL	< 120 ng/mL
(ISS)	> 160 ng/mL	Normal or near normal
(GHD)	> 200 ng/mL	< 90- 100 ng/mL
Noonan Syndrome	> 150 ng/mL	< 80 ng/mL
Thalassemia Major	> 150 ng/mL	< 70 ng/mL
IGF1R Deletion	Fluctuating	Fluctuating

supported, variability in levels across different conditions and populations necessitates cautious interpretation alongside clinical context.

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EP813

JOINT1457

Are children with atopic eczema at higher risk of poor linear growth? - A systematic review of the literature

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Background
The evidence on the association between atopic dermatitis (AD) and linear growth in children in current literature is inconsistent. Some studies have suggested that the presence of AD may negatively impact height, while other studies have not reported similar associations. This systematic review aims to evaluate the association between AD and linear growth in children, and determine factors that may be potentially associated with compromised linear growth in children with AD.
Methods
A PRISMA-compliant systematic review was conducted. Databases included in the review were PubMed, Embase, Scopus and Cochrane. The search timeline was from database inception to June 2024. Inclusion criteria includes articles that reported a quantitative relationship between AD and linear growth in children (< 18 years old). The quality of included articles was assessed using the Joanna Briggs Institute Critical Appraisal Tools, while quality of evidence in these studies was evaluated using Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. A meta-analysis was not performed due to significant clinical and methodological heterogeneity between the studies that met inclusion criteria.
Results
Fourteen studies which comprises 50,146 patients with AD were included. Seven studies reported either a "strong positive" or "positive" association between AD and reduced height standard deviation score (SDS) in children; the remaining 7 studies reported no association between AD and height. Only 3 of the 14 studies had moderate quality of evidence, all of which had reported an association between AD and poorer height SDS; while the remaining 11 studies scored low in quality of evidence. Three studies reported the impact of AD on height to be transient, mimicking constitutional growth delay. In addition, severity of AD, timing of onset of AD, sleep disruption and extent of nutritional restrictions are important risk factors for linear growth impairment in patients with AD. Topical steroid use did not appear to be associated with shorter stature in patients with AD.
Conclusions
The evidence at present reporting on the association between childhood AD and poor linear growth is weak and inconsistent. However, patients with more severe AD, earlier disease onset, poorer sleep quality and higher nutritional restrictions appear more susceptible to linear growth impairment. Therefore, management of patients with AD should not only be focused on treatment and control of the disease, but also on optimizing growth, nutrition, sleep and quality of life.

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EP814

JOINT2429

Clinical features and genetic analysis of an SGA-born patient with IGF1R heterozygous mutation

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Introduction
The *IGF1* and *IGF1R* genes regulate prenatal and postnatal growth processes. Mutations in the *IGF1R* gene can cause intrauterine growth restriction (IUGR), postnatal growth retardation, microcephaly, intellectual disability, neurodevelopmental issues, and brain and cardiac anomalies. Biallelic mutations generally result in more severe phenotypes than heterozygous mutations. *IGF1R* mutations are a significant etiological factor in patients with small gestational age (SGA) and growth retardation. Genetic analysis of these mutations is critical for early diagnosis and treatment strategies.
Case
Report
This report describes a 1-year-4-month-old male patient born SGA (38th week, 1975 g, −3.76 SD) with ongoing growth retardation. The birth length was 45 cm (−2.19 SD), and the calculated mid-parental height was 171.2 cm (−0.81 SD). No consanguinity was identified. Physical examination revealed a height of 72.5 cm (−2.7 SD), body weight of 6.8 kg (−4.09 SD), and head circumference of 43.5 cm (−3.12 SD). Testicular volume was 2/2 ml and penile length were normal for his age. Liver, kidney, and thyroid function tests were normal, and celiac autoantibodies were negative. At the time of the patient's admission, IGF1 levels were measured at 46.1 ng/ml (−1 SD), and IGFBP3 levels at 3008 ng/ml (+1 SD). No abnormalities were observed during blood glucose monitoring. Nutritional support was initiated due to malnutrition, but growth velocity remained insufficient. Genetic analysis identified a heterozygous c.3595G > A p.(Gly1199Arg) variant in the *IGF1R* gene, also detected in the mother. Although growth hormone therapy was recommended, the family declined treatment.
Discussion
Mutations in *IGF1R* lead to phenotypes resembling IGF1 deficiency but require different therapeutic approaches. The IGF1 receptor regulates growth, metabolism, and cell survival via the MAPK/ERK and PI3K → AKT pathways. *IGF1R* defects may mimic Silver-Russell or SHORT syndrome phenotypes, with microcephaly as a distinguishing feature. Walenkamp *et al.* proposed a clinical scoring system for *IGF1R* mutations based on low birth weight, small head circumference, short stature, and elevated IGF1 levels. Recombinant growth hormone (rGH) therapy's efficacy in *IGF1R* mutations remains unclear. Studies report modest height gains (average 1.0 SDS) with rGH but caution against dose escalation due to high IGF1 levels. The genotype-phenotype correlation for *IGF1R* mutations remains unresolved. Heterozygous carriers typically exhibit milder phenotypes than homozygous individuals. This case represents the first Turkish pediatric patient with the *IGF1R* Gly1199Arg variant.

Keywords
IGF1R mutation, SGA, Microcephaly, Recombinant growth hormone
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EP815

JOINT3680

Experience with growth hormone therapy in a rare skeletal dysplasia

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Introduction
Cartilage oligomeric matrix protein (COMP) is a pentameric extracellular matrix glycoprotein that is critical for collagen formation and extracellular matrix stability. Mutations in the COMP gene lead to impaired extracellular matrix stability, secondary chondrocyte apoptosis, and two rare skeletal dysplasias: pseudoachondroplasia (PSACH) and multiple epiphyseal dysplasia (MED). Here, we present a case of a patient diagnosed with a COMP gene mutation, who was followed in our clinic due to short stature.
Case Report
A 6-year-7-month-old girl was referred to our clinic by the rheumatology department for short stature. Her medical history revealed that she was born at 39+4weeks of gestation and gestation weight was 2660grams, she had always been shorter than her peers, and was under follow-up for Familial Mediterranean Fever(FMF) with no attacks after colchicine treatment. There was no consanguinity between her parents. The mother's height was measured as 150.9cm, and the father's height as 165cm(mid-parental height: 151.4cm). Physical examination showed a body weight of 16.5kg(-1.94SD), height of 106.5cm(-2.5SD), and Tanner stage 1 puberty. Laboratory investigations revealed an IGF-1 level of 152ng/ml (+1SD), IGFBP3 level of 4281ng/ml (0/+1SD), normal thyroid function tests, negative celiac antibodies, and a bone age of 6years

and 9months. Growth hormone stimulation testing demonstrated a peak response of 20.4ng/ml. The patient was monitored for growth velocity, which was found to be 3.7cm/year.Subsequently, somatropin therapy was initiated. Under treatment, growth velocities were observed as 7cm/year in the first year,8.3cm/year in the second year, and 7.6cm/year in the third year, with IGF-1 levels at +1SD. Chromosome analysis showed 46,XX, and a genetic panel for short stature identified a heterozygous c.1767C>A (p.Asn589Lys) variant in the COMP gene, classified as a variant of uncertain significance (VUS) close to pathogenicity. As the variant was evaluated as potentially pathogenic and the patient's final bone age was consistent with 14years, somatropin therapy was discontinued. At her last follow-up, the patient was 12years old with a bone age of 14years, a body weight of 35.9kg (-1.28SD), height of 138.1cm (-2.35SD), and Tanner stage 4puberty. The patient's growth velocity declined due to the discontinuation of treatment and her untreated growth velocity was 2.4cm/year.

Discussion/Conclusion

Although COMP gene mutations typically lead to two rare skeletal dysplasias, they can present as idiopathic short stature without overt skeletal dysplasia findings. COMP, which plays a role in extracellular matrix stabilization, has been shown to correlate with serum levels of chondrocytes, growth hormone, and IGF-1. Therefore, growth hormone therapy may contribute to final height outcomes in short stature cases with COMP gene mutations.

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EP816

JOINT1665

Experience after 30 years of acromegaly management at the hospital clínico universitario de valladolid

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Introduction

Acromegaly is a condition primarily treated with surgery.

Objective

To describe the diagnostic and therapeutic evolution of acromegaly patients over the past 30 years in a tertiary hospital.

Material and Methods

A retrospective observational study of patients diagnosed with acromegaly between 1993 and 2023 at the Hospital Clínico Universitario de Valladolid, Spain. Clinical, radiological, and laboratory characteristics were collected at diagnosis, in the immediate postoperative period, and after one year, as well as histopathological findings and treatment details.

Results

A total of 34 patients were analyzed, 55.9% of whom were women, with a mean age of 59.7 (14.2) years. The main clinical presentations were **hormonal excess (62.5%)**, **compressive symptoms (20.8%)**, or both (16.7%). One case of pituitary apoplexy was recorded, and two patients (3%) were diagnosed with MEN-1. The main associated comorbidities are shown in Figure 1. MRI was the first radiological test in **90.9%** of cases, identifying **macroadenomas in 80.8%**. Tumors extended **suprasellarly in 22.2%**, **laterally in 7.4%**, and **demonstrated invasive criteria in 7.4%** (more than two locations). Surgery was performed in **30 patients**, with the **endoscopic approach (63.6%)** being the most common, followed by **direct endonasal (27.3%)**. The mean tumor volume reduction was **88.1%**. Hormonally, a **significant reduction in IGF-1 levels** (563.4 (297.6) vs. 263.2 (206.9); $P < 0.01$) and a **trend toward GH reduction** (20.6 (25.3) vs. 5.3 (7.6); $P = 0.057$) were observed one year post-surgery. Immunohistochemical analysis was performed in **38.2%** of cases, revealing **42.9% prolactin co-secretion**, and **two cases of GH, PRL, and ACTH co-secretion**. Disease persistence was observed in **63.3%** of patients, and **radiotherapy was administered to 11 patients**. Pharmacological treatment was initiated in **56.7%** of patients at diagnosis, **16 patients in the immediate postoperative period**, and **19 in the late postoperative period**. One year post-surgery, **29.4% were receiving Lanreotide**, **8.8% Octreotide**, **one patient Pegvisomant**, and **one Pasireotide**. **Three patients** received concomitant dopamine agonists. **Corticosteroid replacement therapy was required in 51.7% of patients in the early postoperative period** and **23.3% in the late postoperative period**.

Conclusion

Surgery remains the primary treatment for acromegaly, achieving high tumor volume reduction and a significant decrease in IGF-1 levels, although **disease persistence remains frequent (63.3%)**. More than half of the patients required **postoperative pharmacological treatment**, and some underwent **radiotherapy**. These findings highlight the need for a **multidisciplinary approach to optimize disease control**.

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EP817

JOINT2758

Cranio-lenticulo-sutural dysplasia (CLSD) as a rare cause of syndromic short stature: a case report of a complex clinical presentation

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Introduction

Cranio-lenticulo-sutural dysplasia (CLSD), also known as Boyadjiev-Jabs syndrome (ORPHACODE 50814), is a rare disorder characterized by large, late-closing fontanelles, hypertelorism, early-onset cataracts, and skeletal dysplasia. It is primarily inherited in an autosomal recessive manner, though rare autosomal dominant cases have been reported.

Case Report

An 11-year-old male was referred for short stature evaluation. His height was 130.1 cm (<3rd percentile, –2.66 SD), with a growth velocity of 3.5 cm/year (9th percentile). He had a proportionate body structure, normal head circumference (51.5 cm, 10th percentile), and delayed bone age (by ~3 years). Pubertal stage was Tanner P1G1. Born SGA (2480 g, <10th percentile) at 39 weeks via emergency cesarean section, he had cryptorchidism with a right inguinal hernia (surgically corrected at 10 months) and congenital heart defects (ASD and VSD), which closed spontaneously by age four. His cranial fontanelles closed at nine years. Facial dysmorphisms included a prominent forehead, hypertelorism, and low-set ears, with skin hyperpigmentation and a frontal hemangioma. He exhibited mild psychomotor developmental delay (PMDD) with muscular hypertonia, dystonic movements, and facial tics. Due to PMDD, brain and spinal MRI was conducted, revealing an empty sella and a small osteoangioma at D3. However, FRAXA analysis, array-CGH, plasma and urinary amino acid profiles were all within normal limits. Regarding his proportionate short stature associated with empty sella, routine blood tests, celiac serology, pituitary hormone profile, and sweat test were performed, all yielding normal results except for a low IGF-1 level for age. The patient subsequently underwent an arginine stimulation test, which demonstrated a normal GH peak (9.7 ng/ml). Whole exome sequencing ultimately identified a de novo heterozygous missense variant, c.2146C>T (p. Arg716Cys), in the **SEC23A** gene (14q13-q21), classified as likely pathogenic (Class 4). Given his syndromic short stature, SGA birth without catch-up growth, he recently started recombinant human GH (rhGH) at 30 mg/kg/day, with treatment ongoing.

Conclusions

This case presents notable features, including the autosomal dominant inheritance of cranio-lenticulo-sutural dysplasia and the ongoing treatment with rhGH, which has not been previously reported in the literature for this rare disorder. This highlights the importance of comprehensive genetic investigations in patients with suspected syndromic short stature.

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EP818

JOINT509

Differences in treatment efficacy between idiopathic short stature and other conditions with advanced bone age

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Background

Children with advanced bone age (ABA) and short stature present a therapeutic challenge. Idiopathic short stature (ISS) with ABA often involves delayed height gain despite treatment, contrasting with other conditions like congenital adrenal hyperplasia (CAH), obesity-related short stature, precocious puberty, and small for gestational age (SGA), which may show better therapeutic outcomes. The purpose of this review is to compare the efficacy of growth hormone (GH), GnRH analogs (GnRHa), and aromatase inhibitors (AIs) in ISS vs other ABA conditions.

Objectives
To compare therapeutic outcomes in ISS with ABA vs other conditions with ABA, identifying key differences in response to treatment combinations involving GH, GnRHa, and AIs.
Methods
This structured review analyzed 25 studies published between 1994 and 2024, focusing on treatments for ISS and other ABA conditions. Data were extracted regarding patient characteristics, treatment modalities, and main outcomes, and stratified into ISS and specific conditions like CAH, obesity-related short stature, precocious puberty, and SGA. Outcome measures included height standard deviation scores (SDS), predicted adult height (PAH), and bone age progression.
Results
In ISS, combination therapies of GH and GnRHa, or GH and AIs, yielded modest improvements in PAH (5–10 cm), with greater benefits observed in early interventions. However, ABA progression often resumes after treatment discontinuation. Conditions like CAH and precocious puberty responded more robustly to GH, GnRHa, and AI combinations, achieving PAH improvements exceeding 15 cm in certain cases, particularly in prepubertal patients. GH monotherapy showed limited height SDS improvement in obesity-related short stature while adding GnRHa or AIs significantly delayed ABA progression and enhanced final height. SGA cases demonstrated consistent improvements in height SDS with GH and GH+AIs, especially when initiated early, with less adverse impact on ABA. Across conditions, therapy in ISS was less effective at sustaining height gains and controlling ABA compared to CAH, precocious puberty, and obesity-related short stature.
Discussion
The comparative analysis reveals that ISS with ABA has a limited response to GH-based therapies relative to other ABA conditions, underscoring the need for early intervention and tailored approaches. The significant height gains in CAH and precocious puberty highlight the potential of combined therapies in ABA management.
Conclusion
ISS with ABA responds less robustly to therapy compared to other ABA conditions. Combined GH, GnRHa, and AI therapies are more effective in controlling ABA progression and improving height outcomes in CAH, precocious puberty, and SGA, suggesting condition-specific treatment strategies are critical for optimal growth outcomes.

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EP819

JOINT2262

INSIGHTS-GHT: first evaluation of paediatric patients with long-acting growth hormone therapy (LAGH) from the german registry

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Introduction
INSIGHTS-GHT is the world's first cross-product registry study on growth hormone (GH) therapy. It includes patients of all ages across all approved indications, enabling the documentation of real-world GH treatment patterns from childhood through transition to adulthood in Germany, and the analysis of a wide range of associated relevant scientific questions. In particular, since the end of 2023, patients treated with the newly approved long-acting GH preparations (LAGH) Ngenla© (Somatrogron), Skytrofa© (Lonapegsomatropin) and Sogroya© (Somapacitan) are also documented.
Methods
Since its launch in February 2022, more than 1800 patients from 30 endocrinological institutions in Germany have been included in the INSIGHTS-GHT registry. We report on the first interim evaluation of paediatric patients with growth hormone deficiency (GHD) who are receiving therapy with a LAGH. These patients receive LAGH subcutaneously once weekly. Here we report the findings from a database interim analysis dated 10/Jan/2025.
Results
So far, 62 children and adolescents under the age of 18 with GHD under LAGH from 14 centres have been included. Of these, 76 % are male. 42 cases (70 %) suffer from idiopathic growth hormone deficiency, 18 cases (30 %) have organic growth hormone deficiency. The age at the start of LAGH therapy was 9.2 (3.7) years. The majority of patients (81%) were prepubertal at the start of LAGH therapy. 34 patients (57%) had previously received therapy with daily GH for an average of 4.3 (2.9) years ('switch patients'). The body height at the start of LAGH therapy was -1.9 (1.2) SDS, BMI was -0.4 (1.2) SDS. The starting dose of the long-acting products was below the manufacturer's recommendation in 82 % of cases, with a median of 92 % of the recommended dose.
Conclusion
The INSIGHTS-GHT registry provides an excellent research platform to investigate various aspects of somatropin therapy, including data on the use of the preparations and the long-term effects in terms of safety, efficacy and quality of life. Initial baseline data on paediatric patients on long-acting GH therapy provide indications of its acceptance, indicate initial dosing of LAGH slightly below doses recommended by the manufacturers and will enhance our understanding of clinical practice.
Reference
Schnabel D. *et al* for the INSIGHTS-GHT Study Group. Investigating significant health trends in growth hormone treatments registry: rationale, aims and design of a nationwide prospective registry (study protocol). BMC Orphanet Journal of Rare Diseases 2023;18:112. https://doi.org/10.1186/s13023-023-02716-3

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820

JOINT2854

Clinical and biochemical variation in a consanguineous family with heterozygous MAP2K2 variant and hetero/homozygous TSH receptor variant

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Introduction
MAP2K2 defects cause a cardio-facio-cutaneous syndrome (CFC) with characteristic features with high penetrance. The TSH receptor variations may cause hypo- or hyperthyroid state. Here we describe the clinical and biochemical variations of a consanguineous family where a MAP2K2 mutation (CFC4) and a TSHR mutation are encountered. Focus is given to the large clinical variation in this family and possible associations with the gene variations.
Methods and Results
The parents are 1st grade cousins with 9 children out of which 6 were examined. No typical CFC features and no heart disease were encountered apart from short stature in the mother (151,5 cm) and one of the daughters (149,2 cm). Molecular analysis of this woman showed a mutation in MAP2K2 c.464G>T; Gly135Val close to the critical position 134. It was initially judged as relevant but later as VUS. Also, a TSHR mutation was found (c.202C>T; Pro68 Ser) which was judged as VUS. Nobody had a mental or a somatic developmental delay apart from a boy with GH deficiency and delay of puberty. Height was reduced in 2/6 (< = 1 perc) but normal in 3/6 (24 – 58 perc). One patient has a GH deficiency (before GH 7 perc., near final height 20 perc). Central hypothyroidism was found in 3/4 examined patients, in all of them TSHR variation - homozygous (2/2) or heterozygous (1/1). 2/2 examined had a subtle hypoadrenalism (1 homo-, 1 heterozygous for TSHR).
Discussion
There are no association with this MAP2K2 variant and height. The preponderance of neuroendocrine dysfunctions as central hypothyroidism is present. Hypothyroidism is also linked to the TSHR variant but primary hypothyroidism is expected rendering this link irrelevant. The lack of clear clinical associations to the MAP2K2 variant supports the view as allelic variant. Due to the subtle neuroendocrine dysfunctions a mild pathogenic role cannot completely ruled out.

	daughter	son	daughter	daughter	mother	father
Age	8 1/3	17 1/3	20 1/6	25 1/2	43	47
MAP2K2	+	+	+	+	+	-
TSHR	-/-	+/+	+/+	+/-	+/-	+/-
hypothyr.	-	+	+	+	n.e.	n.e.
hypocort	n.e.	+/n. substit.	n.e.	+/n. substit.	n.e.	n.e.
GH def.	n.e.	+ (< 5,69)	n.e.	-	n.e.	n.e.
Δ bone age	0	-1,5	0	0	n.e.	n.e.
height perc.	58	20	24	<1	1	20

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EP821

JOINT3932

Prader-willi syndrome: a journey of resilience againt hyperphagia and developmental challenges

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Introduction
Prader-Willi syndrome (PWS) is a rare genetic disorder caused by the absence of expression of paternally inherited genes on chromosome 15q11-q13. It is characterized by neonatal hypotonia, developmental delay, hyperphagia, obesity, and endocrine dysfunction.
Case Report
We present the case of a 3-year-old boy born to non-consanguineous parents, with a history of neonatal hypotonia at birth. Clinical examination revealed overweight (26 kg, +3 SD), facial dysmorphism characterized by a narrow forehead, almond-shaped eyes, strabismus, and hypoplastic genitalia with non-palpable testes. Due to ambiguous genitalia, a karyotype was performed, revealing a male chromosomal formula (46,XY). Based on the clinical findings, Prader-Willi syndrome was suspected. A methylation-specific PCR analysis of the SNRPN locus was conducted, confirming the absence of paternal contribution in the 15q11-q13 region, thus establishing the diagnosis of PWS.
Discussion
PWS is characterized by hormonal dysfunction, neonatal hypotonia, hyperphagia, learning difficulties, and behavioral disorders. In cases of severe neonatal hypotonia, an etiological investigation is crucial, particularly when associated with early feeding difficulties. The main complications of this syndrome arise from autonomy challenges and obesity, highlighting the importance of a multidisciplinary management approach to improve quality of life and long-term outcomes.
Keywords
Prader-Willi syndrome, neonatal hypotonia, hyperphagia, genetic disorder, methylation analysis, multidisciplinary management.
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EP822

JOINT3686

Childhood growth hormone deficiency and continuation of therapy in adulthood: case series of patients followed at a tertiary center

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Introduction
The transition period in patients undergoing recombinant human growth hormone (rhGH) therapy is a critical developmental phase, beginning at the end of puberty and lasting until early adulthood, typically 6–7 years after reaching final height. Despite slowed linear growth, rhGH remains vital for bone and lipid metabolism, body composition, and quality of life. Re-evaluating the somatotropic axis during this phase is essential, as some individuals diagnosed in childhood may exhibit normal secretion upon retesting. If deficiency persists, therapy continuation ensures complete bone mineralization and mitigates metabolic complications. However, many adolescents discontinue treatment or abandon medical follow-up, highlighting the need for coordinated care between pediatric and adult endocrinologists.
Objective
To characterize adults on rhGH replacement therapy for childhood-onset growth hormone deficiency (GHD) followed at a tertiary endocrinology center.
Methods
A retrospective observational study analyzing clinical records of patients followed until October 2024.
Results
The sample included 18 patients, with a median age of 22.5 (18–48) years, and 66.7% ($n = 12$) were female. The mean age at diagnosis and therapy initiation was 5.4 ($\pm$4.6) years, with a mean final height of 1.61 ($\pm$0.12) meters. The most frequent etiology was congenital structural abnormalities (66.7%), followed by sequelae-related conditions (22.2%), mainly secondary to space-occupying CNS lesions. Multiple hormone deficiencies were present in 88.9% ($n = 16$). Axis re-evaluation occurred at a mean age of 16.9 ($\pm$1.2) years, with a mean IGF-1 level of 97.2 ($\pm$53.9) ng/ml. Dyslipidemia was present in 55.6% ($n = 10$), and 83.3% of those assessed had low bone mineral density (BMD) or were at risk. Fifteen patients continued rhGH therapy without confirmatory testing, while three discontinued due to normal axis function. However, all three resumed therapy following reassessment due to cardiovascular comorbidities, decreased BMD or worsening quality of life.
Conclusion
rhGH replacement is indicated in patients with persistent deficiency during transition, offering long-term benefits. Most patients with persistent GHD had congenital structural abnormalities and multiple hormone deficiencies. Even those who discontinue therapy require active monitoring in adulthood. Continuous management is essential to optimize quality of life and prevent complications associated with chronic GH deficiency.
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EP823

JOINT3544

Noonan syndrome and growth delay: the hope of optimized growth with growth hormone therapy

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Introduction
Noonan syndrome (NS) is a rare autosomal dominant disorder caused by mutations in genes involved in the RAS-MAPK signaling pathway, most commonly the *PTPN11* gene. Patients with this syndrome exhibit characteristic dysmorphic features, cardiac anomalies, and growth delay. Among these manifestations, growth delay is one of the most common signs. Treatment with recombinant growth hormone (rhGH) is a widely used approach to stimulate growth in these patients.
Clinical Observation
We report the case of a 13-year-old boy, born by vaginal delivery with a birth weight of 1,800 g. He presents with characteristic dysmorphic features of Noonan syndrome, including low-set hairline and ears, hypertelorism, a triangular face, a mildly deformed chest, and widely spaced nipples. He measures 140.5 cm ($<$ -3 SD) and weighs 29 kg ($<$ -3 SD), indicating severe growth retardation. His genital examination revealed a penile length of 4.5 cm and testes measuring 2 $\times$ 1.5 cm. Biological investigations revealed an IGF-1 level of 169.2 ng/ml with a Z-score of -0.74. Bone age assessment showed a delay of 1 year and 2 months (bone age of 12 years). Additional investigations, including hypothalamic-pituitary MRI, renal ultrasound, and echocardiography, were normal. Furthermore, an insulin-induced hypoglycemia test showed no growth hormone deficiency. Treatment with recombinant growth hormone (rhGH) was initiated to stimulate growth. Regular follow-up is planned to evaluate the treatment response and monitor potential complications, particularly cardiac ones.
Discussion
Growth delay affects 50 to 70% of children with Noonan syndrome and often becomes apparent between the ages of 3 and 4 years. During childhood, these children generally have a height below the age-related norms. In adolescence, growth delay may worsen due to frequent pubertal delay in both sexes. Multiple factors can contribute to this growth delay, including growth hormone deficiency or IGF-1 resistance. In this context, treatment with recombinant growth hormone (rhGH) is a commonly used strategy to enhance growth. The results are generally positive, with notable improvements in growth velocity. However, cardiac abnormalities and the increased risk of hematological disorders often associated with Noonan syndrome require regular and thorough medical monitoring.
Conclusion
Growth delay in Noonan syndrome requires early and tailored management, along with regular follow-up, to improve growth and enhance the quality of life of patients.
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EP824

JOINT945

Skeletal ciliopathy and short rib dysplasia: a case report with response to growth hormone therapy

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Background
Skeletal ciliopathies are a rare group of disorders affecting bone development. Short rib dysplasia is characterized by a narrow thorax, shortened ribs, and variable metaphyseal abnormalities. This report presents a child with a confirmed genetic diagnosis of KIAA0753-related skeletal ciliopathy and highlights diagnostic and therapeutic challenges.
Case Presentation
A 4-year-old Yamni boy was evaluated for short stature at 5 months, having normal birth parameters but falling below the 3rd centile in height by 5 months. He exhibited facial dysmorphism, short long bones, and a narrow thorax, though BMI and development were normal. His parents were first cousins with no family history of similar conditions. Genetic testing identified a homozygous pathogenic variant in KIAA0753, confirming short rib dysplasia, an autosomal recessive disorder associated with skeletal dysplasia and Joubert syndrome features. At 1 year, he developed severe obstructive sleep apnea (OSA) and underwent adenotonsillectomy at 14 months. By 23 months, his height was -4 SD, and growth velocity was 7 cm/year. GH stimulation testing revealed a peak GH level of 19 ng/ml. A GH trial (0.05 mg/kg/day) was initiated at 2 years, leading to a height improvement of 1.4 SD over 2.5 years, reaching -2.6 SD with normal growth velocity.
Management and Outcome
The patient continues GH therapy with ongoing height improvement and no side effects. His latest anthropometric data at 4 years showed a height SDS of -2.6, weight SDS of -1.08, and IGF-1 level of 201 mg/L (2 SD).
Discussion
Genetic evaluation is essential in cases of disproportionate short stature. GH therapy in skeletal dysplasias has shown variable efficacy. Kochar & Chugh (2020) reported modest height gains in achondroplasia and hypochondroplasia (Kochar & Chugh, 2020). Upadhyay *et al.* (2022) noted that GH therapy might exacerbate skeletal abnormalities in Dyggve–Melchior–Clausen syndrome (Upadhyay *et al*., 2022). Despite uncertainties, our case supports potential GH benefits in skeletal ciliopathies.
Conclusion
Early diagnosis, genetic testing, and individualized GH therapy may optimize outcomes in skeletal ciliopathies. Continued GH therapy is recommended until the final adult height is reached, though further research is needed to refine treatment protocols.
Keywords
Skeletal Ciliopathy, Short Rib Dysplasia, KIAA0753, Growth Hormone Therapy, Rare Genetic Disorders
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EP825

JOINT920

A rare cause of short stature: cases with heterozygous mutations in the PCNT gene

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Introduction
Microcephalic osteodysplastic primordial dwarfism type II (MOPD II) is characterized by severe growth retardation, microcephaly, low to normal intelligence, distinctive facial features, and severe short stature. This study examines the clinical features of four cases with heterozygous mutations in the pericentrin (*PCNT*) gene.
Cases
Case 1: A 7-year-5-month-old male, born at 39 weeks with a birth weight of 2750 grams (-1.68 SD), presented with short stature. His height was 114.4 cm (-1.88 SD), weight 18.3 kg (-1.84 SD), head circumference 48.5 cm (-2.58 SD), and he was prepubertal with a growth velocity of 5.2 cm/year. **Case 2** An 8-year-old male, born at 38 weeks with a birth weight of 2000 grams (-3.67 SD), presented with short stature. His height was 113.3 cm (-2.65 SD), weight 17 kg (-2.68 SD), head circumference 50.5 cm (-1.45 SD), and he was prepubertal with a growth velocity of 4.5 cm/year. **Case 3** A 6-year-11-month-old female, born at 33 weeks + 5 days with a birth weight of 2080 grams (0.15 SD), was under follow-up for thyroid agenesis. Her height was 106.3 cm (-2.93 SD), weight 16 kg (-2.39 SD), head circumference 49.5 cm (-1.34 SD), and she was prepubertal with a growth velocity of 4.8 cm/year. Genetic analysis revealed heterozygous mutations in PCNT and MEN1 genes. **Case 4** A 10-year-9-month-old female, born at 36 weeks with a birth weight of 1500 grams (-3.32 SD), was under follow-up for celiac disease. Her height was 126.4 cm (-2.56 SD), weight 26.5 kg (-1.69 SD), head circumference 48.6 cm (-3.12 SD), and she was at Tanner stage 2. Her growth velocity was 5.3 cm/year. After three years of growth hormone therapy (0.045 mg/kg/day), her final height was 145 cm (-2.4 SD). All cases had heterozygous *PCNT* mutations, normal liver, kidney, and thyroid function tests, and negative celiac antibodies.
Conclusion
Heterozygous mutations in the *PCNT* gene, compared to homozygous or compound heterozygous cases, are associated with milder short stature but can still lead to low birth weight and, in some cases, microcephaly. Genetic analysis is critical in patients with short stature, SGA birth, microcephaly, or a family history of pathological short stature. According to current literature, pediatric cases with heterozygous *PCNT* mutations have not been previously reported. Comprehensive evaluations of the efficacy and safety of growth hormone therapy will play a key role in improving future treatment approaches.
Keywords
PCNT heterozygous, Short stature, Genetic short stature
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EP826

JOINT373

Beckwith wiedemann syndrome associated with transient typical features of classical congenital adrenal hyperplasia: a case report

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Introduction
Beckwith–Wiedemann syndrome (BWS) is a rare syndrome with features of overgrowth, macroglossia, abdominal wall defects, hemihypertrophy and enlarged abdominal organs. It is caused by genetic or epigenetic defects within the chromosome 11p15.5 region which contains imprinted genes that are strong regulators of fetal growth. Molecular diagnosis of BWS is important because of different degrees of predisposition to embryonal tumours in various subtypes. Presentation of BWS is widely variable and may be associated with adrenal involvement. Congenital adrenal hyperplasia (CAH) is the leading cause of atypical genitalia in the female newborn. An elevated blood level of 17-hydroxyprogesterone (17-OHP) indicates 21-hydroxylase deficiency, and is used in neonatal screening of CAH to prevent adrenal crisis and early neonatal death. Previously, BWS was not a recognized cause of false positives for CAH screening but this has been reported recently in some cases of BWS. This case is presented because of a similar presentation.
Case description
A late preterm (36weeks gestational age) female presented at the 3rd hour of life with anterior abdominal wall defect and swelling. Examination revealed coarse facial features, macroglossia, omphalocoele major, prominent labia majora with hyperpigmented and enlarged clitoris. Cardiorespiratory examination was essentially normal. Weight was (3600g) greater than the 97th percentile for age and sex, with length (50cm) and occipitofrontal circumference (32cm) at 95th and 50th percentiles respectively. No hemihypertrophy was noticed. Bedside blood glucose was low (30mg/dl[1.7mmol/l]). Other serum investigations revealed low cortisol, elevated testosterone and 17-hydroxyprogesterone. Pelvic ultrasound scan (USS) showed female internal genitalia suggesting CAH. She was commenced on hydrocortisone while omphalocele major was managed conservatively. There was no enlargement of the adrenal glands and no tumours seen on abdominal USS. Genetic analysis showed *hypomethylation at KCNQ1OT1:TSS-DMR (IC2) within 11p15.5* confirming a diagnosis of BWS. Clitoromegaly resolved at 6 months of age with normal pigmentation of the external genitalia. Steroids have been tailed off and repeat cortisol, testosterone and 17-hydroxyprogesterone are normal. Patient is being monitored as per the protocol for BWS with IC2 mutation (clinical assessment and USS in response to signs and/or symptoms or parental concern).
Conclusions
Beckwith-Wiedemann syndrome can present with features suggestive of CAH. Monitoring and genetic testing is essential for confirmation. In view of risk of adrenal crisis in infants with CAH, it may be better to err on the side of caution by commencing hydrocortisone especially when genetic screening is unavailable and tail off therapy if no longer needed.
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EP827

JOINT3811

Differences in age, gender, and hormonal immunohistochemical profiles among patients with acromegaly and non-functioning pituitary adenomas

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Introduction
Acromegaly is a rare disorder resulting from chronic hypersecretion of growth hormone (GH), typically due to a pituitary adenoma. Conversely, non-functioning pituitary adenomas (NFPAs) are among the most common subtypes of adenohypophyseal tumors, characterized by the absence of clinically significant hormone secretion. Data regarding gender distribution and mean age at diagnosis for these conditions remain inconclusive.
Aim
The study aimed to assess the differences in gender distribution, age, tumor volume, and hormonal immunochemical profiles (IHC) between patients with acromegaly and NFPA at diagnosis.
Methods
We retrospectively analyzed 81 patients diagnosed with acromegaly and 76 patients with NFPAs referred to our Clinic's Endocrinology and/or Neurosurgery Units between 2018 and 2019. Immunohistochemical analysis of adenohypophyseal hormone expression was available in tumor tissue samples from 53 patients with acromegaly and 29 with NFPA.
Results
Patients with acromegaly were diagnosed at a younger age than those with NFPAs (median [IQR]: 43 [39–56] years vs. 50 [40–63] years; $P = 0.034$), while no significant difference in gender distribution was observed between the groups. The median tumor volume in patients with NFPAs (3.8 [1.4–8.4] cm^3) was significantly larger than that in patients with acromegaly (1.4 [0.7–4.8] cm^3; $P = 0.004$). Immunohistochemical analysis revealed that adenomas in acromegalic patients were predominantly plurihormonal, with growth hormone and prolactin being the most frequently co-expressed hormones. In contrast, NFPAs showed most commonly negative hormonal staining. Among patients with acromegaly, males were diagnosed at a younger age than females (median [IQR]: 42.0 [39–50] years vs. 47.0 [38.5–60.5] years; $P = 0.041$). Interestingly, in patients with NFPA, both genders showed no significant differences regarding median age at diagnosis and tumor volume.
Conclusion
Our findings indicate that male patients with acromegaly are diagnosed at an earlier age than females, despite both having no significant differences in pituitary tumor volumetry. This may reflect an earlier onset or more prominent presentation of disease-related signs in males. Additionally, positive immunostaining for growth hormone and prolactin co-expression was a distinctive feature of pituitary tumor cells in patients with acromegaly.

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EP828

JOINT3652

Socio-demographic profile in adult patients with turner syndrome

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Background
Turner syndrome (TS) is characterized by a great variability of clinical manifestations caused by a total or partial loss of X-chromosome. TS is also associated with cognitive and psychosocial impairment
Objective
To describe the socio-demographic profile of adult patients with Turner Syndrome.
Patients and Methods
This was an observational case series with a retrospective chart review of 33 patients diagnosed with TS who are aged over 15 years. These patients were followed at the Farhat Hached University Hospital Sousse.
Results
The mean age of the patients was 25.6‡ 10.6 years, with a mean age at diagnosis of 16.3 ‡ 6.4 years. Chromosomal abnormalities were categorized as follows: monosomy X in 54.4%, solely structural abnormalities in 18.2%, and monosomy with structural abnormalities in 27.3%. Parental consanguinity was observed in 31.3% of the cases and was more frequent among patients with mosaicism. The mean maternal age at birth was 27.57 # 4.27 years, with advanced maternal age noted in only one patient. At the legal age of marriage, 88% of the patients were single, and 12% were married. Regarding educational attainment, 21.2% had completed primary education, 63.6% had completed secondary education, and 15.2% had attained higher education. A higher level of education was noted in patients with mosaicism (27.5% vs. 9.5% in those with homogeneous anomalies), although this difference was not statistically significant. Nine percent of the patients had hearing loss and used hearing aids, while only one patient exhibited cognitive decline.
Discussion
Patients with TS face a multitude of social challenges, including significant difficulties with interpersonal relationships and academic performance, which can profoundly impact their overall quality of life. Furthermore, some studies have emphasized the challenges these patients encounter in effectively identifying emotions and understanding the mental states of others. This inability can lead to misunderstandings in social interactions and can hinder the development of meaningful relationships. Additionally, specific learning difficulties, such as challenges with spatial reasoning or mathematics, are reported to be prevalent among individuals with TS. These factors necessitate not only a comprehensive approach to their medical care but also the establishment of a supportive and understanding social and educational environment conducive to their unique needs. Creating tailored educational programs that focus on emotional intelligence and social skills may significantly benefit patients as they navigate their educational and social landscapes.

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EP829

JOINT881

GH therapy in patients with empty sella syndrome and growth hormone deficiency: two cases with transition to weekly treatment

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Introduction
Empty Sella Syndrome (ESS) is a rare condition in children, often associated with growth hormone (GH) deficiency. We present two pediatric cases of ESS diagnosed with GH deficiency who demonstrated significant growth improvement after receiving recombinant GH (rGH) therapy. Both patients were transitioned to weekly GH therapy at some point through their treatment, showing sustained positive outcomes.
Methods
Case 1 involves a 12-year and 6-month-old male who presented with short stature and rapid decline in height velocity, showing a growth rate of 2.3 cm/year. Medical and birth history were unremarkable. His height was 138.5 cm ($\leq$2nd percentile), and he was in Tanner stage 2-3, with a testicular volume of 7 ml. GH stimulation tests revealed peak GH levels of 6.8 ng/ml (glucagon) and 7.6 ng/ml (L-Dopa), with an IGF-1 of 182 ng/ml. MRI confirmed ESS. GH treatment was started, and the results are shown in table 1. Case 2 involved a 12-year and 10-month-old male referred due to short stature. His height was 140 cm (3rd percentile), weight was 29 kg, and height velocity was 3.1 cm/year. He had a 2-year history of well-managed hypothyroidism, and unremarkable birth history. GH stimulation tests revealed peak GH levels of 6.6 ng/ml (glucagon) and 6.0 ng/ml (L-Dopa). MRI confirmed ESS. GH treatment was started, and the results are shown in table 1.
Results
Both patients showed significant growth improvement with rGH. In Case 1, height increased by 13 cm in 18 months. In Case 2, height increased by 26 cm in 2 years and 7 months. Transitioning to weekly GH therapy midway through treatment maintained sustained or growth improvements in both cases. Interestingly, case 2 benefited more from the weekly GH treatment due to improved compliance.

Table 1. Case 1

Date of Measurement	Age (years)	Height (cm)	Bone Age (years)
8/6/23 **Beginning of treatment**	12+6/12	138.5	12
30/11/23	12+11/12	142.5	12+9/12
3/6/24 **Transition to weekly GH**	13+5/12	145.5	13+3/12
5/12/24	13+11/12	151.5	13+6/12

Table 1. Case 2

Date of Measurement	Age (years)	Height (cm)	Bone Age (years)
3/5/22 **Beginning of treatment**	12+9/12	140	11+6/12
1/11/22	13+2/12	144	12
2/5/23	13+8/12	149	13
30/11/23	14+4/12	155	14
30/5/24 **Transition to weekly GH**	14+9/12	160	15
2/12/24	15+3/12	166	15+3/12

Conclusion
These cases show the effectiveness of recombinant GH therapy in promoting significant growth in pediatric ESS patients with GH deficiency, with sustained or even improved benefits following the transition to weekly GH.

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EP830

JOINT510

Evaluating the IGF-1 generation test as a predictor of growth outcomes across pediatric growth disorders"

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Background
IGF-1 generation is valuable for assessing early and long-term growth outcomes, but its utility varies depending on the disorder and degree of GH sensitivity.
Objective of the Review
To evaluate the predictive and diagnostic significance of the IGF-1 generation-test in determining growth response and GH sensitivity in growth disorders.
Methods
Data were compiled from six studies, encompassing over 800 pediatric patients with conditions such as Growth Hormone Deficiency (GHD), Idiopathic Short Stature (ISS), and GH insensitivity. Studies assessed the correlation between IGF-1 generation, early IGF-1 responses during GH therapy, and long-term growth outcomes.
Results
Table.
1. Predictive Value: Early increases in IGF-1 levels during GH therapy strongly correlated with positive long-term growth outcomes, as highlighted by studies with larger sample sizes-(Smyczynski *et al*., 2013; Blum *et al*., 1993).
2. GH Sensitivity: Changes in IGF-1 levels during therapy positively correlated with improvements in height, confirming GH sensitivity across various conditions-(Kim *et al*., 2021).
3. Utility in Diagnosing GH Insensitivity: The test has limitations in detecting mild GH insensitivity, with some variability in responses among GHD and ISS patients-(Coutant *et al*., 2012; Buckway *et al*., 2001).
4. Combined Markers: IGFBP-3 levels at baseline and during therapy enhance the predictive utility of the test, particularly in short stature children-(Perez-Colon *et al*., 2018).
Discussion
The IGF-1 generation test is a valuable tool for predicting long-term growth responses to GH therapy and assessing GH sensitivity. Its strengths lie in strong early correlations with growth outcomes, but its limitations in detecting mild GH insensitivity highlight the need for additional markers like IGFBP-3.
Conclusions
The IGF-1 generation test is a reliable marker for predicting GH therapy outcomes and assessing GH sensitivity in children. Its utility is enhanced when combined with additional biomarkers like IGFBP-3, although limitations in diagnosing mild GH insensitivity must be considered. Table: Predictive and Diagnostic Findings from IGF-1 Generation Test Across Growth Conditions"

Table 1. Predictive and Diagnostic Findings from IGF-1 Generation Test Across Growth Conditions

Condition	Main Findings
Short Stature and GHD	Early IGF-1 and IGFBP-3 increases correlate with long-term growth response to GH therapy.
GHD and ISS	Early IGF-1 increases predict better growth outcomes over time.
Short Stature (Various Conditions)	Positive IGF-1 changes during therapy correlate with height improvement.
Mild GH Insensitivity (GHIS)	Test has limitations in detecting mild GH insensitivity.
GH Responsiveness (GHD, ISS, GHIS)	GH sensitivity varies; IGF-1 generation test reflects dose-dependent response.
Short Stature with Low IGF-1	Baseline IGF-1 and IGFBP-3 predict growth response to GH or IGF-1 therapy.

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EP831

JOINT1408

A novel IGF1R variant in a patient with short stature in qatar

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Introduction
Short stature (SS) is a common cause of referral to pediatric endocrinology clinics and can arise from a range of underlying causes. Among the endocrine disorders leading to SS are growth hormone and Insulin Growth Factor-1 (IGF-1) signaling defects. Genetic testing plays a crucial role in uncovering variants in genes, such as type 1- insulin-like growth factor receptor gene (*IGF1R*), associated with SS to tailor personalized treatment options. Here we report a novel missense variant in *IGF1R* in a SS patient in Qatar.
Case Presentation
A female patient presented with failure to thrive, SS, and microcephaly at 10 years of age. She was born SGA with birth weight of 2.3kg at term. At evaluation, her height was 121.2cm (-2.89 SD) and weight was 19.15kg (-3.89 SD). Her serum IGF-1 level was 47.7 nmol/L (Normal range: 9.9-71.8) and the growth hormone stimulation test was normal. She has a family history of SS on the paternal side. Whole genome sequencing (WGS) and bioinformatics analysis identified a novel missense heterozygous variant c.2240A>G (p.Asn747Ser) in *IGF1R*. This variant segregated in an autosomal dominant manner, has a Combined Annotation-Dependent Depletion (CADD) score of 22.4, and was predicted to be 'disease-causing' by Mutation Taster. Protein-protein docking of the mutated and wild-type IGF1R with interactor proteins using HADDOCK found that mutant IGF1R showed decreased affinity for IGF1 and higher binding for IGF2 compared to the wild type, thus disrupting the normal IGF1 signaling and leading to IGF1 resistance.
Conclusion
We identified a novel c.2240A>G missense variant in *IGF1R* in SS patient. Her phenotype is consistent with those findings reported in the literature for *IGF1R* mutations. This emphasizes the importance of WGS in SS patients and examining *IGF1R* variants in patients with impaired growth, especially those with elevated or normal levels of circulating IGF-1 in the bloodstream.

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EP832

JOINT1030

Effect of urea ingestion on growth hormone levels in healthy adults – An analysis of a double-blind, randomized, placebo-controlled cross-over trial

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Introduction
Growth hormone (GH) deficiency is commonly diagnosed using stimulation tests such as insulin hypoglycemia or the GH-releasing hormone-arginine test. However, these tests are burdensome and require intravenous access. Macimorelin, an oral GH stimulation test, offers an alternative but is unavailable in many countries, highlighting the need for accessible, non-invasive oral options. Urea, the end product of protein metabolism, is commonly used as an oral treatment for hyponatremia. Since GH promotes protein synthesis and reduces urea production, we hypothesized that high urea levels may stimulate GH secretion via feedback regulation. Therefore, this study investigates whether oral urea could serve as an alternative stimulation test for diagnosing GH deficiency.
Methods
This is a secondary analysis of a double-blind, randomized, placebo-controlled cross-over trial in 22 healthy adults. Participants presented for two visits in the morning after an overnight food fasting and a two-hour fluid restriction. They received a single weight-adapted dose of oral urea (0.5 g/kg body weight; minimum 30g, maximum 45 g) or placebo in random order. Serum GH was measured at baseline, 60 and 120 minutes. The primary endpoint was the serum GH levels after ingestion of urea vs placebo.
Results
Of 22 healthy adults, 12 (55%) were female, with a median [IQR] age of 27 years [26, 32] and a body mass index of 23.3 kg/m^2 [21.6, 25.8]. Before urea ingestion, GH at baseline was 0.83 µg/l [0.28, 5.75], decreased to 0.38 µg/l [0.20, 2.46] after 60 minutes, and increased to 1.00 µg/l [0.71, 2.34] after 120 minutes. Before placebo ingestion, GH at baseline was 0.93 µg/l [0.38, 5.34], decreased to 0.38 µg/l [0.16, 1.51] after 60 minutes, and increased to 0.73 µg/l [0.18, 1.59] after 120 minutes.

Conclusion
Our study demonstrated no relevant changes in serum GH after the ingestion of urea in comparison with placebo. These findings suggest that urea does not stimulate GH secretion and cannot be used as a stimulation test for GH deficiency.

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EP833

JOINT2490

An early diagnosed leri-weill dyschondrosteosis case caused by unusual genetic results

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Introduction
The SHOX gene (Short stature HOmeoboX-containing gene) regulates height growth. It is located in the pseudoautosomal region of the short arms of the X and Y sex chromosomes and encodes a transcription factor called SHOX protein. Haploinsufficiency of the SHOX gene is responsible for the etiology of many diseases such as idiopathic short stature, Turner Syndrome, and Leri-Weil dyschondrosteosis. We present a rare case of Leri-Weil dyschondrosteosis diagnosed at an early age due to a mutation in the SHOX gene in a patient presenting with disproportionate short stature.
Case Presentation
A five-month-old male infant presented with disproportion in the arms and legs and short stature. He was born at 38 weeks gestation, weighing 3700 grams, to a 36-year-old mother in her second pregnancy (second live birth). There was no significant past medical or family history. On physical examination, his weight was 5250 grams (-2.61 SDS), height was 57.3 cm (-3.48 SDS), and head circumference was 38.5 cm (3.43 SDS). His mother's height was 155 cm, his father's height was 176 cm, and his target height was 172 cm(-0.19 SDS). His forearm length was 9 cm, and his upper arm length was 10 cm and had mesomelic shortening. No mutation was detected in the DNA sequence analysis that would explain his short stature. Cytogenetic analysis (karyotype) of the patient revealed a deletion of the SHOX gene on the Y chromosome. The patient's cytogenetic analysis was reported as mos46XY, del(Y)(p11.3)del(Y)(q11.2), t(14;16)(p11.2q11.2)(15)/45,X, t(14;16 p11.2;q11.2)(15). Cytogenetic analyses of both parents were performed. The mother's genetic analysis was reported as 46 XX, t(14:16)(p11.2;q11.2), indicating that she was a carrier of the translocation. Based on these genetic findings, the patient was diagnosed with Leri-Weil dyschondrosteosis. At 1 year and 2 months old, the patient's weight was 6.7 kg (-4.76 sds), height was 64 cm (-5.51 SDS). Growth hormone therapy was initiated. At 1 year 8 months of age the patient's weight was 7.5 kg (-4.58 sds), height was 70 cm (-4.39 SDS) by using growth hormone therapy 2 months.
Conclusion
Leri-Weil Dyschondrosteosis is a skeletal dysplasia characterized by mesomelic shortening. It should be considered in the differential diagnosis of patients presenting with disproportionate short stature. Early determination of the etiology of short stature and initiation of growth hormone therapy may lead to gains in final adult height.

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EP834

JOINT1548

The clinical and mutational spectrum of ulnar-mammary syndrome: two case reports and literature review

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Objective
The aim of this study was to investigate the clinical and genetic characteristics of three cases of short stature caused by the *GHSR* gene mutation.
Methods
A retrospective analysis was conducted on the clinical data and genetic test results of three cases of short stature caused by the *GHSR* gene mutation. The patients were followed up at the Department of Endocrinology Genetics and Metabolism of the Children's Hospital of Soochow University. A literature search (search terms included "*GHSR*" and "short stature") for recently published studies was completed using the China National Knowledge Infrastructure database, WanFang database, PubMed, and the Human Gene Mutation Database.
Results
The peak value of growth hormone provocation test in two cases was >10 ng/ml, and the height of two patients was improved after recombinant human growth hormone therapy. One untreated patient was followed up until lifelong height was reached, and the patient remained with a short stature.
Conclusion
The peak value of growth hormone provocation test in patients with *GHSR* gene variants may be >10 ng/ml, these patients may have precocious puberty, and short stature caused by the *GHSR* gene mutation can be treated with growth hormone.

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EP835

JOINT1466

Empty sella syndrome and growth hormone deficiency in a 6-year-old boy with short stature

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Introduction
Growth deceleration in children may indicate an underlying condition. One such condition is Empty Sella Syndrome (ESS), a radiological finding caused by the herniation of the subarachnoid space into the sella turcica, leading to pituitary gland flattening. While rare in children and often an incidental MRI finding, ESS can be associated with hormonal deficiencies, particularly growth hormone deficiency (GHD), which contributes to growth impairment.
Case Report
A 6-year-old boy was referred to the endocrinology clinic for growth monitoring due to concerns about his growth velocity. Over the past year, his height declined from -1.83 standard deviations (SD) to -2.40 SD, with a growth velocity of 3 cm/year—below the expected rate for his age. His medical history included left cryptorchidism, surgically corrected in infancy, with no family history of endocrine disorders. On physical examination, his height was 105 cm (-2.40 SD, $<$3rd percentile), below the mid-parental height with a Z-score of -2.22. His weight was 23 kg (BMI $=$ 18.6, 95th percentile). He was Tanner stage I, with no other systemic abnormalities or developmental delays. Laboratory tests revealed low IGF-1 (19.3 ng/ml; normal: 36.6–156) and low IGFBP-3 (1.24 µg/ml; normal: 1.94–5.19), with normal thyroid, ACTH, cortisol, and prolactin levels, ruling out other pituitary axis dysfunctions. Bone age assessment showed a 2-year delay, and karyotype analysis confirmed a normal male karyotype. A clonidine stimulation test demonstrated a poor GH peak of 1.77 ng/ml, confirming growth hormone deficiency. MRI revealed an extension of the subarachnoid space into the pituitary fossa, compressing and flattening the pituitary gland—a characteristic finding of ESS. The patient was diagnosed with growth hormone deficiency secondary to Empty Sella Syndrome and was started on recombinant human growth hormone at a dose of 0.025 mg/kg/day (0.55 mg/day). After three months of treatment, he demonstrated significant improvement, with a height increase of 5.5 cm, reaching 110.5 cm. His Z-score improved by approximately 1 SD (from -2.49 to -1.59), reflecting notable catch-up growth. He will continue to be closely monitored for growth response and other potential pituitary hormone deficiencies.
Conclusions
ESS is rare in children, presenting as either an incidental finding or with hormonal deficiencies. Growth hormone deficiency, the most common pituitary disorder in ESS, affects 12% to 60% of patients. Early diagnosis and timely growth hormone therapy are essential for optimizing growth outcomes in affected children.

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EP836

JOINT2702

A clinical case of rasopathies caused by a mutation in the SHOC2 gene

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RASopathies is a multisystem genetic disorder characterized by such clinical manifestations as growth retardation, craniofacial and skeletal anomalies, varying degrees of intellectual disability, congenital heart defects and a predisposition to myeloproliferative disorders. Girl E., 5 years old, from the 2nd pregnancy, during the ultrasound examination at the 1st screening an expansion of the collar area nuchal was revealed, at the 20th week of gestation - chorioangioma of the placenta. The 2nd birth

was by cesarean section at the 38th week of gestation. At birth, body weight was 3120 g (0.06SD), body length was 48 cm (-0,35SD), according to the Apgar scale 8/9 points. The early neonatal period was unremarkable. Family history of endocrinopathies is not burdened, target height is 163.5 cm, SDS of target height: 0.025 SD. At 3 months, the girl suffered from mixed-etiology sepsis and iron-deficiency anemia. She is being observed by an ophthalmologist with the following diagnosis: OU - compensated convergent sensory, unilateral OD strabismus, accommodative. High myopia OD. Lesion of the central section of the visual analyzer, partial atrophy of the optic nerve OD > OS. OD - madarosis, trichiasis, deformation of the upper eyelid margin. OS - partial ptosis of the upper eyelid stage 1, compensated. Congenital renal defects are excluded. A functioning oval window up to 2 mm remains. Growth retardation is observed from an early age. Karyotype: 46,XX. During examination at 4 years, blood tests showed IGF-1 - 65.8 ng/ml (SDS IGF-1 - 0.82), no data for deficiency of other tropic hormones were obtained. At the age of 5 years his height was 98.2 cm (- 2.4 SD), his weight was 16.5 kg (BMI + 1.1 SD), Tanner 1. Phenotypic features were noticed: low-set ears, left eyelid ptosis, strabismus, scaphocephaly, hoarse voice, short neck, chubby cheeks, dark skin, light, sparse, falling out hair. Bone age corresponded to chronological age. Additional molecular genetic testing was performed: a mutation in the SHOC2 gene (chr10:112724120A > G) was detected in a heterozygous state, leading to a substitution of an amino acid in position 2 of the protein [NM 001324336.1:c.4A > G; p.(Ser2Gly)]]. The presented clinical case demonstrates the classic phenotype of RASopathies with loss of anagen, caused by a pathogenic variant in the SHOC2 gene. The issue of treatment with somatropin remains controversial due to the lack of published randomized clinical trials with long-term observation of patients until the period of achieving final height.

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EP837

JOINT722

Pharmacological treatment of growth in boys with delayed or slow progression of puberty

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At puberty, male sexual differentiation restarts with nightly pulsatile stimulating impulses of hypothalamic gonadotropin-releasing hormone to the pituitary gland, which releases luteinizing and follicle-stimulating hormones. This nocturnal increase in gonadotropins results in growth, too. The aim of the research work was to correct the height of children the use of testosterone enanthate (TE), 50 mg intramuscularly (i.m.)/month, for the treatment of boys with delayed puberty or slow progression to induce puberty. For this purpose, 25 boys were examined. The average age of children was 13.9 ± 1.03 years. In children, they were evaluated according to the Tanner table and measured their height, body mass and injected 0.2 ml of Omnadren-250 (testosterone, mixture of esthers). Children took this drug once a month. The boys are called back after 3 months for clinical evaluation and to follow up on pubertal and growth progression. The boys were examined by study doctors twice before the study, at inclusion, and after 3 months. After 3 months, their physical development was assessed. Physical development indicators of children are given in table 1 below. The results show that 50 mg (0.2 ml) of TE administered once every months for 3 months can be used to induce growth development in boys with delayed or slow progression of puberty, while did not record an honest increase in body mass.

Table 1. Indicators of physical development of children

Parameters	Before	After	p
Height	144,4 ± 4,83	147,1 ± 4,45	p < 0,0001
Weight	36,5 ± 7,03	39,0 ± 6,62	p > 0,05
SD Height	-2,3 ± 0,25	-2,1 ± 0,23	p < 0,0001
SD Weight	-0,9 ± 1,39	-0,7 ± 1,24	p > 0,05
BMİ kq/m^2	17,5 ± 3,10	17,9 ± 2,77	p > 0,05
Body percent %	78,7 ± 21,07	86,4 ± 12,89	p > 0,05

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EP838

JOINT3727

Spontaneous pregnancy in a patient with turner syndrome

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Introduction
Turner syndrome (TS) is the most common chromosomal abnormality in women, occurring in approximately 1 in 2,500 live births. Spontaneous pregnancies in individuals with TS are rare, with an incidence ranging from 1.8% to 7.6%. We report a case of three spontaneous pregnancies in a patient with TS.
Observation
A 31-year-old female with no significant past medical or family history presented for evaluation. She reported menarche at the age of 12, with subsequent regular menstrual cycles. Physical examination did not reveal any evidence of growth retardation or dysmorphic features typically associated with TS. The patient had three spontaneous pregnancies throughout her reproductive life. The first pregnancy was terminated in the second trimester after the discovery of a malformation syndrome. Chromosomal analysis confirmed a diagnosis of Turner's mosaic syndrome, with a karyotype of 45,×/46, XX. Further evaluation for common comorbidities associated with TS, including cardiac anomalies, was negative, with no evidence of cardiac malformations. The patient then conceived two more times, with both pregnancies progressing without significant complications. Both were carried to term, delivered vaginally, and resulted in the birth of two healthy female neonates, each with a normal karyotype (46,XX).
Discussion
TS is strongly associated with hypergonadotropic hypogonadism and ovarian dysgenesis, which typically result in infertility in most affected individuals. The issue of fertility in individuals with TS has been extensively studied. Cryopreservation of mature oocytes and embryos is a well-established method for fertility preservation, while cryopreservation of ovarian tissue represents a promising, though still investigational, approach, with a growing number of successful live births. Spontaneous pregnancies, such as those observed in the present case, are rare and are more commonly seen in individuals with mosaic forms of Turner syndrome or those with distal X chromosome deletions. Cardiac malformations are considered absolute contraindications to fertility treatments due to the substantial maternal and fetal risks involved. Pregnancies in individuals with TS are associated with a significantly increased risk of miscarriage and other obstetric complications, which necessitates vigilant monitoring by a multi-disciplinary medical team to optimize both maternal and fetal outcomes.

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EP839

JOINT1664

Shaff yang syndrome and growth hormone therapy

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Introduction
Schaaf-Yang syndrome (SYS) is the result of loss of function of the MAGEL2 gene (point mutations in the gene) within chromosome 15q11-13. A microdeletion or paternal disomy (pUPD) region of chromosome 15q11-13 is the cause of the better known Prader-Willi syndrome (PWS). Due to the genetic basis, both syndromes show a high similarity of symptoms in infancy, i.e. hypotonia, feeding problems, sleep apnoea, hypogonadism, but also intellectual developmental delay and low stature. Autism spectrum disorders and joint contractures are additionally observed in SYS patients. Studies show undeniable benefits of rhGH therapy in PWS patients during childhood, as well as after end of growing. Benefits include, in addition to improved growth rate, improved body composition, improved lipid profile, increased bone mineral density and improved mental status along with quality of patientś life.
Aim
This study presents 4 children with genetically confirmed Schaaf-Yang syndrome. Health problems observed in the children were hypotonia, respiratory distress in the neonatal period, hypoglycaemia, psychomotor developmental delay, low stature and epilepsy, autism, joint contractures. Three children were qualified for growth hormone treatment under the programme for children with somatotropin hypopituitarism. We will compare anthropometric parameters including growth rate during therapy, biochemical parameters of blood, lipid, endocrine and carbohydrate metabolism, overall psychomotor development of the children and the impact of growth hormone treatment on family quality of life.
Conclusions
1. Growth GH deficiency has been documented in Schaaf-Yang syndrome, therefore it is reasonable to treat these children with growth hormone from early life. 2. The validity of the child's eligibility for growth hormone treatment from a different programme than for children with SNP based on the genetic diagnosis of the disease (no need for pituitary stimulation tests and radiological imaging) should be considered. 3. Given the similarity of SYS with PWS and the benefits of growth hormone therapy taking into account the promotion of growth and the

positive metabolic impact, it is advisable to determine the optimal initial therapeutic dose of rhGH.

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EP840

JOINT1218

Design of a randomized, multicentre, phase 2 study of vosoritide in children with turner syndrome, noonan syndrome, or short stature homeobox-containing gene (SHOX) deficiency

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Turner syndrome, Noonan syndrome, and short stature homeobox-containing gene deficiency disorders (SHOX-Ds) are associated with excess extracellular-signal-regulated kinase (ERK) signalling, similar to achondroplasia. All 3 are characterized by short stature, among other phenotypes. Treatment with human growth hormone (hGH) is standard of care, but response generally declines over time. Vosoritide, an analogue of the master growth regulator C-type natriuretic peptide, is an approved targeted therapy for achondroplasia that stimulates endochondral bone growth by reducing ERK activity. Phase 2 proof-of-concept studies in children with short-stature disorders including Noonan syndrome (NCT04219007) and Turner syndrome (NCT05849389) are ongoing. Study 111-211 (NCT06668805) is a phase 2, randomized, active-controlled, multicentre basket study to generate efficacy and safety data across a range of vosoritide doses vs hGH in children with genetically confirmed Turner syndrome, Noonan syndrome, or SHOX-D with inadequate response to hGH. Participants will be aged ≥ 3 years and < 11 years (females) or < 12 years (males) and prepubertal with height Z-scores ≤ -2.00 from US Centers for Disease Control and Prevention (CDC) average-stature references. Participants must have been receiving ≥ 0.35 mg/kg/week hGH for ≥ 1 year or an optimized dose according to the local standard of care without dose changes in the previous 6 months. They must have an inadequate hGH response that is less than age- and sex-matched average-stature annualized growth velocity (AGV) determined using median heights from CDC growth charts. Baseline AGV will be prospectively established during a 6-month growth assessment phase while participants continue their hGH regimen. Randomization will be 1:1:1:1 to 7.5, 15.0, or 22.5 μg/kg/day vosoritide or daily hGH at a dose equivalent to participants' previous regimen. Study-site personnel and participants will be blinded to vosoritide doses; hGH will be open-label. Transition to the selected therapeutic vosoritide dose will occur after the 6-month dose-finding phase for vosoritide participants and after 24 months for hGH participants, if desired. Treatment will continue until participants are near final adult height (FAH), and follow-up will continue until FAH. The primary objective is to evaluate the efficacy of 3 doses of vosoritide vs hGH as measured by change from baseline (CFB) AGV after 6 months of treatment. Secondary endpoints include CFB height and height Z-score at 6 months; CFB height, height Z-score, and AGV over 24 months (therapeutic dose vs hGH); and adverse event incidence. This study may support vosoritide as a second-line treatment for these conditions if hGH treatment becomes inadequate.

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EP841

JOINT4022

Youn adults with prader willi syndrome - chalenge for endocrinologist, single centre observation

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Introduction
Prader-Willi syndrome (PWS) is a complex genetic disorder characterized by a set of phenotypic traits, which include infantile hypotonia, short stature, and morbid obesity. Hypothalamic disorders observed in patients with PWS are responsible for a variety of symptoms, including severe hyperphagia and endocrine disorders, such as growth hormone deficiency, hypothyroidism, hypothyroidism, and hypogonadotropic hypogonadism. Growth hormone (GH) deficiency is a common endocrine problem in PWS patients not only in childhood but also in adults. Recombinant human growth hormone (rhGH) therapy and hormonal replacement therapy, serves to achieve an ultimate height and compensate for metabolic abnormalities. Hormonal disorders diagnosed and treated in childhood require continuation and constant monitoring in adulthood. In some patients, hypothyroidism or adrenal insufficiency doesn't appear until adulthood. Patients with PWS require constant multidisciplinary care, including an endocrinologist.
Aim
The aim of the study was to assess the metabolic and hormonal profile of young adults with PWS. Additionally, we compared patients treated with GH since childhood with PWS never treated with growth hormone.
Material and Methods
This study including 52 young adults with PWS, 25 woman and 27 men. The average age of patients is 23 years (man) and 24 years (women). PWS patients were divided into two groups: treated with growth hormone since childhood (37 patients) and not treated with GH (15 patients). Body weight, BMI and percentage of body fat were assessed in all patients. Fasting glucose and insulin levels, lipid profile and hormone levels were assessed and statistically analysed comparing both groups. The GH treatment was monitored with IGF-1 serum levels.
Results
In all patients with PWS (100%) were diagnosed growth hormone deficiency and hypogonadism, requiring substitution treatment. Hypothyroidism was found in 68%, and adrenal axis impairment in 50% patients. The group of GH treated patients, had statistically lower body fat percentage and BMI degree and normal IGF-1 level in comparison to untreated group. HOMA-IR index was statistically lower in the GH-treated group. There were no differences in the incidence of hypothyroidism or adrenal insufficiency in both groups.
Conclusions
The main aim of PWS clinical management in adulthood is prevention of obesity and its comorbidities, treatment of hormonal disorders, mental health stabilization, nutritional guidance, as well as on-going physiotherapy. Integrated multidisciplinary therapeutic interventions, including endocrine ones are necessary if patients with such a complex genetic condition as PWS are to not only achieving average life expectancy, but also to enjoy higher quality of life.

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EP842

JOINT1706

Paediatric langerhans cell histiocytosis disease: long-term sequelae in the hypothalamic endocrine system

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Introduction
Langerhans cell histiocytosis (LCH) is a disorder of the mononuclear phagocyte system that can affect almost any organ and system. The most common central nervous system (CNS) manifestation in LCH is the infiltration of the hypothalamic-pituitary region leading to destruction and neurodegeneration of CNS tissue, causing the most frequent endocrinological manifestation which is central diabetes insipidus (CDI), and less often anterior pituitary hormone deficiency (APD). Growth hormone is the most commonly affected anterior pituitary hormone.
Case Report
We report the case of an 11-year-old boy who had been treated since the age of 1.5 years for multisystemic Langerhans cell histiocytosis with chemotherapy and who was admitted for short stature. Magnetic resonance imaging showed a moderate reduction in the thickness of the extra-axial mass of the brain scythe, with no detectable abnormalities in the pituitary or pituitary stalk. Endocrinological examinations revealed a profound growth hormone deficiency and partial central hypocorticism. The patient was put on hydrocortisone and growth hormone, with a good progression in height to the mean at the age of 19. The patient did not present with diabetes insipidus nor any other antehypophyseal deficiency.
Discussion/Conclusion
Patients who develop endocrine LCH disorders are at a high risk of neurodegeneration of CNS tissueand require long-term follow-up. Despite significant advances in the knowledge of LCH in recent years, little progress has been made in preventing long-term sequelae such as those affecting the hypothalamic-pituitary system.

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EP843

JOINT2786

Statural advance: a challenge for diagnosis and management

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Introduction
Tall stature is defined as a height greater than or equal to +2 standard deviations (SD) on the reference growth curves, or a height greater than 1.5 SD in relation to the genetic target height. While stunted growth is a frequent reason for consultation, overgrowth is often a rarer and more specialized problem. The interest lies in the identification and management of the cause, as well as the indication of a restraining treatment when the psychological repercussions are significant.
Observation
This is a 14-YEAR-OLD patient with no notable pathological history, menarche at the age of 11, who consulted us for tall stature with no similar cases in the family: A height of 174 cm situated between plus 2DS and3DS on the reference curves with a target height of 164 cm, greater than 2DS of the genetic height, the pubertal stage is S4P4, there were no dysmorphic features or signs of associated hyperandrogenism in our patient, the karyotype was normal, the thyroid work-up was normal FSH:3.9UI/L LH:2.8UI/l OESTRADIOL:29.7 pg/ml IGF1: 325 ng/ml z score -0.42. pituitary MRI was without abnormality and bone age was 13 years. a pre-therapeutic blood and morphological workup was requested which was without anomaly.
Discussion
Normal growth requires the integrity of the endocrine and bone systems, regulated by intrinsic (genetic) and extrinsic factors. The causes of early stature are likely to be genetic, endocrine or constitutional. Depending on the presence of body dysmorphia and disproportion, and neurodevelopmental disorders such as sotos, marfan or klinfelter sd (chromosomal anomaly). And for endocrine causes, the existence of hyperthyroidism, an excess of sex hormones as in aromatase deficiency, or GH hypersecretion in somatotropic adenomas. The diagnosis of contitutional tall stature remains a diagnosis of elimination after a rigorous search for other causes with karyotyping. In our patient, no cause was identified, but the indication for treatment was given in view of the psychological impact. Therapeutic options are limited, and only high-dose sexual steroids have benefited from sufficient clinical trials. Treatment is most effective when administered before the bone age of 12 years. In our patient, the choice of treatment was ethynil estradiol 6 mg/day, after elimination of contraindications to this treatment, combined with a progestin for 10 days.
Conclusions
Any child presenting with tall stature should be carefully evaluated to exclude any underlying pathology. Psychological impact remains the main indication before starting treatment.

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EP844

JOINT1553

Clinical and genetic analysis of three cases of short stature caused by the GHSR gene mutation in chinese

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Objective
The aim of this study was to investigate the clinical and genetic characteristics of three cases of short stature caused by the *GHSR* gene mutation.
Methods
A retrospective analysis was conducted on the clinical data and genetic test results of three cases of short stature caused by the *GHSR* gene mutation. The patients were followed up at the Department of Endocrinology Genetics and Metabolism of the Children's Hospital of Soochow University.A literature search (search terms included "*GHSR*" and "short stature") for recently published studies was completed using the China National Knowledge Infrastructure database, WanFang database, PubMed, and the Human Gene Mutation Database.Results: The peak value of growth hormone provocation test in two cases was > 10 ng/ml, and the height of two patients was improved after recombinant human growth hormone therapy. One untreated patient was followed up until lifelong height was reached, and the patient remained with a short stature.
Conclusion
The peak value of growth hormone provocation test in patients with *GHSR* gene variants may be > 10 ng/ml, these patients may have precocious puberty, and short stature caused by the *GHSR* gene mutation can be treated with growth hormone.

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EP845

JOINT3707

Endocrine comorbidities in adult patients with Turner syndrome

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Background
Turner syndrome (TS) is characterized by a great variability of clinical manifestations caused by a total or partial loss of X-chromosome. Among these manifestations, numerous endocrine disorders have been associated with TS.
Objective
To evaluate the prevalence of endocrine comorbidities developed in adulthood in patients with TS.
Patients and Methods
Prospective longitudinal study including patients with TS aged over 15 years old and followed in the endocrinology department of Farhat Hached university Hospital Sousse.
Results
A total of 33 female patients aged between 15 and 54 years with an average age of 25.6 years were enrolled. Age at diagnosis was 16.3 ± 6.4 years, with 42.2% of cases diagnosed after the age of 18 years old. Chromosomal abnormalities were classified as monosomy X in 54.4%, structural abnormality alone in 18.2% and monosomy with structural abnormality in 27.3%. The most frequent circumstance for discovery was delayed stature and puberty (39.4%). Statural retardation was present in 87.9%, with 9.1% having a severe form. Ovarian insufficiency was found in 87.9% of cases, with delayed puberty in 44.8%. Diabetes was diagnosed in 3 patients, one with type 1 diabetes and two with type 2. The mean BMI was 24.62 kg/m 2, with 18.1% obese. One third of patients developed dysthyroidism, in the form of hypothyroidism in 90% of cases. The mean age of onset was 19 ± 9.32 years, with antithyroid antibodies positive in 90%. Celiac serology was negative in all patients. Hypovitaminosis D was diagnosed in 97%.
Discussion
In addition to ovarian insufficiency, patients with TS may present with several comorbidities, notably endocrine and metabolic, and this is progressive over time, indicating an adapted and prolonged monitoring rhythm to detect these different pathologies in time. This follow-up should ideally be carried out by an endocrinologist.

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EP846

JOINT1975

Somatotroph non functionnal pituitary adenoma: a case report

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Introduction
Clinically nonfunctioning pituitary adenomas (NFPAs) include all pituitary adenomas that are not hormonally active. They account for 15-30% of pituitary adenomas, and are usually diagnosed by signs and symptoms related to a mass effect (headache, visual impairment, sometimes pituitary apoplexy), but also incidentally. In histopathology, somatotroph nonfunctional pituitary adenomas are considered rare, the majority of NFPAs are gonadotroph. They are associated to increased comorbidities, and reduced long-term survival.
Material and Methods
We report the case of a patient presenting NFPA which expressing anti-GH antibody. He is followed up in the Endocrinology, Diabetology and Metabolic diseases department of the Mohamed VI university hospital center in Marrakech.
Case presentation
A 56-year-old man, presented a tumoral syndrome made of decrease of visual acuity, and retroorbital headache. He had no particular medical history. He reported a decrease of the libido and erectile dysfunction evolving over the past 6 months. Laboratory workup revealed a normal insulin-like growth factor I (IGF1), 8 a.m. cortisol level, Thyroid-stimulating hormone (TSH) and prolactin, a gonadotropic deficiency FSH: 2,1 UI/l, LH: 0,6 UI/l Testosterone: 0.5. Pituitary MRI showed intra- and supra-sellar tumor process compressing the optic chiasm, suggesting in the first instance a pituitary adenoma measuring 45 x 33 mm. The ophthalmologic examination showed bilateral blindness. A transsphenoidal adenomectomy was performed in the neurosurgical department, and the anatomopathological and immunohistochemical study revealed a non-secreting pituitary adenoma expressing the anti-GH antibody. During follow up, biological tests showed in addition to the known gonadotropic deficiency, corticotropic and thyreotropic deficiencies were also

present, which we substituted. The MRI imaging showed persistence of the sellar lesion process measuring 12 x 22 x 19 mm. Blindness persisted even after surgery. Radiotherapy treatment was indicated, but the patient refused it.
Conclusion
Somatotroph adenomas are usually accompanied by symptoms of acromegaly and an elevated plasma growth hormone (GH) and IGF-1 level. GH-immunopositivity occurs in a rare case of all tumor types of clinically non-functioning adenomas. Because of that, the diagnosis should be done by immunohistochemical techniques, which may provide information on tumor cell proliferation and biologic behavior.
Keywords
Non-functional pituitary adenomas, Gonadotroph adenoma, MRI, Adenomectomy, immunohistochemical techniques.

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EP847

JOINT4031

A new prospective for the growth suppression in children with profound mental disability; case report and ethical consideration

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Introduction
- In children with profound mental disability, the normal linear growth and pubertal maturation can affect their life and their caregivers' life in a negative way especially with limited mobilization and increased body size.
- The three most prevalent disabilities in Saudi Arabia are: motor disability at a rate of (1.0%), followed by visual impairment and communication disability at a rate of 0.6% each.
- There is limited data on the use of high dose estrogen dose to close the growth plates earlier and cause growth suppression.

Case
- 10 years old boy, diagnosed with Spastic paraplegia type 86 based on genetic test. Which is an autosomal recessive complex neurological disorder, expressed by early childhood developmental delay, progressive spasticity that mainly affect the lower limbs, with inability to walk and cause intellectual developmental impairment.
- Currently; he speaks 10 to 15 words, can sit, crawl and stand, but cannot walk. He was referred to endocrine service with growth failure, went under growth hormone stimulation test, which was indicate growth hormone deficiency based on peak of GH 0.9.
- We counseled the family to start a high dose of growth hormone for growth and metabolic effect or use a low dose of growth hormone for metabolic impact only, and they elected to choose the high dose GH therapy.

Discussion
- Growth suppression in children with profound cognitive and physical disabilities consider ethically questionable. It can be viewed from several perspectives:

1- Construct Argument:
- **Beneficences:**
- **Direct benefit to the patients and their families** by improving quality of life (mobilization, decreasing bed sores, and risk of obesity).
- **-Indirect benefit to the society**
- **Justice:**

-No research in this field is Not harmful but avert benefice.
-No research in this field Augment vulnerability.

2- Counter Argument:
- **Consent and conflict of interest**

Estrogen therapy for growth suppression is a research medication and consent by third party (not by family) is indicated.
- **Harm.**
- **Social Injustice.**

Conclusion
- Growth attenuation offers the possibility of an improved quality of life for children with profound cognitive disability.
- It can be achieved naturally by allowing precocious puberty to run its course or by treating GH deficiency with metabolic dose (Passive suppression).
- Estrogen therapy is ethically questionable

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EP848

JOINT848

Glucose metabolism disorders in patients with acromegaly

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Background
Glucose metabolism disorders are common complications of acromegaly, contributing significantly to morbidity in affected patients. Understanding the factors associated with these disorders is essential to optimize their management. This study aims to investigate the frequency and the characteristics of glucose metabolism disorders in patients with acromegaly.
Methods
This was a retrospective study involving 32 patients with acromegaly treated at the Endocrinology Department of Hedi Chaker University Hospital, Sfax, over a 16-year period. The patients were divided into two groups: Group 1, consisting of 24 patients with glucose metabolism disorders, and Group 2, consisting of 8 patients without such disorders.
Results
la fréquence du trouble du métabolisme glucidique était de 75%. Diabetes Mellitus was identified in 17 patients (71%), while glucose intolerance was noted in 7 cases (29%). Glucose metabolism disorders were diagnosed, on average, 7.5 years after the onset of acromegaly. Treatment consisted of dietary measures alone in 11 cases (45%), oral antidiabetics in 7 cases (29%), insulin alone in 3 cases (12.5%), and a combination of insulin and oral antidiabetics in 3 cases. The underlying cause of acromegaly was a Somatotroph macroadenoma in 14 patients, microadénoma in 7 patients, and ectopic secretion of growth hormone-releasing hormone in 1 patient. Among 20 patients who received treatment for acromegaly, 5 showed improvement in glucose metabolism. After successful treatment of acromegaly, the overall improvement rate in glucose metabolism was 21%.
Conclusion
Acromegaly is a multifaceted disease that requires careful evaluation and management. Advancing our understanding of its metabolic impact is crucial for optimizing care strategies.

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EP849

JOINT3807

Pituitary acrogigantism from diagnosis to effective treatment- case study

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Introduction
Pituitary acrogigantism is a very rare endocrine disease that is caused by chronic growth hormone (GH) and its mediator, insulin-like growth factor 1 (IGF-1) axis excess, that begins during childhood and adolescence. As such, it represents one of the most severe manifestations of acromegaly. In most cases, acrogigantism is caused by a pituitary adenoma. The disease leads to numerous complications, including metabolic, cardiovascular, and oncological issues. Despite advances in diagnosis and treatment, delays in recognition remain a challenge. Treatment of pituitary acrogigantism involves a multimodal approach, combining surgical, pharmacological, and in some cases radiotherapy interventions. The use of somatostatin analogues first and second generation has significant role, especially in patients with incomplete tumor resection or persistently high levels of GH and IGF-1.
Case study
The study is based on the case analysis of a 21-year-old patient, diagnosed with pituitary acrogigantism due to a pituitary macroadenoma. A pituitary tumor was revealed during the diagnosis of chronic otitis. Diagnostics included laboratory tests (levels of GH in OGTT *oral glucose tolerance test,* IGF-1) and imaging studies (pituitary MRI, thyroid and abdominal ultrasound, echocardiography). Treatment involved surgical intervention (endoscopic tumor resection), pharmacological therapy (lanreotide) and monitoring of therapy progress. After tumor resection, partial normalization of GH and IGF-1 levels was achieved; however, symptoms of active acromegaly persisted. Lanreotide treatment was initiated, leading to further improvement in hormonal parameters and the patient's well-being. Nevertheless, in the following months, recurring symptoms such as chronic fatigue, excessive sweating, and joint pain were observed. A second generation

analogue -pasireotide were used, resulting in normalization of IGF1 and good disease control. Actually patient is a is a first-year medical student.
Conclusions
Patients with pituitary acrogigantism have a heavy burden of disease and a complex treatment journey. Rapid implementation of surgical and pharmacological treatment is crucial. The use of somatostatin analogues is effective in controlling GH and IGF-1 levels in patients with residual disease activity. A second generation somatostatin analogues are perspectives for patients with hard-to-control acromegaly.

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EP850

JOINT353

Two-year-old dizygotic twins diagnosed with rabson-mendenhall syndrome

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Rabson-Mendenhall Syndrome (RMS) is a rare, autosomal recessive disorder caused by mutations in the *INSR* gene, leading to severe insulin resistance, dysmorphism and multisystemic complications. The features of RMS overlap with other metabolic and genetic disorders which can lead to delayed diagnosis. To our understanding, the twins presented in this case report are the youngest diagnoses of RMS globally. Lilac was brought to the attention of the general paediatricians with dysmorphic features, failure to thrive, developmental delay and significant polyuria and polydipsia. As her twin, Marigold, was found to have similar features, she was also investigated. A high HbA1c resulted in a referral to the diabetes team who put together the clinical features of dysmorphism, acanthosis nigricans and insulin resistance for a suspicion of Rabson-Mendenhall Syndrome; this was confirmed some months later for both fraternal twins by genetic testing. Following a difficult discussion explaining the diagnosis to parents, a multidisciplinary approach was taken that initially focused on continuous blood glucose monitoring to detect early morning hypoglycaemia and nutritional support. Metformin was started at 100 mg once-daily and then Increlex (Mecasermin) injections were started at 0.04 mg/kg once-daily under inpatient observation, titrated to 0.04 mg/kg twice-daily after six weeks. General monitoring for growth and development is ongoing. The early stage of RMS poses significant metabolic challenges due to early morning hypoglycaemia and postprandial hyperglycaemia and thus nutritional interventions are invaluable at this time. Early recognition and management of Rabson-Mendenhall Syndrome is extremely preferable over a presentation in treatment-resistant diabetic ketoacidosis which is often the case. Prompt diagnosis and use of targeted therapies can be essential in mitigating severe complications. Given the young age at diagnosis and the rarity of RMS, this case is being managed in collaboration with national experts however there is little evidence base for the treatments being offered. We hope this report will highlight the need for further research into novel therapeutic options and long-term management strategies for this challenging condition.

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Metabolism, Nutrition and Obesity

EP851

JOINT2661

CiR-EIS sponges miR-548 to ameliorate metabolic dysfunction-associated steatohepatitis via regulating macrophage polarization

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Introduction
Metabolic dysfunction-associated steatohepatitis (MASH) is a significant public health concern, with macrophage phenotypes implicated in its progression. Although Extensive Inflammation-Suppressing Circular RNA (CiR-EIS) has been implicated in inflammation regulation, its role in macrophage polarization within the context of MASH remains unexplored. This study aimed to clarify the effect of CiR-EIS on macrophage polarization in MASH.
Methods
Immunofluorescence-fluorescence *in situ* hybridization was used to evaluate the localization of CiR-EIS in human liver sections. Real-time quantitative polymerase chain reaction (RT-qPCR) was used to detect the expression of CiR-EIS in serum and cells. Flow cytometry was employed to evaluate macrophage polarization. Enzyme linked immunosorbent assay (ELISA) was used to detect the content of inflammatory factors. Dual luciferase reporter assay was used to identify the downstream targets of CiR-EIS.
Results
CiR-EIS was downregulated in patients with MASH and localized in liver macrophages. Compared with the control group, the expression of CiR-EIS in M1 macrophages was decreased. Overexpression of CiR-EIS significantly inhibited M1 macrophage markers CD86, interleukin-1 beta (IL-1β), and tumor necrosis factor-alpha (TNF-α) while enhancing M2 macrophage markers CD163 and CD206. MiR-548 was screened and identified as a downstream target of CiR-EIS. Up-regulation of miR-548 promoted M1 macrophage polarization and reduced M2 macrophage polarization. CiR-EIS had a region that binds to miR-548. CiR-EIS sponged miR-548 to regulate the polarization of macrophages. In addition, the serum CiR-EIS content of MASH patients was lower than that of healthy people. The content of CiR-EIS in serum was negatively correlated with the content of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).
Conclusions
CiR-EIS regulates macrophage polarization by sponging miR-548, thereby ameliorating MASH. It demonstrates potential as a diagnostic marker and therapeutic target for MASH.

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EP852

JOINT1128

Clinical and therapeutic characterization of patients with familial hypercholesterolemia: multicenter cross-sectional study

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Familial hypercholesterolemia (FCH) is a hereditary disease that presents with elevated LDL, xanthomas and early coronary heart disease. Genetic tests are not essential for the diagnosis of FH but are useful to assess cardiovascular risk and response to treatment regardless of LDL levels. Our main objective is to describe the genetic findings in the patients studied and describe the clinical, analytical and treatment characteristics in people with hypercholesterolemia with a genetic study performed, as well as the comparison of the same among those in which genetic variants of HCF are detected. and not those who don't.
Material and Methods
Observational, cross-sectional and analytical study in which all patients with hypercholesterolemia in whom a genetic study of HCF has been performed in 5 hospital centers in the province are collected. For genetic diagnosis, next-generation sequencing (NGS) techniques were used, which include the genes LDLR, APOB, PCSK9, APOE, LDLRAP1 and LIPA. Clinical, analytical and therapeutic data were collected from the patients. Statistical inference is performed using Student's t-test for comparison of means and Chi-square for comparison of proportions between groups. A statistically significant difference is considered with a p-value less than 0.05.
Results
117 patients were included, with a mean age of 11.66 +/-3.64 years and a mean BMI of 19.14 +/-4.91. The most reported gene was LDLR (53 patients; 76.8%) followed by APOB (9 patients; 13%). The average total cholesterol is 259.61 60.82 mg/dl with an average LDL cholesterol of 186.68 64.52 mg/dl. In the group of patients with positive genetics, the mean LDL cholesterol is 210.87 66.94 mg/dl while in the control group it is 151.17 40.21 mg/dl ($p < 0.01$). Of the total sample, 71 (60.7%) received lipid-lowering treatment, being more frequent in patients with positive genetics (71% vs. 45.9%) ($P = 0.02$), in addition, 12 patients had a combination of > 2 drugs (16.9%), all of them belonging to the group with positive genetics. The most commonly used drugs are atorvastatin and rosuvastatin. No statistically significant differences were observed in LDL levels after starting treatment in both groups, although the mean reduction in LDL levels was greater in the group with positive genetics (99.15 78.92 mg/dl vs. 50. 05 40.25 mg/dl).
Conclusions
- Total and LDL cholesterol levels were higher in the group with positive genetics findings.
- In patients with positive genetics we observed a greater proportion of lipid-lowering treatment as well as a greater combination of them.

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EP853

JOINT2794

Time-restricted feeding in children and adolescents with obesity (the transform study): a randomized controlled trial evaluating anthropometric, metabolic, and gut microbiome outcomes

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Introduction
Time-restricted feeding (TRF) has demonstrated metabolic improvements in adults with obesity, although evidence in pediatric populations is limited. The TRansForm study (*ClinicalTrials.gov* ID: NCT05174871) evaluated the safety and effectiveness of a 2-month TRF intervention in children and adolescents with obesity, focusing on anthropometric, metabolic, and gut microbiome outcomes.
Design
This open-label, parallel-group randomized controlled trial allocated (1:1) participants (ages 8–18, BMI-SDS > 2) stratified by gender and age into TRF (late 8-hour feeding window, 6 days/week, plus usual care) or Control groups (usual care only). Primary outcomes included safety and BMI-SDS changes at 2 and 12 months. Secondary outcomes encompassed metabolic parameters and gut microbiome. Analysis was conducted using multiple linear regression, adjusted for sex and pubertal status.
Results
Sixty-five participants completed the intervention, and 53 attended the 12-month follow-up. Baseline characteristics included 54% female, average age 13.8 ± 2.5, 18% prepubertal, and BMI-SDS 3.06 ± 0.64. No major adverse events were documented. Median self-reported adherence was 5 ± 3 days/week, with 50% attaining adherence > 80% (≥ 5 fasting days/week). Males and prepubertal individuals exhibited higher probabilities of high adherence than females and postpubertal (X^2 P = 0.029 and P = 0.040, respectively). TRF (n = 32) and Control (n = 33) groups showed similar BMI-SDS improvements at 2 (−0.09 ± 0.16vs−0.07 ± 0.12, respectively) and 12 months (−0.11 ± 0.41vs−0.09 ± 0.38). Regression models with high-adherence participants revealed significant BMI-SDS improvements following TRF compared to controls (−0.24 ± 0.11vs.−0.07 ± 0.12) (Table 1). TRF increased LDL-cholesterol levels at 2 and 12 months while marginally reducing HDL-cholesterol (Table 1). No differences were observed in physical activity or energy intake. Microbiome analysis from TRF participants revealed decreased α-diversity (P < 0.05), lower fecal short-chain fatty acids, and increases in potentially pathogenic bacteria, including *Yersinia*, *Escherichia coli*, and *Salmonella enterica* strains.
Conclusions
While TRF may improve BMI-SDS, its potential association with worsening lipid profiles and gut dysbiosis raises safety concerns. These findings highlight the necessity for personalized TRF protocols and rigorous metabolic monitoring for pediatric obesity. Further research is required to determine the long-term impact of TRF on pediatric health, as well as the mechanisms linking feeding windows to microbiome-host interactions.

Table 1. Multiple linear regression models adjusted for sex and pubertal status in high-adherence TRF and control groups.

	8 weeks		12 months	
	β (95% CI)	*P* val	*β* (95% CI)	*P* val
BMI-SDS	-0.04(-0.00,- 0.07)	0.048	-0.05(0.10,-0.19)	0.523
Cholesterol (mg/dL)	2.94(7.30,-1.42)	0.180	1.79(9.81,-6.24)	0.654
LDL-Cho (mg/dL)	5.34(9.82,0.86)	0.021	7.89(15.04,0.75)	0.031
HDL-Cho (mg/dL)	-1.62(1.02,-4.26)	0.222	-2.92(0.22,-6.07)	0.067

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EP854

JOINT1055

Evolution after bariatric surgery in patients with genetic mutations related to monogenic obesity

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Study Objectives
Monogenic obesity, linked to more than 130 identified genes, is often characterized by hyperphagia and early-onset obesity. This study aims to analyze changes in anthropometric and clinical parameters in a cohort of patients with genetically confirmed obesity-related mutations, one year after undergoing bariatric surgery.
MaterialS And Methods
A descriptive, cross-sectional study was conducted on a cohort of subjects with grade 3 or higher obesity and positive genetic findings, managed at the Bariatric Surgery Clinic (Endocrinology) of Puerta del Mar Hospital. An obesity gene panel was used, based on whole-exome sequencing of 80 genes, including copy number variation analysis.
Results
The study included 52 patients meeting the specified criteria. Of these, 79.6% were female. The median age at the time of surgery was 49.46 years. The median age of obesity onset was 11.5 years (range 6–23.5), and 71.1% had a family history of obesity. The majority of patients (75%) underwent vertical sleeve gastrectomy, while the remaining 25% had a gastric bypass. Preoperative weight was 109.52 ± 16.56 kg (BMI 41.19 ± 4.95 kg/m^2), and postoperative weight at one year was 81.05 ± 13.45 kg (BMI 30.49 ± 4.47 kg/m^2). The percentage of excess weight lost was 58.47 ± 20.06%, the percentage of total weight lost was 25.79 ± 8.16%, and the percentage of excess BMI lost was 69.39 ± 26.16%. Regarding the HQ-CT questionnaire validated for hyperphagia, the median score was 13 (9.75–16). The mean score on the BAROS scale (quality of life) was 5 ± 2.52, with 27.8% achieving excellent outcomes, 27.8% very good, 27.8% good, 5.6% fair, and 11.1% classified as treatment failures.
ConclusionS
Our cohort demonstrates that bariatric surgery can be an effective tool for weight loss, at least in the short term, in individuals with grade 3 obesity and genetic alterations associated with obesity. It would be of interest to compare these results with patients with negative genetic findings and those undergoing medical treatment targeting specific pathways related to MC4R (e.g., setmelanotide).

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EP855

JOINT2433

Higher daytime systolic blood pressure, prepregnancy body mass index and an elevated sFlt-1/PlGF ratio predict the development of hypertension in normotensive pregnant women

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Background
The risk of hypertensive disorders of pregnancy (HDP) varies in women with gestational diabetes mellitus (GDM), depending on the degree of insulin resistance and is also influenced by obesity. The aim of this study was to evaluate clinical features, blood pressure (BP) profiles and inflammatory markers, to identify patients with an elevated risk of developing HDP.
Methods
A total of 146 normotensive pregnant women were studied. We analysed the relationships of BP profiles detected by ambulatory blood pressure monitoring (ABPM) with serum biomarkers and angiogenic factors and their association with the development of HDP.
Results
Fourteen (9.6%) women developed HDP. The table shows the association between the development of HDP, biomarkers' levels and ABPM parameters.

Table 1. Pearson correlation coefficients between hip geometry variables and fat mass at different sites

Variable	HDP (n = 14)	Non-HDP (n = 132)	p Value
Cytokines and biomarkers levels *			
Adiponectin, (pg/ml)	10.22 ± 2.54	13.08 ± 2.93	0.06
Resistin (pg/ml)	7.43 ± 3.82	8.28 ± 3.28	0.37
PAI-1 (pg/ml)	8.04 ± 4.08	8.69 ± 3.48	0.51
Leptin (pg/ml)	10.97 ± 0.82	10.2 ± 1.11	**0.018**
HGF (pg/ml)	6.65 ± 1.07	7.03 ± 1.23	0.41
MCP-1 (pg/ml)	5.24 ± 0.60	4.9 ± 0.55	**0.044**
TNFα (pg/ml)	0.35 ± 2.02	0.59 ± 1.13	0.49
sFlt-1 (pg/ml)	7.56 ± 0.93	7.25 ± 0.97	0.26
PlGF (pg/ml)	3.18 ± 1.79	5.1 ± 1.12	**0.002**
sFlt-1/PlGF ratio	4.37 ± 2.2	2.2 ± 1.43	**0.003**
BP parameters			
24h SBP (mmHg) *	113.1 ± 14.4	104.2 ± 7.9	**0.04**
24h DBP (mmHg) *	69.7 ± 9.2	64.1 ± 5.6	**0.04**
Daytime SBP (mmHg) *	115.7 ± 13.4	106.7 ± 8.6	**0.001**
Daytime DBP (mmHg) *	72.3 ± 8.2	66.6 ± 6.0	**0.002**
Nocturnal SBP (mmHg) *	107.5 ± 17.5	98.7 ± 7.8	0.08
Nocturnal DBP (mmHg) *	63.5 ± 12.1	58.5 ± 5.6	0.15
Pathological circadian pattern †	9 (64.3%)	62 (46.9%)	0.17

Multivariate analysis showed that a higher sFlt-1/PlGF ratio was associated with an increased risk of developing HDP [Or=2.02; IC 95%: 1.35–3.05]. Furthermore, higher daytime systolic BP [Or=1.27; IC 95% 1.00–1.26] and prepregnancy body mass index (BMI) [Or=1.14; IC 95%: 1.01–1.30] significantly increased the risk of developing HDP.
Conclusions
Higher daytime systolic BP values, prepregnancy BMI and the sFlt-1/PlGF ratio are useful for identifying normotensive pregnant women with an increased risk of developing HDP.

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EP856

JOINT966

SGLT-2 inhibitors do not decrease tsh levels despite weight reduction, unlike GLP-1 agonists

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Introduction
TSH (Thyroid Stimulating Hormone) elevation in obesity is a recognized phenomenon. While various mechanisms have been proposed, a clear pathogenic mechanism remains undefined. Weight reduction is typically accompanied by a decrease in TSH levels, particularly with GLP-1 receptor agonist treatment. This study aimed to compare the effects of SGLT-2 inhibitors and GLP-1 receptor agonists on TSH levels in relation to weight reduction in patients with type 2 diabetes mellitus (T2DM).
Patients and Methods
This retrospective analysis included T2DM patients who started treatment either with SGLT-2 inhibitors or GLP-1 receptor agonists at our centre. Biochemical and anthropometric data were collected before treatment and after 12 months of therapy. The aim was to compare the effects of both drug classes on body weight, HbA_{1c}, and TSH levels.
Results
Data from 90 patients treated with SGLT-2 inhibitors and 38 treated with GLP-1 receptor agonists were analysed. In the SGLT-2 group, 66 were men and 24 were women, with a mean age of 65.7 years (range 34–88). In the GLP-1 group, 27 were men and 11 were women, with a mean age of 61 years (range 36–74). In the SGLT-2 group, mean BMI decreased from 34.57 $\pm$ 3.6 to 32.8 $\pm$ 3.55 ($p < 0.001$) after 12 months. HbA_{1c} decreased from 65.49 $\pm$ 8.15 mmol/mol to 55.91 $\pm$ 6.73 mmol/mol ($p < 0.001$). TSH levels decreased from 2.16 $\pm$ 0.82 mIU/L to 1.96 $\pm$ 0.6 mIU/L, but the change was not statistically significant ($P = 0.0968$). In the GLP-1 group, mean BMI decreased from 32.93 $\pm$ 4.80 to 30.48 $\pm$ 5.36 ($p < 0.001$). HbA_{1c} decreased from 59.44 $\pm$ 10.25 mmol/mol to 47.69 $\pm$ 7.80 mmol/mol ($p < 0.001$). TSH levels decreased from 3.42 mIU/L to 2.25 mIU/L ($p < 0.001$).
Conclusion
Both GLP-1 receptor agonists and SGLT-2 inhibitors led to significant reductions in BMI and HbA_{1c}. However, a significant decrease in TSH levels was observed only with GLP-1 treatment, suggesting that its impact on metabolism may be broader and more complex, potentially involving mechanisms beyond weight reduction alone.

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EP857

JOINT3297

Gut microbiota and cytokine in children with nonalcoholic fatty liver disease

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Objective
Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in children worldwide. The gut microbiota plays a critical role in human metabolism, and has been appointed as driver of meta-inflammation observed in lipid metabolism and NAFLD, which has not been fully studied in children with obesity.
Methods
Clinical data were collected between June, 2019 and December, 2019 at the Fuzhou Children's Hospital of Fujian Medical University, in China. Data of 89 participants aged between 5 and 15 were examined. Subjects with any endocrine disorder, history of antibiotic therapy, hospitalization (>24 h) in the past 6 months prior to the enrollment, chronic gastrointestinal illness or use of gastro-intestinal-related medication, or diarrheal disease (World Health Organization definition) in the past one month were excluded. Participants with body fat (BF)% $\geq$ 30% were diagnosed as obesity. Serum adropin and leptin levels were measured by ELISA, and the composition of gut microbiota was investigated by 16S rRNA-based metagenomics.
Results
The mean age of the 89 participants were 9.75 $\pm$1.92 years old. Based on BF%, the study population were divided as normal weight ($n = 29$), obesity without NAFLD ($n = 39$) and obesity with NAFLD ($n = 21$) groups. Alpha-diversity such as Shannon index, Observed index and ACE were significantly lower in NAFLD group compared with the Obesity and the Con groups ($P < 0.05$). PCoA analysis revealed that gut microbiota of the NAFLD group were clustered together and separated partly from the Obesity and the Con groups ($P < 0.05$). Compared to the Obesity and the Con groups, subjects with NAFLD had significantly lower prevalent members of phylum Bacteroidetes, genus Alistipes, Anaerotruncus, Bacteroides, Holdemania, Lactonifactor, Oscillospira, Sutterella, and more members of genus Aggregatibacter, Catenibacterium, Morganella, Paraprevotella (all $P < 0.05$). Spearman's correlation analysis revealed that leptin negatively correlated with phylum Bacteroidetes, genus Alistipes, Bacteroides, Holdemania and Lactonifactor. Adropin positively correlated with phylum Bacteroidetes, genus Alistipes, Anaerotruncus, Bacteroides, Lactonifactor, Oscillospira.
Conclusions
The composition of the gut microbiota in children with NAFLD differs from Con. Alterations in the microbiota that produce short-chain fatty acids may contribute to the development of NAFLD by affecting levels of cytokine.

Keywords
gut microbiota, lipid metabolism, nonalcoholic fatty liver disease, cytokine
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EP858

JOINT2771

Streamline - machine learning guided development of novel GLP-1 receptor agonists with improved drug properties

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We have developed streaMLine, an innovative platform for peptide drug discovery that greatly shortens the time from initial hit to clinical drug candidate. The platform allows for high throughput synthesis and screening. Thousands of peptides are systematically screened in *in vitro* assays and on chemical and physical parameters, whereby the streaMLine platform enables complete sequence exploration and simultaneous optimization of key parameters. Using the streaMLine platform, we developed novel GLP-1R agonists from a secretin peptide backbone, to demonstrate how high throughput screening of peptide libraries and machine learning guided drug design can be applied to accelerate drug discovery. We systematically synthesized and screened a total of 2,688 peptides in a parallelized optimization workflow. Using this approach, we were able to generate potent, selective, and long-acting GLP-1R agonists with improved physicochemical properties. To validate the developed QSAR pipeline, we conducted an in-depth profiling of a developed GLP-1R agonist, GUB021794. GUB021794 was tested for cross-reactivity towards other receptors in the glucagon superfamily of receptors and showed no activation of the GIPR, GLP-2R or GCGR when tested at concentrations up to 3000 nM. With a GLP-1R potency of 0.018 nM and a SCTR potency of 190 nM, GUB021794 thus showed high receptor selectivity for GLP-1R. In addition, GUB021794 (S.C., 10 nmol/kg QD) showed potent body weight loss in diet-induced obese (DIO) mice and a half-life in rats compatible with once-weekly dosing in humans. Overall, the preclinical data demonstrate that GUB021794 is a potent, long-acting GLP-1R agonist promoting robust body weight loss in DIO mice comparable to clinically approved GLP-1R agonists such as semaglutide.

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EP859

JOINT2722

High prevalence of MASLD already in children aged below 10 years

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Introduction
Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic steatotic liver disease (NAFLD), is currently the most common liver disease in children due to the increasing prevalence of obesity. MASLD occurs with (mainly) visceral type obesity, dyslipidaemia and/or insulin resistance. The aim of this study was to determine the prevalence of MASLD in obese children.
Methods and patients
Obese patients aged 2.5 to 18.9 years examined at the Endocrinology and Gastroenterology outpatient clinics of the Children's Clinic of the LFUK and NÚDCH in 2018-2023 were included in the study.
Results
In a cohort of 383 obese children and adolescents (179 girls, 204 boys), with a mean age of 13.3 ± 3.4 years and BMI-SDS of 15.4 ± 2.6, MASLD occurred in 222 children (58%). The prevalence of MASLD was not significantly different in children under 10 years (52.2%) and over 10 years (59.2%) ($P = 0.341$). MASLD patients had significantly higher BMI-SDS (5.8 ± 2.6 vs. 4.8 ± 2.5, $P < 0.001$), higher AST, ALT and GMT ($P < 0.001$), as well as HOMA index ($P = 0.002$) and higher liver steatosis and fibrosis index (PNFI), liver function index (FLI) ($P = 0.039$) and liver fibrosis index (HSI) scores ($P < 0.001$ and $P = 0.039$, respectively).
Conclusion
More than half of obese children already have steatotic liver disease associated with metabolic dysfunction, with an alarmingly high prevalence even in children under 10 years of age. *Grant support: APVV-22-0310 and VEGA 2/0128/23*

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EP860

JOINT3449

Predictive factors of fat-free mass loss in obese patients after weight loss interventions

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Background
Muscle loss, particularly in the context of obesity, is a significant concern due to its association with various health complications, including insulin resistance, impaired mobility, and an increased risk of chronic diseases [1]. The aim of our study was to evaluate fat free mass loss in obese patients after weight loss intervention and to identify its predictive factors.
Methods
We conducted a prospective study of 100 obese adult patients over 6 months. Body composition was analyzed at baseline and at 6-month follow-up. Gait speed over 4 meters assessed physical performance. Sarcopenic obesity (SO) was defined in accordance with the 2022 EASO-ESPEN consensus statement. A balanced hypocaloric diet was prescribed and patients received regular follow-ups. A significant loss of fat-free mass (FFM) was defined as a reduction of more than 5% in FFM.
Results
The mean age was 44.42 ± 13.25 years and the sex ratio (M/F) was 0.11. At baseline, the mean BMI was 40.07 ± 5.77 kg/m^2. About 20% of the participants had a below-average fat-free mass index of 20.34 ± 2.53 kg/m^2, and 19% were identified as having SO. At 6 months, 78 patients completed the study. The average weight loss and the average FFM loss were 4.13 ± 6.98% and 0.42 ± 5.63%, respectively. Significant loss of FFM was identified in 11% of patients after weight loss intervention. The level of physical activity was comparable between patients with significant FFM loss and those without ($P = 0.42$). Significant FFM loss was associated with a higher prevalence of binge eating disorder (62.5% vs 18.5%;$P = 0.014$) and prediabetes (75% vs 36.9%;$P = 0.039$) at baseline. However, sarcopenic obesity and functional impairment were not significantly associated with FFM loss ($P = 0.14$ and $P = 1.0$, respectively). Dietary survey revealed that significant loss of FFM was associated deficiency in vitamin B9 intake (87.5% vs 36.9%;$P = 0.009$), and deficiency in vitamin C intake (87.5% vs 27.5%;$P = 0.002$) at baseline. However, total caloric intake as well as protein intake were comparable ($P = 0.15$ and $P = 0.07$, respectively). Furthermore, FFM loss was negatively correlated with vitamin B6 intake (r = -0.24;$P = 0.04$) and vitamin B9 intake (r = -0.41;$P = 0.041$). Multivariate analysis identified prediabetes, vitamin B9 deficiency, and binge eating disorder syndrome as independent factors associated with significant FFM loss ($P = 0.045$;OR = 7.48, $P = 0.012$;OR = 23.43, $P = 0.018$;OR = 10.93, respectively).
Conclusion
Our study highlights the importance of targeted nutritional and behavioral interventions to mitigate muscle loss in obese patients and enhance overall health outcomes in this population.
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EP861

JOINT1951

A novel MED12 variant associated with early childhood-obesity

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Introduction
The *MED12* gene is located on the X chromosome and encodes a protein involved in the initiation of gene transcription. Pathogenic variants in *MED12* have been reported to cause three X-linked recessive syndromes (FG syndrome type 1, Lujan-Fryns syndrome and X-linked Ohdo syndrome) and one X-linked dominant syndrome (Hardikar syndrome). Pathogenic variants in *MED12* have been reported to cause nonspecific intellectual disability (NSID) and other neurological features as hypotonia, behavior issues, seizures as well as growth delays. Here, we report the case of an infant with precocious obesity and neurodevelopmental delay.
Case presentation
A 19-month-old female was seen in our outpatient clinic for pediatric obesity. She was the second child of Venezuelan parents, born at 38 weeks by caesarian section with a birth weight of 2.9kg (-0.75SDS). Her 5-year-old sister, was healthy and not overweight. At the referral, the patient weighted 13.4 kg (2.37SDS) for a length of 82 cm (0.1SDS), BMI 19.9kg/m^2 (2.63SDS). She had some dysmorphic features: prominent forehead, tented upper lip, protruding and backwardly rotated ears. At the clinical examination, she had a mild global hypotonia and was not yet walking. A blood analysis revealed normal cortisol, TSH and fT4. Genetic analysis, CGH and methylation profile of the 15q11q13 region were normal. Trio- exome sequencing revealed a de novo heterozygous mutation in the *MED12* gene (c.4453G > T, p.(Val1485Leu)). This variant is considered likely pathogenic by two prediction tools (Polyphen and SIFT).
Conclusion
Pathogenic variants in *MED12* have been already reported to cause various neurological symptoms and some have been also implicated as oncogenic in tumour tissue for leiomyoma or leiomyosarcoma. So far, only one female patient has been reported with a de novo *MED12* variant (c.4669T > C, p.Trp1557Arg) and severe obesity. This patient had obesity, neurodevelopmental delay and abnormalities of the corpus callosum. Some recent studies in Human adipose-derived stem cells hASCs and in murine models suggest that *MED12* could promote adipogenesis by acting as transcriptional coactivator for adipogenic genes and by repressing inhibitory pathways like Wnt signaling. Here we report another patient with a *MED12* de novo variant, presenting with precocious obesity and neurodevelopmental delay. Genetic counseling is very helpful in pediatric obesity clinics and exome sequencing is a powerful tool for identifying novel rare variants and understanding the pathogenesis of obesity in a subset of patients.

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EP862

JOINT1290

Comparison of glucose-insulin-metabolism indices in obese male and female adolescents with equivalent height-normalised visceral and subcutaneous adipose tissue areas

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Background
Obesity is a global health challenge affecting a significant number of adolescents worldwide. Abdominal obesity, in particular, is closely linked to insulin resistance and is a well-established risk factor for type 2 diabetes. Although differences in body fat distribution between boys and girls become pronounced during puberty, it remains unclear whether glucose-insulin metabolism and height-normalised abdominal fat indices differ between male and female adolescents with obesity.
Methods
This cross-sectional study included 90 obese adolescents (56 female). An oral glucose tolerance test (OGTT) was performed, and the following indices were calculated: the homeostatic model assessment of insulin resistance (HOMA-IR), insulin sensitivity index (ISI), insulinogenic index (IGI), and oral disposition index (oDI). Abdominal adipose tissue was estimated using single-slice magnetic resonance imaging (MRI) at the third lumbar vertebral level. Height-normalised visceral (VATa) and subcutaneous (SATa) tissue areas were used to derive the visceral adipose tissue index (VATI) and subcutaneous adipose tissue index (SATI). Sex differences in glucose-insulin metabolism, VATI, and SATI were assessed using the Mann-Whitney test.
Results
The participants had a median age of 14.8 years (range: 10.8–18) and a median body mass index (BMI) of 34.7 kg/m^2 (range: 25.2-54.4). Boys had significantly higher BMI z-scores ($p < 0.001$), VATa ($P = 0.030$), and SATa ($P = 0.023$) compared to girls. However, height-normalised VATI and SATI did not significantly differ between sexes ($P = 0.371$ and $P = 0.212$, respectively). Similarly, no significant differences were observed in HOMA-IR ($P = 0.339$), ISI ($P = 0.523$), IGI ($P = 0.382$), or oDI ($P = 0.247$) between boys and girls. Prediabetes was identified in 19 adolescents (13 female, 6 male), and type 2 diabetes was detected in one female adolescent.
Conclusions
Adolescents with obesity face a high risk of impaired glucose metabolism. However, no significant sex-based differences in glucose-insulin metabolism indices were found among obese adolescents with comparable VATI and SATI, despite differences in overall adiposity.

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EP863

JOINT3341

Metabolic syndrome and its components in overweight and obese children

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Background
although many studies have been conducted in adults to determine the prevalence and complications of the metabolic syndrome, few studies in children are available, particularly in developing countries. The aim of this study is to determinate the prevalence of the metabolic syndrome and its components in children and adolescents consulting the endocrinology department of the Hédi Chaker Hospital in Sfax, Tunisia, for exploration of overweight and obesity.
Methods
This cross-sectional study involved 84 obese and overweight children and adolescent, admitted to the endocrinology department of the Hédi Chaker Hospital in Sfax to explore overweight or obesity between 2015 and 2019.
Results
44 boys and 40 girls. The average age was 11.83 years (2-17). Family history of obesity was noted in 84.5% of cases. Seventy-seven percent had a family history of cardiovascular diseases. The average weight at the 1st visit was 72.68 kg (20-125 kg) with an average BMI of 31.55 kg/m^2. Obesity was reported in 78.6% of patients and overweight without obesity in 21.4% of cases. According to the criteria of NCEP ATP III adapted; 16.7% of patients had metabolic syndrome. La frequence des different criteres/Metabolic syndrome was observed in 15.9% of boys and 17.5% of girls, with no significant difference. Certain components, particularly abdominal obesity and hyperTG were far more prevalent.
Conclusion
The prevalence of metabolic syndrome was high in our study. we suggest targeted screening programs for at-risk children and adolescents in order to control obesity and metabolic syndrome in Tunisia.

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EP864

JOINT174

Effect of gliflozins on serum fetuin-a in patients with type 2 diabetes and nonalcoholic steatohepatitis

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Background and aims
Particularly the association between type 2 diabetes (T2D) and comorbid disorders were linked to an increased risk of nonalcoholic steatohepatitis (NS). Early biomarker such as fetuin-A can help predict of insulin resistance, dyslipidemia and metabolic disorders in patients with NS. The use of gliflozins on hepatokines in patients with T2D and NS has encountered conflicting opinions. We aimed to compare the effectiveness of gliflozins on NS.
Materials and methods
36 participants with T2D and NS (58,3% males, 41,7% females; aged - 57,54 $\pm$ 9,24 years; duration of T2D-14,67 $\pm$ 5,14 years; body mass index (BMI)- 37,49 $\pm$ 4,32 kg/m^2; waist circumference (WC)-122,24 $\pm$ 11,32 cm; glycated hemoglobin (HbA_1C)-8,12 $\pm$ 0,23%; hepatic fibrosis (index FIB-4)-1,34 $\pm$ 0,25; METAVIR score at liver elastography-8,63 $\pm$ 0,46 kPa) were comprehensively investigation including physical examination, laboratory and instrumental results at baseline and 3 months following the treatment. Fetuin-A using kits for the enzyme-linked immune-sorbent assay. All patients were divided into three groups: Gr A ($n = 12$) received basic medical therapy (BMT) which included metformin (MET- 2000 mg/day), alpha-lipoic acid (600 mg/day) and rosuvastatin (10 mg/day) in combination with insulin therapy; Gr B ($n = 12$) subjects add-on to BMT and dapagliflozin (DAPA -10 mg/day); Gr C ($n = 12$) received BMT and empagliflozin (EMPA-10-25 mg/day).
Results
After 3 months of treatment the greater reduction in WC were observed in Gr B (-3,12 $\pm$ 0,04 cm, $P < 0,01$) and Gr C (-2,89 $\pm$ 0,02 cm, $P < 0,01$) vs compared to Gr A (-0,75 $\pm$ 0,02 cm), concurrently BMI decreased significantly in the subjects receiving DAPA (-1,92 $\pm$ 2,35 kg/m^2, $P < 0,05$) and EMPA (-1,22 $\pm$ 2,48 kg/m^2, $P < 0,05$). HbA_1C level was lowered by 0,76% (Gr A); 0,99% (Gr B) and 0,96% (Gr C). FIB-4 decreased significantly in patints of Gr B (1,28 $\pm$ 0,13 to 0,61 $\pm$ 0,05, $P < 0,01$) and Gr C (1,22 $\pm$ 0,19 to 0,63 $\pm$ 0,03, $P < 0,01$) that in the Gr A (1,27 $\pm$ 0,13 to 1,20 $\pm$ 0,08). Due to the positive result of METAVIR score was higher in subjects of Gr B (8,64 $\pm$ 1,33 vs 5,61 $\pm$ 0,25 kPa, $P < 0,01$) and Gr C (8,59 $\pm$ 1,45 vs 5,59 $\pm$ 0,32 kPa; $P < 0,01$) compared with the Gr A (8,49 $\pm$ 1,53 vs 7,74 $\pm$ 1,22 kPa). As regards to effect DAPA and EMPA on fetuin-A positive effect (0,8-0,9-time) in both groups. Fetuin-A was positively correlated with BMI ($r = 0,662$, $P = 0,004$), WC ($r = 0,758$, $P = 0,001$), FIB-4 ($r = 0,672$, $P = 0,003$) and METAVIR score ($r = 0,524$, $P = 0,002$). The gliflozins resulted in a decrease in content hepatic fibrosis, fetuin-A compared Gr A.
Conclusions
Our study demonstrated the positive effect of gliflozins activates additional hepatoprotective mechanisms and would become an innovation therapeutic option for the treatment of persons with NS.

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EP865

JOINT1672

Dapagliflozin protects against oxLDL-induced endothelial inflammation and oxidative damage by modulating the AMPK mechanism

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Atherosclerosis is a chronic cardiovascular condition characterized by the accumulation of oxidized low-density lipoprotein (ox-LDL) and the aggregation of vascular cells, leading to endothelial dysfunction and plaque formation. This study investigates the potential anti-atherogenic properties of Dapagliflozin (DAPA), a sodium-glucose cotransporter-2 inhibitor (SGLT2i) primarily used in managing type 2 diabetes (T2D). Recent clinical trials have highlighted DAPA's cardiovascular benefits, particularly in reducing heart failure and cardiovascular mortality, suggesting a broader therapeutic role beyond glucose regulation. In this study, we aim to explore the protective mechanism of DAPA in oxLDL-caused endothelial damage. The 150 μg/ml oxLDL dosage was stimulated to human umbilical vein endothelial cells (HUVECs) for 24 h with or without DAPA co-treatment. We found that DAPA increased the phosphorylation of AMPK in a dosage-dependent and time-dependent manner. DAPA reversed oxLDL-impaired cell viability by MTT assay. However, silencing AMPK by siRNA obliterates this finding. DAPA reduced oxidative stress markers, such as superoxide and

hydrogen peroxide production, under oxLDL stimulation. This reduction is regulated by AMPK-mediated NADPH oxidase activity and enhances the antioxidant defense system. We also found that DAPA mitigates oxLDL-induced apoptosis in endothelial cells by reducing intracellular calcium levels, stabilizing mitochondrial membrane potential, and modulating the expression of pro-apoptotic and anti-apoptotic proteins. Silencing AMPK by siRNA obliterates this finding. Together, those results contribute to developing novel therapeutic strategies for managing cardiovascular diseases related to atherosclerosis and providing insights into the broader clinical applications of SGLT2 inhibitors.

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EP866

JOINT3407

Challenges in the management of childhood obesity in primary care

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Introduction
Lifestyle changes in industrialized societies have contributed to a rising prevalence of childhood obesity (CO). As frontline healthcare providers responsible for screening and family counseling, family physicians (FPs) face increasing challenges in addressing this silent epidemic. This study aims to explore the barriers to optimal CO management among FPs.
Methods
This was a cross-sectional descriptive and analytical qualitative study using a standardized questionnaire targeting FPs of all practice settings in southern Tunisia during 2024. Data were collected online or through direct interviews. Open-ended questions were assessed using a Likert scale from 0 to 10. The study focused on three main dimensions: CO management, patient adherence to treatment recommendations, and FP satisfaction. Statistical analysis was performed using SPSS software.
Results
We collected 100 responses from FPs with a mean age of 48.5 $\pm$ 11 years, predominantly female, with an average of 17.4 $\pm$ 11 years of practice experience. The main barriers to CO management were a lack of theoretical training (62%), patients' socioeconomic status (47%), and workload (30%). These challenges were more pronounced among physicians working in rural areas ($P = 0.03$) and in public healthcare settings ($P = 0.024$). Patient adherence to dietary and lifestyle recommendations provided by FPs was estimated at 4.5 $\pm$ 1.85/10 on average, with significantly lower adherence in private practice ($P = 0.01$), rural settings ($P = 0.0001$), and for dietary recommendations compared to physical activity advice ($P = 0.02$). Overall, FP satisfaction with CO management was below average (4.55 $\pm$ 1.9/10) and was significantly lower among private practitioners and those working in rural or semi-urban areas ($P = 0.003$ and $P = 0.045$, respectively).
Conclusion
Our study highlights disparities in CO management depending on the location and sector of FP practice. These differences suggest that access to resources, training, and specialized care networks directly impacts medical practices. The limited adherence of patients to dietary and lifestyle recommendations, particularly in rural areas, underscores the need for a more personalized approach tailored to socioeconomic constraints. Additionally, the low satisfaction among FPs regarding their ability to manage CO may reflect a lack of institutional support and excessive workload, hindering the implementation of effective strategies. These findings advocate for strengthening continuous medical education programs and improving healthcare structures to enhance CO management in primary care settings.

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EP867

JOINT3923

Phenotypic expression of biomolecular abnormalities in the leptin gene: a case report

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Introduction
Over the past four decades, the prevalence of childhood obesity has increased drastically. Congenital leptin deficiency (CLD) is a very rare recessive genetic disorder caused by homozygous mutations in the *LEP* gene, leading to early-onset obesity. Children with CLD have a normal birth weight but rapidly gain weight within the first few months of life, resulting in severe hyperphagia and extreme obesity.
Objective
This study elucidates the phenotype associated with CLD through the report of an exceptional case involving a homozygous nonsense mutation in the exon of the leptin gene, of which only three other similar cases have been described.
Case Report
The patient, N.A., a 17-month-old girl, exhibited drastic weight gain from the age of 2 months, associated with an eating disorder characterized by severe hyperphagia. Her psychomotor development was normal, and she showed no signs of dysmorphic syndrome. The diagnosis was confirmed biologically by detecting a severely reduced circulating leptin level (< 1 ng/ml). Genetic analysis revealed a nucleotide change in exon 3 of the leptin gene, caused by a homozygous nonsense mutation in the *LEP* gene. Due to a lack of resources, our patient did not receive recombinant human leptin therapy. Managed solely with dietary and lifestyle interventions, her condition worsened, with an aggravation of the eating disorder, evolving into constant food-seeking behavior. By the age of 3 years and 7 months, she weighed 38 kg.
Conclusion
Given the genetic and therapeutic complexity of CLD cases, adaptations in healthcare pathways are necessary to alleviate both the socioeconomic burden of medical care and the financial strain on affected children and their families. To achieve this, frontline pediatricians must be trained and made aware of the importance of early detection of these rare cases. Additionally, significant efforts should be made to develop more accessible pharmacological leptin replacement therapy, ensuring that children in need can also benefit from treatment.

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EP868

JOINT2018

Evaluation of phenotypic age to improve screening and prognosis in patients with type 2 diabetes mellitus

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Background
According to the World Health Statistics 2024, diabetes mellitus (DM) remains a major metabolic risk factor for non-communicable diseases. Early screening and timely assessment of prognostic markers such as carotid artery stiffness (CAS), pulse wave velocity (PWV) in carotid and femoral arteries, carotid intima-media thickness (CIMT) are important for prevention of cardiometabolic complications. The use of phenotypic age (PA) is gaining popularity in clinical practice as it more accurately predicts age-associated changes than chronological age (CA).
Aim
The aim of our study was to evaluate the association of PA with cardiovascular risk factors compared with CA among patients with newly diagnosed type 2 diabetes mellitus (DM-2).
Methods
98 patients with type 2 DM (mean age 50.9 [47.5; 55.1] years) were compared with 20 age-reciprocal control patients (mean age 51.0 [48.4; 55.2] years) without DM-2. All patients were divided into two groups: aged <50 years and ≥ 50 years, based on CA ($n = 24$ vs $n = 74$, respectively) and PA ($n = 54$ vs $n = 44$), according to the method described by Levine *et al*., 2018. Anthropometrics, carbohydrate, lipid profiles, glomerular filtration rate (GFR), CAS, PWV and CIMT were assessed in all participants. The Mann-Whitney test was used to assess intergroup quantitative differences.
Results
There were significant differences in body mass index, carbohydrate and lipid profiles ($P < 0.01$), PA ($P = 0.001$), CAS ($P = 0.018$), PWV ($P = 0.0001$) and CIMT ($P = 0.0001$) between patients with newly diagnosed DM-2 and controls. Among all subjects with newly diagnosed DM-2, both CA and PA were associated with HOMA-IR ($r = 0.384$, $P = 0.0001$ and $r = 0.760$, $P = 0.003$), TC ($r = 0.620$, $P = 0.0001$ and $r = 0.825$, $P = 0.0001$), HDL-C ($r = 0.258$,

$P=0.003$ and $r = 0.562$, $P = 0.001$), LDL-C ($r = 0.612$, $P = 0.0001$ and $r = 0.814$, $P = 0.0001$), GFR ($r = 0.523$, $P = 0.001$ and $r = 0.869$, $P = 0.001$), CIMT (r 0.570, $P = 0.0001$ and $r = 0.836$, $P = 0.0001$). Meanwhile, CAS ($P = 0.027$), PWV ($P = 0.034$) and CIMT ($P = 0.0001$) were significantly higher in patients with newly diagnosed DM-2, in the PA subgroup $\geq$50 years. Glycated haemoglobin levels in the subgroup with PA <50 years were significantly higher than the subgroup of CA <50 years ($P = 0.001$), as was the HOMA-IR score ($P=0.01$).

Conclusions

Assessment of PA compared to CA in patients with DM-2 allows earlier diagnosis not only of disorders in carbohydrate metabolism, but also allows timely detection of the consequences of cardiometabolic changes based on CAC, PWV, CIMT than an increase in CA, which means preventing the addition of new patients with high and very high cardiovascular risk.

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EP869

JOINT3137

Changes in body composition among women users of anabolic androgenic steroids - suggestions of long-term impact on trunk fat accumulation

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Background and objectives

The illicit use of anabolic androgenic steroids (AAS) has moved from competitive sports to the broader population and to women. The current knowledge on long-term impact of AAS in women is sparse. Women use AAS to gain a more muscular appearance and lose body fat but the impact on body composition has never been assessed. The objective of this study was to evaluate muscle and fat distribution in current and previous female illicit AAS users compared with never-users.

Methods

Cross-sectional study including women engaged in recreational strength training. Participants were grouped as current or previous users with a 3-month cut-off value for last AAS use. Dual-energy x-ray absorptiometry (DXA) was used to measure body composition with lean mass, fat mass and fat distribution.

Results

The study included 25 current AAS users, 14 previous users and 20 healthy never-users as controls. Mean (SD) age of all participants was 36 (9) years and mean (SD) body mass index was 24.7 (3.0) kg/m^2, with no difference between groups. Accumulated median (25th-75th percentiles) duration of AAS use did not differ between current and former users, 1.4 (0.3-4.5) vs 0.9 (0.6-1.9) years, ($P = 0.95$). The median (25th-75th percentiles) duration since AAS cessation among former users was 4.2 (1.8-5.6) years. Compared with controls, current AAS users displayed lower total body fat percent, 23.9 (4.0) vs 29.6 (5.1)% ($P <0.001$), and lower total fat mass, 15.5 (3.7) vs 19.9 (5.2) kg ($P = 0.002$). Current users also had a higher lean mass index than controls, 18.1 (2.4) vs 16.9 (1.4) kg/m^2 ($P = 0.038$), yet the fat distribution demonstrated a higher trunk to limb fat ratio, 0.78 (0.22) vs 0.63 (0.11) ($P= 0.006$). Notably, while total body fat percent, total fat mass and lean mass index did not differ between former users and controls, former users retained a higher trunk to limb fat ratio, 0.72 (0.12) vs 0.63 (0.11) ($P = 0.036$). There were no significant differences between groups when examining android to gynoid fat ratio and visceral adipose tissue.

Conclusions

Women previously engaged in illicit AAS use display increased trunk to limb fat ratio several years after cessation, suggesting long term adverse impact on fat metabolism.

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EP870

JOINT3860

The association between objectively meaured sleep duration and glucose regulation in healthy adolescents: insights from continuous glucose monitoring

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Introduction

Sleep duration is increasingly recognised as a modulator of metabolic health, yet its acute effects on glucose regulation in healthy populations remain poorly understood. This study explores the relationship between sleep duration and post-sleep glucose metrics in healthy 18-year-olds.

Methods

This study included 206 participants (112 females, 94 males) from the COPSAC2000 cohort, with a mean age of 17.7 years. Sleep duration was assessed using actigraphy over a median of 13 nights per participant (IQR: 3), totaling 2,246 individual nights of sleep data. Concurrent glucose metrics (mean, median, variability) were derived from continuous glucose monitoring (CGM) during the waking period following each sleep measurement. Multivariate linear mixed-effects models, adjusted for age, sex, physical activity, social circumstances, and other confounders, were used to assess associations. Subanalyses focused on the 4-hour post-waking and 2-hour pre-waking periods to account for dietary confounding and the cortisol awakening response.

Results

Females slept longer on average than males (6:56 vs. 6:25 h,$P < 0.001$) and had earlier sleep onset times (00:10 vs. 00:50,$P < 0.001$). In multivariable modelling, longer sleep duration (per hour of sleep) was associated with higher mean ($\beta = 0.28$, 95% CI: 0.05–0.52) and median glucose levels ($\beta = 0.39$, 95% CI: 0.15–0.63) and reduced glucose variability (SD: $\beta = -0.12$, 95% CI: -0.23 to -0.01; CV: $\beta = -0.16$, 95% CI: -0.28 to -0.04). Associations for glucose levels were stronger in the 4-hour post-waking window (mean: $\beta = 0.56$, 95% CI: 0.29–0.83; median: $\beta = 0.66$, 95% CI: 0.37–0.94). In the 2-hour pre-waking period, glucose levels rose at a population level by 10mg/dL (0.6mmol/l), consistent with the cortisol awakening response. This rise in glucose may explain why longer sleep duration was associated with higher pre-waking glucose variability (SD: $\beta = 0.27$, 95% CI: 0.09–0.45; CV: $\beta = 0.29$, 95% CI: 0.09–0.48). Mediation analysis revealed that the morning glucose slope partially mediated the association between sleep duration and median glucose levels (indirect effect: 0.019, 95% CI: 0.0015–0.0448). Effect sizes were modest and unlikely to be clinically meaningful.

Conclusion

Sleep duration is associated with glucose levels and variability in healthy adolescents, with longer sleep linked to higher waking glucose and lower variability. The pre-waking glucose rise underscores the role of circadian rhythms in glucose dynamics. While these findings provide mechanistic insights, the modest effect sizes suggest limited clinical relevance in this healthy cohort.

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EP871

JOINT3542

LDL-cholesterol calculation methods influence on clinical management

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Introduction

Most clinical laboratories use the Friedewald equation to account for VLDL-cholesterol and subsequently calculate LDL-cholesterol. This equation has known limitations at high triglyceride levels or low LDL-cholesterol levels. Alternative equations, such as the Martin-Hopkins and Sampson-NIH equations, have been proposed. This study aims to compare LDL-cholesterol estimates derived from these three equations with directly measured LDL-cholesterol and to assess whether the choice of equation affects patients' clinical management.

Methods

In this retrospective, monocentric study, all LDL-cholesterol samples analyzed at Amiens University Hospital between august 1st, 2022 and July 31st, 2023 were included ($n = 7895$). LDL-cholesterol levels calculated by the three equations were compared with measured LDL values using Pearson correlation coefficient. Comparisons were stratified by total triglyceride (TG) (0-400 mg/dL, 400-800 mg/dL and >800 mg/dL) and LDL-cholesterol levels (below or above 70 mg/dL). Subsequently, random samples were selected from each category (TG 0-400 mg/dL, TG 400-800 mg/dL and LDL-cholesterol <70 mg/dL), cardiovascular risk was estimated for each individual and the misclassification rates attributable to each equation were determined.

Results

In the TG 0-400 mg/dL category, all three equations yielded equivalent correlation coefficients ('r') around 0.95 but the Sampson equation showed the highest concordance rate (24.85% vs 22,01% for Martin-Hopkins 20.45% for Friedewald). In the TG 400-800 mg/dL category, the correlation coefficients ('r') was around 0.83 and both the Martin-Hopkins and Sampson-NIH equations had the highest concordance rates (14.51% and 13.70% vs 3.22% for Friedewald). In the LDL-cholesterol <70 mg/dL category, The Martin-Hopkins and Sampson-NIH equations had correlation coefficients ('r') of 0.70 and 0.71, respectively,

compared to 0.61 for Friedewald; concordance rates were 27.55% for the Martin-Hopkins, 26.78% for the Sampson-NIH and vs 24.25% for the Friedewald equation. Among people with TG 0-400 mg/dL, the proportion of misclassified individuals was 4,4% for the Sampson-NIH, 4,9% for the Martin-Hopkins and 6,4% for the Friedewald equation. Among people with TG 400-800 mg/dL, the proportion of misclassified individuals was 7,4% for the Sampson-NIH, 3,7% for the Martin-Hopkins and 14,8% for the Friedewald equation. The respective proportions were 14,7%, 14,7% and 17,6% among individuals with LDL-cholesterol $<$70mg/dL.

Conclusion

This study demonstrates that the three methods perform very well in people with TG 0-400 mg/dl, relatively good in people with TG 400-800 mg/dL and less well in people with LDL-cholesterol $<$ 70 mg/dL. However, the Sampson and Martin-Hopkins equations are less prone to therapeutic misclassification errors than the Friedewald equation.

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EP872

JOINT423

Exploration of metabolic signatures or biomarkers associated with obesity in children and adolescents

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Introduction

Obesity is an escalating health issue globally, impacting both adults and children. Despite its prevalence, the precise mechanisms driving the development of obesity in children remain unclear. Metabolomics, the comprehensive study of metabolites within biological systems, offers a powerful approach to better define the phenotype and understanding the complex biochemical alterations associated with obesity.

Aim

The aim of our study was to summarize the current knowledge in the field of metabolomics in childhood obesity, and to identify metabolic signatures or biomarkers associated with obesity in children and adolescents (within the framework of the BIO-STREAMS project (https://www.bio-streams.eu/); a 4-year (2023–2027) Horizon Europe project (No101080718)).

Methods

We performed a systematic search of Medline and Scopus databases according to PRISMA guidelines. The review was registered in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO 2023 CRD42023494461). We included only longitudinal prospective studies, randomized-controlled trials with $\geq$12-month follow up, and meta-analyses of the above that assessed the relation between metabolic signatures related to obesity and body mass index (BMI) or other measures of adiposity in children and adolescents aged 2-19 years with overweight or obesity. Initially, 595 records were identified from PubMed and 1565 from Scopus. After removing duplicates and screening for relevance, 157 reports were assessed for eligibility. From the additional search, 75 new records were retrieved, from which none was eligible for our study. Finally, 7 full-text articles were included in our study.

Results

The majority of the included studies stated an association of lipids with changes of BMI, insulin resistance and the risk for metabolic syndrome. More specifically, these include certain lipoproteins, apolipoproteins, cholesterols, fatty acids, glycerides and phospholipids, ketone bodies, lysophosphatidylcholines as well as acyl–alkyl phosphatidylcholine. Among the overarching class of amino acids, peptides and analogues, included are glycylproline, citrulline, formiminoglutamic acid, 4-hydroxyproline, alanine, phenylalanine, tyrosine, gluta-mine, methionine, serine and alanine. Furthermore, numerous lipids act as signaling molecules in inflammation pathways or insulin resistance, contributing to obesity-related complications, such as DM2 and cardiovascular disease. Acylcarnitines are the by-products of noncomplete fatty acid oxidation.

Conclusion

Our findings reveal specific biomarkers in the amino acid and lipid pathway that could serve as early indicators of obesity and its related cardiometabolic complications. Continued exploration of metabolomic profiles in childhood obesity is warranted, particularly in pediatrics, to develop targeted interventions and prevent the long-term consequences of this condition.

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EP873

JOINT2648

Comparative accuracy of glycemic parameters in identifying dysglycemia in obese indian children and adolescents

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Background-

Dysglycemia is a significant cause of concern in children and adolescents with obesity. The beneficial impact of early intervention makes timely identification desirable. The current diagnostic cutoffs for dysglycemia based on adult recommendations have not been validated in Indian children and adolescents. In particular, the validity of hemoglobin A1C (HbA1C) cutoffs has been questioned.

Aim

To compare the diagnostic accuracy of glycemic parameters (glucose tolerance test, HBA1C, and continuous glucose monitoring measures) in identifying dysglycemia in obese Indian children and adolescents.

Methodology

An oral glucose tolerance test and HbA1C were performed in 170 obese children and adolescents (110 boys; age 12.8 $\pm$ 3.2 and BMI SDS 2.3 $\pm$ 0.6). Twenty subjects also underwent 14-day ambulatory blood glucose monitoring. The prevalence of dysglycemia according to different measures and the correlation between different parameters were compared. A ROC curve was generated to determine the diagnostic cutoff of HbA1C to identify glucose tolerance test-detected dysglycemia.

Results

Dysglycemia was identified by eight subjects according to fasting glucose (all pre-diabetes, 4.7%), fifteen as per 2-hour value (13 with prediabetes, 2 with diabetes; 8.8%), and 37 by to HbA1C (36 with pre-diabetes and 1 with diabetes, 21.8%). Twenty-eight subjects (77.8%) identified as pre-diabetes by HbA1C had normal glucose tolerance tests. Both the subjects with abnormal glucose profiles on continuous glucose monitoring (16.2%) had glucose tolerance tests determined dysglycemia. Average blood glucose in CGM data correlated with fasting (r = 0.9, P = 0.001) and 2-hour blood glucose (r = 0.8, p=$<$0.001) with no correlation with HBA1c (r = 0.5, P = 0.09). The ROC curve for diagnostic efficacy of HbA1C in identifying dysglycemia had an area under the curve of 0.730 (P = 0.02). An increase in HBA1C cutoff to 6% would have avoided the diagnosis of dysglycemia in 8 subjects with normal glucose tolerance tests.

Conclusion

Dysglycemia is common in Indian children and adolescents, highlighting the need for early identification. HbA1C tends to overestimate dysglycemia, suggesting the need for higher cutoffs. ABGM is a promising tool for screening dysglycemia but needs further exploration before widespread use.

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EP874

JOINT23

Screening accuracy of single-point insulin sensitivity estimator (SPISE) for metabolic syndrome: a systematic review and meta-analysis

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Background

Metabolic syndrome (MetS) is a multifactorial condition linked to increased risk of cardiovascular disease and type 2 diabetes. Insulin resistance underpins its pathophysiology, yet traditional diagnostic methods are invasive and costly. The Single-Point Insulin Sensitivity Estimator (SPISE), a non-invasive index, offers a practical alternative for assessing insulin sensitivity. This systematic review and meta-analysis aim to evaluate the diagnostic accuracy of SPISE in detecting MetS.

Methods
We conducted a systematic review and meta-analysis following PRISMA guidelines. We searched databases such as MEDLINE, Scopus, Web of Science, and Embase, focusing on studies evaluating SPISE's screening accuracy for MetS. Eligible studies were observational, reporting mean SPISE values and its diagnostic performance. Meta-analyses were performed using Hedges' g standardized mean differences (SMD) and pooled area under the curve (AUC) estimates.
Results
Seven studies comprising 12,919 participants were included. Individuals with MetS had significantly lower SPISE scores than controls (SMD = -0.94, 95% CI: -1.25 to -0.63). The pooled AUC for SPISE as a predictor of MetS was 0.86 (95% CI: 0.83 to 0.90), surpassing other insulin sensitivity indices like HOMA-IR and the triglyceride/HDL-C ratio. Meta-regression showed that systolic and diastolic blood pressure were potential sources of heterogeneity.
Conclusions
SPISE is a highly accurate and non-invasive tool for predicting MetS, potentially outperforming traditional indices like HOMA-IR. Its ease of use and diagnostic precision make it a valuable clinical screening tool, especially in diverse populations.

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EP875

JOINT3070

ACTH as the liver fibrosis predictor in non-cushing syndrome population

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Introduction
The data on the impact of adrenocorticotropic hormone (ACTH) and cortisol on liver function are scarce and conflicting. To the best of our knowledge there are no studies evaluating cortisol and ACTH as liver fibrosis (LF) biomarker in non-Cushing syndrome (CS).
Objectives
To evaluate the role of ACTH and cortisol in LF among non-CS.
Materials and Methods
We analyzed retrospectively 350 consecutive patients (66%female, median age 65 [56-70]) with non-secretive adrenal adenomas. CS was excluded on 1 mg dexamethasone suppression test (C-DST [morning cortisol <1.8 mg/dL]). FIB4 (Age$\times$AST/PLT$\times$ALT 1/2) was used as a LF predictor (<1.3 low risk [LR-LF], 1.3-2.67 intermediate risk [IR-LF], >2.67 high risk [HR-LF]). Multimodal logistic regression analyses were performed (RStudio version 4.2.2, $P<0.05$). Age, gender, bmi diabetes mellitus and hypercholesterolemia were included as co-variates to account for its potential influence on FIB-4.
Results
For every 1, 2, 10 and 30pg/ml ACTH rise, the odds for IR-LF rise by 3%, 6%, 16%, 35% and 148% ($P = 0.039$) and for HR-LF increase by 6%, 13%, 35%, 83% and 517% $P = 0.006$). The OR for the association between LF and cortisol (morning, midnight, C-DST) was statistically non-significant.
Conclusions
ACTH may have an impact on LF in non-CS population. Further studies examining the relation between ACTH, cortisol and liver fibrosis are needed.

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EP876

JOINT3794

Metabolic bariatric surgery reduces markers of aging in patients with obesity, independent of achieving optimal total weight loss

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Introduction
Obesity is a chronic metabolic disorder associated with accelerated biological aging, systemic inflammation, and oxidative stress. Metabolic bariatric surgery (MBS) is an effective intervention for obesity; however, the extent to which improvements in biological age markers are contingent upon achieving optimal weight loss remains unclear.
Objective
To investigate whether the postoperative changes in aging biomarkers following MBS are dependent on achieving optimal weight loss outcomes.
Methods
In this prospective observational study, 100 patients with obesity scheduled for MBS between July 2020 and May 2021 were enrolled and followed for 24 months postoperatively. Biological aging markers assessed included telomere length (TL) measured by quantitative polymerase chain reaction (qPCR), DNA damage, C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), total oxidant status (TOS), and metabolic age. Patients were stratified into two cohorts: those achieving optimal weight loss (% total weight loss [TWL] $\geq$20%, % excess weight loss [EWL] $\geq$50%) and those with suboptimal weight loss outcomes (%TWL $<$20%, %EWL $<$50%). Correlations between weight loss parameters and changes in biological aging markers were analyzed.
Results
Forty patients completed the 24-month follow-up (22 in the optimal weight loss group, 18 in the suboptimal group). Significant postoperative improvements were observed in TL, DNA damage, CRP, IL-6, TNF-α, TOS, and metabolic age in both cohorts. Notably, metabolic age demonstrated a significantly greater reduction in the optimal weight loss group ($p < 0.05$), whereas changes in other biomarkers did not differ significantly between groups.
Conclusions
MBS induces significant reductions in biomarkers associated with biological aging, independent of the extent of weight loss achieved. These findings suggest that conventional weight loss metrics (%TWL, %EWL) may not fully capture the therapeutic benefits of MBS, underscoring its broader impact on molecular aging processes.

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EP877

JOINT2525

Weight evolution in children of mothers with gestational diabetes: an analysis of the early years of life

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Introduction
Gestational diabetes (GD) is associated with metabolic complications and an increased risk of childhood obesity. This study aimed to analyze weight evolution and factors associated with overweight and obesity in children of mothers with GD, as well as to identify maternal factors that influence weight gain during the early years of life.
Methods
This retrospective cohort study included 186 mothers diagnosed with GD and their offspring, born between January 2018 and December 2019 at our center. Sociodemographic and clinical data of the mothers were collected, including pre-pregnancy body mass index, weight gain during pregnancy, type of GD treatment, and data on the children, such as anthropometric measurements up to the age of 6, breastfeeding practices, and neonatal health parameters. Weight/length z-scores and BMI z-scores were calculated for the children at different age ranges. Associations between maternal and child variables and the children's weight evolution up to 6 years were tested.

Results
The mean (SD) age of the mothers was 34.7 (5.7) years, with an average (SD) pre-pregnancy BMI of 24.4 (5.2) kg/m^2. A total of 44.6% of the women required pharmacological treatment for glycemic control. Births were 62.4% vaginal deliveries and 37.6% cesarean sections. During the follow-up of the children, 5.0% were found to be overweight, and 4.4% were obese between the ages of 4 and 6. In the adjusted model, the presence of a family history of diabetes and earlier introduction of complementary feeding were associated with a higher BMI z-score at ages 4-6 years ($\beta = 0.442$, 95% CI: 0.087, 0.796; $\beta = -0.249$, 95% CI: - 0.448, -0.051, respectively).
Conclusion
This study suggests that having family history of diabetes is associated with a higher risk of overweight and obesity in children of mothers with GD. The introduction of complementary feeding closer to 6 months appears to be associated with a lower risk of obesity. These findings reinforce the importance of early preventive strategies and continuous monitoring of the weight evolution in these children.

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EP878

JOINT3609

Bariatric surgery and conception timing: maternal and neonatal outcomes

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Introduction
The recommended interval between bariatric surgery and conception varies, generally ranging from 12 to 24 months. Some studies associate conception within two years post-surgery with an increased risk of preterm delivery, neonatal intensive care unit(NICU) admission, and small-for-gestational-age(SGA) newborns. However, other studies show no significant differences.
Objective
To evaluate the impact of the interval between bariatric surgery and conception ("early conception", $\leq$12 months vs "late conception", $>$12 months) on pregnancy outcomes.
Materials and Methods
A retrospective study was conducted on pregnancies following bariatric surgery at a Portuguese tertiary center. Maternal and neonatal complications were compared between two groups based on surgery-to-conception interval. Composite maternal complications included preeclampsia, polyhydramnios, and miscarriages, while composite fetal complications encompassed preterm births, need for phototherapy, and admission to the NICU. Statistical analyses were performed using IBM SPSS Statistics.
Results
The study included 102 pregnancies (92 women) between 2015 and 2023. The median maternal age was 34 years (23-45). Most patients underwent gastric bypass (66.7%, $n = 68$), while 33.3% ($n = 34$) had sleeve gastrectomy. The median surgery-to-conception interval was 34 months, with 22.5% ($n = 23$) conceiving within 12 months post-surgery. The median gestational age at delivery was 39 weeks (23-41), and the median birth weight was 3030g (1000-4140g). The cesarean section rate was 33.0%. Pregnancy complications included 12 cases (12.2%) of preeclampsia, 2 cases (2.1%) of polyhydramnios, 3 miscarriages (3.1%) and 15 preterm births (15.6%). Neonatal outcomes included 20 large-for-gestational-age newborns (20.8%), 11 SGA (11.5%) and 11 congenital malformations (11.5%). Additionally, 28(29.2%) required phototherapy, and 9(9.4%) were admitted to the NICU. No statistically significant differences were found between groups in terms of maternal-fetal complications, whether analyzed individually or as composite outcomes(Table 1).

Table 1. Pregnancy outcomes in early *vs* late conception group

	Early conception ($n = 23$)	Late conception ($n = 79$)	p-value
Cesarean section(n, %)	7(33.3)	25(32.9)	0.970
Preeclampsia(n, %)	1(4.8)	11(14.3)	0.452
Polyhydramnios(n, %)	1(5.0)	1(1.3)	0.378
Miscarriages(n, %)	2(9.5)	1(1.3)	0.120
Preterm births(n, %)	1(5.0)	14(18.4)	0.183
Large-for-gestational-age(n, %)	4(20.0)	16(21.1)	0.918
SGA(n, %)	1(5.0)	10(13.2)	0.449
Congenital malformations(n, %)	1(5.0)	10(13.2)	0.449
Need for phototherapy(n, %)	8(40.0)	20(26.3)	0.273
Admission to the NICU(n, %)	0(0)	9(11.8)	–
Maternal complications(n, %)	4(19.0)	13(17.6)	0.876
Fetal complications(n, %)	9(45.0)	31(40.8)	0.801

Conclusion
While current guidelines recommend delaying conception, our findings suggest that pregnancy within one-year post-surgery may be safe. However, the small sample size may have limited the ability to detect significant differences, highlighting the need for further studies.

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EP879

JOINT4045

A rare syndrome hidden behind obesity

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Introduction
Obesity is a chronic and complex disease that can affect your overall health and quality of life. A number of conditions could be hidden behind obesity. Pseudohypoparathyroidism (PHP) is a rare inherited disorder characterized by end-organ resistance or unresponsiveness to parathyroid hormone (PTH) resulting in increased serum PTH levels, hypocalcemia and hyperphosphatemia. Physical features of PHP are specific somatic and developmental abnormalities such as round facies with a 'short, thick figure', heterotopic subcutaneous ossifications (SCOs), brachydactyly and cognitive impairment.
Case report
We present a female patient who consulted with us in her late twenties due to extreme obesity. Her menarche was at age 13, after which her menstruations have always been irregular according to the type of oligomenorrhea, with the longest period without menstruation being of 3 months. In childhood, she was examined for obesity under the suspicion of hypercortisolism, which was ruled out. She gained weight in early childhood, with a maximum of 120 kg at the age of 12. Psychological examination showed mild cognitive impairment. During the physical examination we identified general obesity type with phenotypic characteristics of AHO (Albright hereditary dystrophy): brachydactyly, short stature, stocky habitus, macrocephaly, round face, short fingers on both hands, except for thumbs, SCOs in the pretibial region of lower extremities. Hand radiography showed shorter metacarpal bones of the fourth finger bilaterally with discrete degenerative changes. Cranial and chest radiography, neck and abdominal ultrasound, and ophthalmological examination were normal. Bone density was normal. Karyotype was 46, XX. Calcium and phosphorus homeostasis were intact with elevated calcitonin and PTH.
Consusion
Patients with PHP faces a wide range of problems due to hormone resistance that can lead to hypothyroidism, hypogonadism, growth impairment, ectopic ossifications, cognitive disorders and obesity. This highly heterogeneous clinical picture requires a multidisciplinary approach.

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EP880

JOINT1701

Distribution of lipid levels and prevalence of hyperlipidemia in a multi-ethnic young male population

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Introduction
The prevalence of hyperlipidemia among adolescents and young adults is rising globally, contributing to an increased risk of atherosclerotic cardiovascular

disease (ASCVD) later in life. Identifying dyslipidemia requires understanding normal lipid ranges, which prior studies have defined in discrete age brackets: childhood and adolescence ($\leq$19 years) and young adulthood (20-40 years). However, lipid concentrations likely change continuously with age. This study aims to describe lipid levels and associated factors in a population-wide cohort of multi-ethnic Asian males aged 16-25 years who underwent mandatory military health screening.

Methods

The study included more than 19,000 males aged 16-25 years eligible for military conscription from 1 July 2021 to 30 June 2022. Data collected comprised anthropometric variables (height, weight, body mass index [BMI], body fat percentage), clinical measures (blood pressure), and non-fasted lipid levels (total cholesterol [TC], triglycerides [TG], high-density lipoprotein cholesterol [HDL-C]). Low-density lipoprotein cholesterol (LDL-C) was estimated using the Friedewald equation. Subgroup analysis was performed on older adolescents (16-19 years). Hyperlipidemia prevalence was determined using National Cholesterol Education Program (NCEP) Adult Treatment Panel III criteria for the overall cohort and NCEP Pediatric Panel criteria for older adolescents.

Results

The mean lipid values were: TC (4.38 mmol/l), TG (1.23 mmol/l), HDL-C (1.37 mmol/l), and LDL-C (2.46 mmol/l). Nearly 44% of participants were overweight or obese. Body fat percentage and blood pressure were positively correlated with TC levels. The prevalence of hyperlipidemia was significant: 12.5% had TC $>$5.2 mmol/l, 19% had TG $\geq$1.7 mmol/l, 5.1% had HDL-C $<$1.0 mmol/l, and 35.6% had LDL-C $>$2.6 mmol/l. The prevalence of severe hypercholesterolemia (LDL-C $\geq$4.9 mmol/l) was 0.6%, and severe hypertriglyceridemia (TG $\geq$4.5 mmol/l) was 0.5%. Familial hypercholesterolemia was diagnosed in 0.3% of participants. In the older adolescent subgroup, 16.2% had abnormal TC levels, and 8.2% had abnormal LDL-C levels.

Conclusion

We described the lipid distribution in a population-wide cohort of Asian males aged between 16 to 25 years old. Unsurprisingly, mean lipid values appear to be between that described in childhood and adult populations. While the high proportion of older adolescents with dyslipidemia may be due to normative differences in that age range as compared to younger children, it is also matched by similarly high prevalence of dyslipidemia even when using adult thresholds - suggesting that the true prevalence of hyperlipidemia is indeed high and may portend future cardiovascular risk.

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JOINT1526

Semaglutide as a potential treatment for a child with ADCY3 mutation

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Aim

ADCY3 mutations, a rare cause of monogenic obesity, are associated with hyperphagia, obesity, insulin resistance, hyposmia, and intellectual disability. Although no specific treatment is approved, GLP-1 receptor agonists have shown potential benefits. Here, we present our experience with Semaglutide in a patient with an *ADCY3* mutation.

Case

A $4^{7/12}$ years-old female presented with hyperphagia and excessive weight gain starting at 2 months. She was born at term with a birth weight of 3050g ($-$0.08 SDS), her weight increased to 6.5 kg ($+$2.03 SDS) at 2 months,19 kg ($+$6.98 SDS) at 10 months, and 34 kg ($+$8.42 SDS) at 2.5 years. The family had a history of consanguinity but no reported obesity. At presentation, her height was 118.5 cm ($+$2.59 SDS), weight 64 kg ($+$7.86 SDS), and BMI 45.5 ($+$5.70 SDS). Physical examination revealed severe acanthosis nigricans, Blount's disease impairing ambulation, stage 2 hypertension with left ventricular hypertrophy, atypical autism, and astigmatism. Laboratory findings are summarized in Table-1. Whole Exome Sequencing identified a novel homozygous warm variant of uncertain significance in the *ADCY3* gene (c.1102G$>$A), confirmed by segregation analysis. Due to uncontrolled hyperphagia, rapid weight gain, and severe obesity-related complications, treatment with Semaglutide was initiated at a dose of 0.125mg/week. The dose was titrated to 0.50mg/week at monthly intervals, as no adverse effects were observed. The patient's weight stabilized after 1 month at 0.50mg/week. As hyperphagia persisted without adverse effects, the dose was increased to 1 mg/week. During the first month at this dose, she lost 4.4 kg, and her weight remained stable over the following 3 months. Her BMI-SDS improved from $+$5.54 SDS to $+$4.88 SDS at seventh month of treatment (Table-2). The patient is currently under follow-up without experiencing significant adverse effects.

Table 1. Laboratory findings

	Result	Range
Fasting-Glucose(mg/dL)	79	70–100
Insulin(μIU/ml)	34.8	2–25
Hba1c(%)	5.6	4.8-5.9
TSH(mIU/L)	2.5	0.54-4.53
Free-T4(pmol/L)	18.6	11-22.5
Total Cholesterol(mg/dL)	171	8-200
HDL(mg/dL)	56	40-60
Triglyceride(mg/dL)	70	0-150
Leptin(ng/ml)	74	12-135
AST/ALT(U/L)	43/41	7-35

Table 2. Treatment Progress and Outcomes with Semaglutide

	Semaglutide Dose(mg/-week)	Weight-SDS	Height-SDS	BMI(kg/m^2)	BMI-SDS
Base-line($4^{10/12}$ years-old)		7.90	2.24	48.0	5.54
1st-month	0.125	8.01	2.12	49.8	5.51
2nd-month	0.25	8.14	2.01	51.2	5.44
3rd-month	0.5	7.47	2.82	44.6	5.14
6th-month	1.00	7.14	2.48	46.3	4.95
7th-month	1.00	6.96	2.40	45.6	4.88

Conclusion

GLP-1RA may be considered a potential treatment option for patients with *ADCY3* mutations presenting with uncontrolled hyperphagia, excessive weight gain, and severe obesity-related complications.

Keywords

ADCY3, monogenic obesity, semaglutide

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EP882

JOINT2298

Assessing allostatic load as a chronic stress marker in adolescents with anorexia nervosa: the impact of malnutrition

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Introduction

Allostatic load (AL) refers to the physiological response associated with the burden of chronic stress. Malnutrition is an important source of physiological stress that promotes a detrimental chronic low-inflammation state. In order to define a correlation between cumulative biological dysregulation and severe malnutrition, we measured AL scores in in adolescents with AN

Patients and Methods

We enrolled 40 adolescents (15,99 $\pm$ 1,40 yrs) with AN. Data based on 15 biomarkers were used to create the AL score. A dichotomous outcome of high AL was defined for those who had $\geq$2 dysregulated components (aligning with the population median). Body mass index (BMI)-standard deviation score (SDS) $<$-3and biochemical markers ($\geq$2) defined severe malnutrition.

Results

High AL and severe malnutrition were noted in 31/40 (77.5%) and 9/40 (22.5%) subjects respectively. Subjects with a high AL, in addition to a lower BMI z-score (P =0.02), showed higher triglycerides (P = 0.03), ALT (P $<$ 0.01), AST (P = 0.01) and lower VitD (P $<$0.01) and Vit B12 (P = 0.02) levels than subjects with a low AL. The risk of the cumulative biological dysregulation is correlated with severity of malnutrition (P =0.02). The AUROC of malnutrition upon detection of cumulative biological dysregulation was 0.759.

Conclusions
A high AL was associated with severe malnutrition in AN. AL may be considered a significant factor correlated with increased morbidity in adolescents who present AN.

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JOINT1138

Is gender affirming hormone therapy a risk factor for liver health? - 1-year follow-up data from a prospective study

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Objective
Evidence about hepatic risk profile of gender affirming hormone therapy (GAHT) is low. Most previous studies are small, retrospective and focused on the assessment of liver enzymes. Our objective was to challenge fewer findings with prospective data using modern investigation methods. We analysed the impact of GAHT on metabolic risk factors and on the development of pathological remodeling in the liver
Design
Prospective cohort study in 39 transgender individuals (20 transmen and 19 transwomen). Data were collected from 2021 to 2023.
Methods
Sonographic examinations including CAP (controlled attenuation parameter) measurement and transient elastography, the current non-invasive gold standard methods to evaluate the development of metabolic-associated fatty liver disease (MAFLD) and MAFLD-related fibrosis, were performed in all participants. Furthermore, we assessed parameters of glucose and lipid metabolism. Data were gathered each before and one year after initiation of GAHT. A relevant increase, respectively decrease was defined, if values changed $>$ 50 % of the respective standard deviation of the baseline value.
Results
Median age of the participants was 24.3 $+$ 7.2 years. 16.7 % of the cohort were obese, defined by a BMI $\geq$ 30 kg/m^2. While BMI increased during the first year of GAHT ($P = 0.024$), we could exclude an increase of fasting glucose ($P < 0.001$) as well as HbA1c ($P = 0.006$). In transmen, we recorded an increase in LDL- ($P = 0.016$) and a decrease in HDL-cholesterol ($P < 0.001$), however, all parameter remained within the reference range. Triglycerides showed a trend to increase in transmen and to decrease in transwomen, but results were not significant and parameter remained within the reference ranges. Sonographic methods could exclude an increase of liver steatosis ($P = 0.001$) as well as fibrosis ($P < 0.001$).
Conclusion
Neither virilising nor feminising gender affirming hormone therapy is a risk factor for the development of MAFLD or MAFLD-related fibrosis within the first year. A further measurement after five years of therapy will per performed to evaluate long-term effects.

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EP884

JOINT2812

Gene diagnostic challenge of extreme early-onset obesity before 5 years old

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Background
Clinical parameters, such as differential white blood cell counts, are linked to metabolic diseases and insulin resistance. However, the closely clinical markers associated with early-onset obesity, particularly genetic obesity, remain undefined. Given the increasing consensus around the necessity of genetic testing for severe early-onset obesity, there's a need to enhance the efficacy of such tests. This study endeavors to distinguish between hereditary and non-hereditary obesity using clinical indicators. The goal is to offer a foundation for the early diagnosis of hereditary obesity and subsequent genetic screening. Therefore, we conducted this observational study.
Methods
We identified early-onset obesity in children below five years old, defined by a BMI exceeding the 95th percentile. Recommended interventions included hospitalization for comprehensive obesity assessments encompassing physical examinations, biochemical tests, hormone levels, and genetic screenings.
Results
When compared to the negative Whole Exome Sequencing (WES) group, six distinct gene mutations were identified in the positive WES group: BBS1, MC4R, NCOA1, SH2B1, UCP3, and 15q11-13. This group also demonstrated a significant increase in differential white blood cell count, monocytes, serum ALT, AST, and cortisol levels ($P < 0.05$).
Conclusions
By examining disparities in clinical indicators, this research highlights the potential for genetic obesity screening in early-onset cases. Our findings provide valuable insights for the clinical genetic testing of early-onset obesity.
Keywords
Early-onset obesity, genetic detection, gene mutations, monocyte, white blood cell count.
Disclosure of interest
The authors have not any conflict of interest or competing interest to declare.

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JOINT3315

Patients with early-onset monogenic obesity: genetic approach and therapeutic challenges

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Introduction and Purpose
Children with severe, early-onset obesity before the age of 5, accompanied by extreme episodes of hyperphagia, should be investigated for monogenic forms of obesity. The MC4R (melanocortin-4 receptor) pathway orchestrates the energy homeostasis, and deficiencies along the pathway may cause monogenic obesity. MC4R pathway deficiencies include mutations in the genes encoding leptin (*Lep*) and its receptor (*LepR*), pro-opiomelanocortin (*POMC*), MC4R, prohormone convertase subtilisin/kexin type 1 (*PCSK1*), nuclear receptor coactivator 1 (*NCOA1*), and SH2B Adaptor Protein 1 (*SH2B1*). The aim is to present three cases of children with early-onset obesity and to explore its genetic basis.
Patients and Methods
Three male patients were included aged $11^{7/12}$, $8^{10/12}$, and $9^{3/12}$ years at their first visit to the Endocrinology Units. Detailed family and personal history was taken, along with comprehensive laboratory and imaging tests. Due to the early onset of obesity, resistance to dietary restrictions, and exercise, a suspicion of monogenic disease was raised. DNA analysis was performed using an obesity panel with next-generation sequencing (NGS) technology.
Results
All patients exhibited severe, early-onset obesity with hyperphagia and hepatic steatosis. From early infancy, they showed a strong interest in food intake, with a gradual increase in body mass index (BMI). Despite efforts to modify their lifestyle (changes in dietary habits, exercise, and psychological support), no improvement in BMI was observed. The first patient exhibited a potentially pathogenic variant, NM_005912:exon1:c.380C$>$T:p.S127L, in the *MC4R*, which was also confirmed in the father. It may disrupt MC4R function by altering its expression on the cell membrane and its biophysical properties. In the second child, the rs17782313 NC_000018.9:g.57851097T$>$C polymorphism in the MC4R gene was detected in heterozygous form. The polymorphism is significantly associated with hyperinsulinemia and severe obesity. Disruption of the transcriptional control of MC4R has been proposed as the potential functional mechanism for this variant. In the third child the variant of unknown significance NM_003743.5: c.3954C$>$T p. (Thr1318$=$) was detected in heterozygosity in the *NCOA1* gene. In all children, the administration of metformin did not help control appetite or BMI. Following the genetic test results, treatment with setmelanotide will be initiated, which is approved for children with syndromic or monogenic obesity associated with the hypothalamic MC4R pathway.
Conclusions
The study demonstrates the importance of genetic investigation of children with the two hallmark symptoms of early-onset, severe obesity and hyperphagia,

enabling timely selection of appropriate therapeutic approaches, prevent obesity consequences, and provide genetic counseling.

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JOINT3611

Successful reversion of vision loss in dysthyroid optic neuropathy (DON) by adjuvant diuretic therapy

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Thyroid eye disease (TED) is the most frequent extrathyroideal complication of Graves' disease. Severe, sight threatening TED poses a risk of complete vision loss and requires treatment with high dose intravenous methylprednisolone and, in the absence of an immediate response, urgent orbital decompression surgery.

Case Presentation

A 77-year-old female patient was presented at the Thyroid-Eye Clinic in Debrecen in May 2024 due to progressive vision deterioration and eyelid swelling. Upon examination, the visual acuity of the right and left eyes were 0.0 and 0.1 respectively. The diagnosis of TED was confirmed by elevated TRAb level (11.5 U/L), and by MRI and ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA) SPECT/CT imaging. Clinical activity score (CAS) was 5 on the 7 item scale in both sides which, in combination with the high DTPA uptake, indicated active GO. Orbital MRI revealed optic nerve compression in both sides, with more severe apical crowding in the right side. According to our institutional protocol, in addition to standard of care including high-dose intravenous glucocorticoids and orbital irradiation, parenteral diuretic therapy was initiated, while the patient was closely monitored by the multidisciplinary team. During follow up, visual acuity of the left eye gradually improved from the initial 0.1 to 0.9, while vision did not return in the right eye. Proptosis by Hertel-score decreased from the initial 17 and 19 mm to 12 and 13 mm, right and left eye, respectively. This is the second report of a patient in whom the addition of intravenous diuretics to the standard glucocorticoid treatment facilitated the decrease in orbital pressure, and orbital decompression surgery could be avoided.

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JOINT3455

A rare case of hypertriglyceridaemia in infancy secondary to lipoprotein lipase deficiency

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Background

Lipoprotein lipase (LPL) deficiency is a rare genetic disorder of lipid metabolism. The LPL enzyme induces the hydrolysis of triglycerides from lipoproteins to generate free fatty acids. LPL deficiency results in severe hypertriglyceridemia and chylomicronaemia and is associated with recurrent pancreatitis (1).

Case Presentation

We report the case of a previously well male infant, who presented at 6 months of age with fever, vomiting and dehydration. He was admitted for intravenous rehydration. His CRP and urea were unanalysable as the blood sample was lipaemic. Subsequent testing revealed a cholesterol of 9.26mmol/l (3.0-5.0) and triglycerides of 34.6 mmol/l (0.4-2.0). His family history was significant for a paternal history of hypercholesterolaemia and fatty liver disease. Both of his parents are members of the Irish travelling community and are third cousins. Repeat bloods tests two days later showed a downtrending cholesterol (3mmol/l) and triglycerides (4.5mmol/l). His HDL cholesterol was low 0.46mmol/l (1.0-2.0) and he had normal liver function. He clinically improved and was discharged home with planned outpatient follow-up. He was readmitted 2 weeks later with poor feeding and a tender abdomen. His bloods were lipaemic with a raised lipase 181IU/L (13-60), raised triglycerides 22.6mmol/l and raised cholesterol 6.3mmol/l. His amylase and liver function tests were within normal limits. Following this he was diagnosed with acute pancreatitis and suspected familial chylomicronaemia syndrome, most commonly associated with LPL deficiency. This male infant was transitioned to Monogen, a formula low in long-chain triglycerides and solid fat intake was restricted with supplementation of fat soluble vitamins. His target triglyceride level is $<$10mmol/l. His triglycerides (2.6mmol/l) and cholesterol (3.7mmol/l) levels have remained low on this diet and at 2 years old he is growing well along the 75thto 91st centile for height and weight.

Results

Genetic testing revealed that he was Heterozygous for the variant c.897_1018+1939dup p.? in the lipoprotein lipase gene. Parental samples have been sent and are pending.

Discussion

Familial LPL deficiency is a rare disorder. We report the only case in the Republic of Ireland associated with this mutation. This genetic variant has been detected in five individuals in the Amsterdam UMC laboratory, only two of these, like our case, had hypertriglyceridaemia. Restriction of dietary fat is usually sufficient to reduce chylomicronaemia and hypertriglyceridaemia. Drugs that lower lipids levels in the body are ineffective in these cases.

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EP888

JOINT1885

Semaglutide treatment in hypotalamic obesity

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Introduction

Hypothalamic obesity (HO) is a rare and severe form of obesity due to hypothalamic damage, often resulting from neurosurgical interventions. It is characterized by alterations in food control mechanisms and decreased energy expenditure, resulting in refractory weight gain. HO is unresponsive to conventional weight loss strategies like lifestyle modifications, pharmacotherapy, and bariatric surgery. GLP-1 receptor agonists (GLP-1RAs) represent a successful pharmacological paradigm to treat general obesity delaying gastric emptying and improving satiety by multiple mechanisms. We present three cases of HO successfully treated with off-label weekly semaglutide.

Case 1

A 36-year-old female with panhypopituitarism and diabetes insipidus secondary to multiple craniopharyngioma surgeries developed severe HO. She reached a maximum weight of 138.5kg (BMI 44.7), that was managed with sleeve gastrectomy in 2017. Her weight dropped to 119kg but gradually returned to 138kg (June 2024). At this point we started semaglutide (0.25mg to 2.4mg). The result was a 16kg weight loss (-11.6%) reaching 122kg (BMI 39.4) in just six months (date of the last visit).

Case 2

An 18-year-old male with panhypopituitarism and diabetes insipidus post-craniopharyngioma surgery in 2020 developed HO. Before surgery, he weighed 75kg (BMI 28.6) dropped to 54kg due to hyporexia. After surgery, he rapidly gained weight, reaching 97kg (July 2021) and 123kg (BMI 46.9) by June 2022. Semaglutide (0.25mg to 2mg) led to a 26.8% weight loss, reaching 91kg by March 2023, weight maintained to this day. He reported improved appetite control and no significant adverse effects.

Case 3

A 16-year-old female with panhypopituitarism following craniopharyngioma double resection (2019, 2020) developed HO, with weight increasing from 51.2kg (BMI 22.5) to 75kg (BMI 33.0). Due to progressive and refractory weight gain, semaglutide was started in 2023 (0.25mg to 1mg), leading to significant weight reduction (-27.3%), reaching 54.5kg (BMI 24.8) by December 2023. By January 2025, her weight stabilized at 62kg (BMI 28.5). The only side effect was mild nausea.

Discussion

Although GLP-1RAs' efficacy is well-documented in general obesity, their role in HO remains under investigation. These cases align with recent real-world studies, showing significant weight loss with semaglutide, alongside improved appetite regulation. Long-term treatment appeared necessary to maintain weight loss. Semaglutide's effects could extend beyond hypothalamic signalling, involving extrahypothalamic pathways such as the brainstem and vagus nerve. Advances in obesity treatment, including dual and tri-agonists, could represent a promising

approach for achieving significant weight loss and improved appetite control without major side effects even in HO patients.

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EP889

JOINT2727

Clinical follow-up data of patients diagnosed with obesity

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Objective
Childhood obesity is a growing public health concern worldwide, posing long-term risks such as type 2 diabetes, hypertension, dyslipidemia, and cardiovascular diseases. Effective treatment strategies primarily focus on lifestyle modifications(LSM), with pharmacological interventions considered in resistant cases. This study aims to assess the effectiveness of LSM alone vs LSM combined with metformin therapy in children diagnosed with obesity at Ankara Etlik City Hospital. By analyzing anthropometric and biochemical changes over a one-year follow-up, this study seeks to contribute to the development of optimal treatment strategies for pediatric obesity management.
Materials and Methods
This retrospective study included 162 pediatric patients between 5-18 years, diagnosed with exogenous obesity, who were followed at the Pediatric Endocrinology clinic for one year. Patients were categorized into two groups: those receiving only LSM and those receiving LSM + metformin therapy. Collected data included demographic characteristics, body mass index(BMI), fasting blood glucose(FBG), lipid profile and liver function tests. These parameters were measured at baseline and at 3, 6, 9, and 12 months, with statistical analyses conducted to evaluate intra-group and inter-group differences over time.
Results
Among 162 patients, 52.29% were male and 47.71% were female, with a mean age of 12.49 ± 3.19 years. Both groups showed only a limited reduction in BMI, with no significant improvements in waist circumference, systolic blood pressure, or diastolic blood pressure over the study period. However, a significant decrease in BMI SDS was observed in the LSM group between baseline and the third month, but this reduction was not sustained in subsequent follow-ups. Both groups exhibited significant reductions in fasting blood glucose (FBG) and HbA1c levels, with greater reductions in the LSM + metformin group, a difference that was statistically significant. LDL cholesterol levels significantly declined only in the LSM + metformin group, while other lipid parameters showed no significant changes. The proportion of metabolically unhealthy obesity (MUO) increased in the LSM-only group, whereas in the LSM + metformin group, MUO prevalence significantly decreased from 86.67% to 67.86% over 9 months.
Conclusion
This study highlights the critical role of regular follow-ups in obesity treatment, emphasizing that adherence is essential for long-term success. While metformin therapy provided additional metabolic benefits, its effect on BMI reduction was minimal. Personalized treatment approaches, family involvement, and structured patient education programs may enhance adherence and improve long-term outcomes. Ultimately, effective obesity management requires a multifaceted approach that combines medical intervention with continuous behavioral support and patient engagement.

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EP890

JOINT1144

Predicting models in patients with COVID-19 and metabolic syndrome

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Background
Patients with metabolic syndrome have a significantly higher risk of severe COVID-19 complications, such as in-hospital mortality and acute kidney injury (AKI). The combination of chronic low-grade inflammation, endothelial dysfunction, and metabolic dysregulation worsens clinical outcomes, increasing the need for early risk assessment and targeted management strategies.
Aim
This study aimed to evaluate mortality and AKI risk in hospitalized COVID-19 patients by developing predictive models and proposing targeted interventions to improve patient outcomes.
Methods
A retrospective case-control study was conducted on 129 hospitalized COVID-19 patients from 2020 to 2021. Patients were classified into survivors ($n = 88$) and non-survivors ($n = 41$) for mortality risk analysis, while the AKI group included 19 patients with kidney injury and 110 without. Logistic regression models were developed and validated using receiver operating characteristic (ROC) analysis. The mortality model included respiratory insufficiency (OR 22.6; $P < 0.001$), lymphocyte count (OR 0.000144; $P < 0.001$), C-reactive protein (CRP) (OR 1.2; $P < 0.001$), minimal albumin (OR 0.716; $P < 0.001$), eGFR minimum (OR 0.951; $P < 0.001$), and lung involvement on MSCT above 50% (OR 4.96; $P < 0.001$). The AKI model incorporated respiratory insufficiency (OR 12.3; $P < 0.001$), PADUA score ≥ 4 (OR 3.9; $P < 0.01$), CRP > 100 mg/L (OR 2.7; $P = 0.02$), and hyperglycemia (OR 1.8; $P = 0.04$). The models were implemented as web-based calculators and Excel tools to assist clinical decision-making.
Results
Metabolic syndrome significantly influenced outcomes. Patients with respiratory insufficiency had a 22.6-fold increased risk of mortality and a 12.3-fold increased risk of AKI. Hyperglycemia and obesity contributed to AKI risk, reinforcing the need for tight metabolic control, including glucose maintenance below 10 mmol/l, early insulin therapy, and SGLT2 inhibitors for renal protection. CRP levels above 100 mg/L were strongly associated with both mortality (OR 1.2, $P < 0.001$) and AKI (OR 2.7, $P = 0.02$), supporting the benefit of early anti-inflammatory therapy such as IL-6 blockade with tocilizumab and metformin continuation if tolerated. The mortality risk calculator achieved an AUC of 0.976 (95% CI 0.951-1) with 95% sensitivity and 92.6% specificity, while the AKI model had an AUC of 0.848 (95% CI 0.731-0.944), with 89% sensitivity and 80% specificity. Obese patients demonstrated mortality risks comparable to elderly individuals, emphasizing the need for hospitalization criteria based on MetS severity rather than age alone.
Conclusion
Metabolic syndrome is a critical determinant of COVID-19 severity, significantly increasing mortality and AKI risk. The predictive models developed in this study offer high accuracy and practical clinical application, allowing for early identification of high-risk patients.

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EP891

JOINT414

Unraveling factors behind childhood obesity

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Background
Childhood obesity and overweight have become pressing global health concerns, with an ever-growing number of children affected. These conditions carry profound consequences for both physical and mental health, making them a critical issue for society. The underlying causes of this epidemic are multifaceted. This study seeks to explore and uncover the primary drivers of childhood obesity and overweight.
Methods
This cross-sectional case-control study, conducted in 2022, involved children from school health clinics in Tunis, Tunisia. Participants aged 5 to 15 years were included, with exclusions for conditions causing secondary obesity. Overweight was classified as an age-specific BMI $>$ 1 standard deviation (SD) above the WHO growth standards median, while obesity was defined as a BMI $>$ 2 SDs above the median. According to the WHO, early diversification of diet is defined as starting before the age of 6 months. The children were divided into two groups: G1 (overweight or obese) and G2 (normal weight). A 41-item questionnaire was distributed to both children and their parents to assess obesity risk factors.
Results
The study included 216 participants, with 54 classified as overweight or obese (G1) and 162 as having a normal weight (G2). While no significant relationship was found between the occurrence of overweight or obesity and age ($P = 0.07$), it was significantly higher in male children ($P = 0.038$). The presence of allergies in G1 was not significant ($P = 0.200$). The average birth weight was higher in G1 (3400g) compared to G2 (3000g) ($P = 0.01$). The average duration of

breastfeeding was longer in G1 although the difference was not significant ($P = 0.800$). The duration of artificial feeding was not associated with childhood obesity ($P = 0.08$). The practice of having meals at the table was similarly observed in both groups ($P = 0.91$). Obesity was less frequently observed in children who had their meals in a daycare setting ($P = 0.47$). No significant association was found between watching TV during meals and the presence of obesity or overweight in children ($P = 0.92$). G1 consumed more fast food ($P = 0.539$) and G2 engaged in more physical activity outside of school ($P = 0.894$). Additionally, no significant correlation was found between TV time and the presence of obesity or overweight in children ($P = 0.9$).

Conclusion

Tackling the underlying causes of childhood obesity and overweight, with a focus on understanding and addressing key contributing factors, is essential to reversing this escalating epidemic.

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EP892

JOINT2195

Assessment of nutritional status in obese adults undergoing weight loss interventions

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Background

Obesity is associated with a paradoxical nutritional imbalance, where excessive energy intake often coexists with deficiencies in essential micronutrients. This imbalance contributes to an increased risk of various comorbidities and mortality in obese patients. The aim of our study was to assess the nutritional status in a population of obese adult patients.

Methods

This is a descriptive, cross-sectional observational study involving 100 obese adult patients. Body composition was assessed using a SECA MBCA 515 bioelectrical impedance analysis. Dietary data were analyzed using Nutrilog software. The diagnosis of sarcopenic obesity (SO) was established according to the latest consensus proposed by ESPEN and EASO [1].

Results

The mean age was 44.42 ± 13.25 years with a sex ratio (M/F) of 0.11. The mean BMI was 40.07 ± 5.77 kg/m^2, with morbid obesity identified in 48% of the patients. The mean arm muscle circumference was 32.31 ± 3.01 cm and 26.06 ± 3.34 cm, respectively in male and female patients with 82% of patients exhibiting normal values. The mean skeletal muscle mass and appendicular skeletal muscle mass were 26.83 ± 6.63 kg and 16.07 ± 4.06 kg, respectively. A decrease in fat-free mass index was noted in 20% of patients. The average muscle strength was 39.14 ± 11.79 kg in male patients and 23.40 ± 5.79 kg in female patients with muscle strength impairment observed in 21% of the patients. SO was diagnosed in 19% of the study population. Biological nutritional assessment revealed anemia in 18% of patients, hypophosphatemia in 4% of patients, 25(OH) vitamin D insufficiency was found in 37% and deficiency in 62% of patients. The mean albumin level was 41.91 ± 2.31 g/L, with normal albumin and calcium levels in all patients. Dietary survey data analysis revealed a hypercaloric intake in the majority of patients (75%), a high carbohydrate intake in 48%, a high lipid intake in 93%, and a low protein intake in 9% of patients. The majority of the study population had insufficient intake of EPA (95%) and DHA (96%). Micronutrient deficiencies were mainly marked by deficiencies in vitamin A (90%), vitamin D (88%), calcium (55%), vitamin B9 (44%), and vitamin C (32%).

Conclusion

The results of our study highlight the critical need for a comprehensive nutritional assessment in obese patients to detect malnutrition or associated nutritional deficiencies, and to optimize their management.

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EP893

JOINT3338

Phase angle as a predictor of nutritional status in middle-aged obese patients

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Background

In the context of obesity, phase angle (PhA) is considered a potential marker for evaluating health status and monitoring weight loss interventions [1]. Research has shown that higher PhA values are associated with improved nutritional status. The aim of our study was to evaluate the relationship between PhA and nutritional status in obese patients.

Methods

This is a cross-sectional study conducted on 100 obese patients. Body composition was assessed using SECA MBCA 515 bioimpedance and low PhA was defined as $< 6°$. Muscle strength was assessed by measuring grip strength using a digital dynamometer. Dietary survey data were analyzed using Nutrilog software.

Results

The mean age was 44.42 ± 13.25 years, with female predominance (90%). The mean BMI was 40.07 ± 5.77kg/m^2. The mean fat mass and fat mass index values were 52.50 ± 12.39kg and 19.74 ± 4.03kg/m^2, respectively. The average PhA was $5.11 \pm 0.54°$ and the majority of patients had a low PhA (94%). Specifically, 56% of patients had a PhA between 5 and 6, 35% had a PhA between 4 and 5, only one patient had a PhA below 4, and 6% had a PhA above 6. PhA showed a positive correlation with skeletal muscle mass ($r = 0.30$; $P = 0.002$), appendicular muscle mass ($r = 0.25$; $P = 0.012$), fat-free mass ($r = 0.25$; $P = 0.011$), and muscle strength ($r = 0.45$; $P = 0.015$). Additionally, PhA was inversely correlated with fat mass (r=-0.48; $P < 0.0001$). The nutritional biological assessment revealed a positive correlation with albumin levels ($r = 0.26$; $P = 0.009$). The dietary survey indicated a positive correlation between daily protein intake and PhA ($r = 0.27$; $P = 0.006$), with significant correlations for both animal proteins ($P = 0.015$) and plant-based proteins ($P = 0.04$). Furthermore, the analysis of micronutrient intake revealed positive correlations between PhA and the intake of several micronutrients, including vitamin B3 ($r = 0.20$; $P = 0.047$), vitamin B5 ($r = 0.22$; $P = 0.039$), vitamin B6 ($r = 0.23$; $P = 0.021$), vitamin B12 ($r = 0.20$; $P = 0.049$), calcium ($r = 0.25$; $P = 0.012$), phosphorus ($r = 0.26$; $P = 0.01$), and iron ($r = 0.20$; $P = 0.049$).

Conclusion

The findings of our study suggest that PhA may serve as a useful marker for assessing nutritional health and guiding interventions in obesity management.

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EP894

JOINT2885

Does co-administration of lactate to an oral glucose tolerance test lower the glucose response – a randomized controlled cross-over study

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Introduction
Fermented dairy products have been associated with a reduced risk of type 2 diabetes, but the mechanisms remain unclear. Oral lactate has previously been shown to increase insulin levels and delay gastric emptying in healthy individuals. This study investigated whether orally administered lactate affects glucose tolerance, insulin secretion, appetite, and gastric emptying in individuals with pre-diabetes during an oral glucose tolerance test (OGTT).
Methods
In a double-blind, randomized crossover design, 12 individuals with pre-diabetes (HbA1c 39–47 mmol/l) were studied twice after an overnight fast using a 75 g glucose solution: 1) with 25 g sodium lactate (LAC) added, and 2) with a placebo (iso-osmotic sodium chloride, CTR) added. Blood samples and appetite questionnaires were collected, and gastric emptying was assessed using the paracetamol absorption test.
Results
Lactate increased plasma lactate concentrations to 2.6 mmol/l compared to 1.5 mmol/l on the placebo day (incremental area under the curve (iAUC), $P < 0.001$). No differences were observed between interventions for glucose iAUC (-53 (95%CI: -189-86) mmol x min/L, $P = 0.42$). Insulin concentrations were similar, but C-peptide concentrations trended to be higher on the lactate day compared to the placebo day (iAUC: 62 (95% CI: -2–125) nmol x min/L, $P = 0.06$). No differences were observed between interventions regarding paracetamol absorption or appetite sensations.
Conclusion
Oral lactate did not improve glucose tolerance in individuals with pre-diabetes and had no effect on insulin secretion, appetite, or gastric emptying. This indicates that adding lactate into carbohydrate-rich meals is unlikely to reduce postprandial glucose excursions in individuals with pre-diabetes.

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EP895

JOINT2056
Genetic analysis of pediatric severe obesity in a single japanese instituition

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Background
Childhood and adolescent obesity is increasing, and childhood obesity often persists into adulthood. The causes of obesity are complex, involving environmental, social, and genetic factors. Genetic factors are estimated to contribute between 40% and 75%. Both polygenic and monogenic obesity are influenced by genetic predisposition and environmental factors. Monogenic obesity frequently leads to severe obesity from early childhood and, although rare, recent advances have enabled treatment for genetic abnormalities in the leptin-melanocortin pathway. Identifying genetic causes can contribute to treatment, as well as aid in predicting future prognosis and genetic counseling.
Objective
The aim of this study is to identify the genetic causes of pediatric patients with severe obesity in a single institution in Japan and to contribute to future treatment.
Methods
We enrolled 14 pediatric patients with pediatric severe obesity (BMI percentile $\geq$120). Genetic panel testing for monogenic obesity was performed.
Results
The variants identified in unrelated 5 cases included 4 in *GHRL* and 1 in *PCSK1*.
Conclusion
Monogenic obesity is rare, however, in this cohort, variants were identified in 35.7% of children with severe obesity. Identifying genetic variation in obesity-related genes may provide insights into personalized therapeutic approaches, particularly for cases linked to the leptin-melanocortin pathway. A patient with *PCSK1* variant in this cohort may be eligible for treatment with setmelanotide in the future if it becomes covered by insurance in Japan.

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EP896

JOINT1864
Comparison of metabolic disorders and obesity characteristics by household composition among korean adults: analysis of DINKs, married individuals with children, and unmarried individuals

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Objective
In South Korea, increasing stress levels resulting from political turmoil and economic instability have accelerated declines in marriage and childbirth. Assuming that post-COVID restrictions on outdoor activities adversely affected blood glucose and body weight, we evaluated metabolic health among three groups: married individuals with children (MIWC), DINKs (Dual Income, No Kids), and unmarried individuals. To exclude pregnant women, the 40–50-year-old cohort was selected.
Methods
This cross-sectional study analyzed 13,178,582 Korean adults (7,004,014 males and 6,174,568 females) aged 40–59 who participated in the Korean National Health and Nutrition Examination Survey (2020–2021). Prediabetes or diabetes was identified based on HbA1c levels, hospital diagnoses, or prescriptions for insulin or oral anti-diabetic agents. Obesity was classified into Grade 1 ($25 \leq$ BMI < 30 kg/m^2), Grade 2 ($30 \leq$ BMI < 35 kg/m^2), and Grade 3 (BMI ≥ 35 kg/m^2). A complex sampling design and cross-tabulation analyses were used to examine socioeconomic and laboratory factors.
Results
MIWC represented 72.8% of the sample, DINKs 16.1%, and unmarried individuals 11.1%. In the MIWC group, gender distribution was approximately 51% male and 49% female; in DINKs, 47.8% male and 52.2% female; and in the unmarried group, 75.1% male and 24.9% female. DINK females exhibited a significantly higher prevalence of metabolic disorders compared to MIWC and unmarried females. Specifically, prediabetes was present in 53.4% of DINKs vs 41.1% in MIWC and 24.3% in unmarried females ($P < 0.001$); diabetes in 13.1% vs 7.2% vs 3.7% ($P = 0.005$); dyslipidemia in 31.6% vs 24.0% vs 22.3% ($P = 0.030$); and hypertension in 26.8% vs 16.7% vs 12.8% ($P = 0.001$). Anthropometric and laboratory measurements paralleled these findings, with DINK females showing higher BMI, waist circumference, systolic blood pressure, HbA1c, and fasting glucose compared to unmarried females. Unmarried females had the lowest waist circumference and LDL cholesterol levels. Although male groups did not differ significantly in disease prevalence, unmarried males had higher total cholesterol, triglyceride levels. In addition, Grade 3 obesity was lower in DINKs and higher in MICW compared to unmarried individuals (DINKs: Exp(B)=1.934, 95% CI 0.417, 8.917; MIWC: Exp(B)=0.449, 95% CI 0.068, 2.990; $P = 0.017$).
Conclusion
Our findings indicate that DINK females bear a greater metabolic disorder burden and exhibit more adverse anthropometric and laboratory profiles than MIWC and unmarried females, while unmarried males are at increased risk for dyslipidemia and obesity. These results underscore the importance of considering household composition in metabolic risk assessment and tailoring preventive strategies accordingly.

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EP897

JOINT3677
Evaluation of attitudes and beliefs of medical faculty students towards patients with obesity across turkey: a cross-sectional study

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Introduction
Weight bias is common in health care settings, where negative attitudes about overweight patients have been reported by physicians, nurses, and medical students [1-3]. Weight biases present among health professional students are significantly influence students' treatment decisions and beliefs about obesity [4]. In this study, we examined weight bias among medical students in preclinical (1st-2nd-3rd year) and clinical (4th-5th-6th-year) classes, as well as their observations of weight bias among instructors and peers. We then compared the findings across these groups.
Methods
This study utilized a cross-sectional design. A non-randomized sampling was used. Through an online survey, data was conducted among medical students, between January 2023 and July 2023. Three questionnaires previously developed by Puhl *et al*. were utilized [4]. Additionally, the Attitude Towards Obese Persons (ATOP) and Beliefs About Obese Persons (BAOP) scales were used. The scales used in Turkish were previously validated in earlier studies (5).
Results
The survey questions were completed by 1,358 students. Among the participants, 60.4% were female. Of the students who completed the survey, 45.7% ($n = 620$) were from preclinical classes. More than half of the students reported hearing jokes from fellow students about people with obesity. Also clinical students (26.9%) were more than twice as likely as preclinical students (13.2%) to report hearing negative comments or jokes from professors or instructors about people with obesity. ATOP and BAOP scores did not show a statistically significant difference between the preclinical and clinical groups.
Conclusion
These findings suggest that weight stigma is progressively reinforced throughout medical education. Addressing this issue requires systematic educational interventions, including anti-stigma training, curriculum modifications.
Keywords
Weight bias, stigma, medical students
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EP898

JOINT652
The problem of sarcopenia in patients with obesity undergoing liraglutide therapy
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Introduction
Sarcopenia, that is characterized by a decrease in muscle mass and strength, is a significant concern for obese patients undergoing treatment with GLP-1 receptor agonists such as liraglutide. While liraglutide has proven to be effective in weight reduction and metabolic improvement, its impact on body composition, particularly lean mass, requires further investigation.
Objective
To assess the impact of liraglutide therapy on muscle mass parameters in obese patients, identify risk factors for sarcopenia, and develop preventive approaches.
Materials and Methods
An observational study was conducted on patients ($n = 110$) with obesity (BMI ≥ 30 kg/m^2) who received liraglutide for ≥ 12 months. The following methods were used:
• Body composition assessment using bioelectrical impedance analysis (BIA)
• Laboratory tests, including serum albumin levels, insulin-like growth factor-1 (IGF-1), total testosterone, and C-reactive protein (CRP) high sensitivity
• Functional diagnostics, handgrip strength assessment.
• Nutritional analysis to identify protein and micronutrient deficiencies.
Results
• A decrease in lean body mass $>10\%$ from baseline was observed in 18% of patients.
• Main identified risk factors for sarcopenia were:
• Low protein intake (≤ 0.8 g/kg body weight);
• Insufficient physical activity (<150 minutes of moderate exercise per week);
• Age over 50 years;
• Insulin resistance and vitamin D deficiency. • In the group with preventive inclusion of physical exercise activity and increased protein intake (≥ 1.2 g/kg), muscle mass reduction was minimal.
Conclusions
1. Liraglutide therapy in obese patients may be associated with the development of sarcopenia, especially in the absence of adequate nutritional support and physical activity.
2. The incorporation of a high-protein diet, resistance training, and nutritional support is crucial for preventing muscle mass loss.
3. Monitoring body composition using DXA or BIA should be an essential part of the comprehensive management of patients receiving GLP-1 receptor agonists.
Practical Significance: A personalized approach considering the nutritional status and physical activity levels can minimize the risks of sarcopenia and enhance the effectiveness of liraglutide therapy, ensuring not only weight loss but also the preservation of patients' functional health.
Keywords
sarcopenia, liraglutide, obesity, muscle mass loss, GLP-1, nutritional support.
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EP899

JOINT594
What is the minimum dose of vitamin B 12 required to correct the deficiency during long -term metformin use?
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Background
Vitamin B12 deficiency, which inevitably occurs during lifelong metformin therapy in patients with type 2 diabetes, requires timely and adequate vitamin replacement. Moreover, vitamin B12 deficiency mimics the symptoms of diabetic polyneuropathy. However, there are no clear recommendations on the dose and duration of vitamin B12 intake in such patients.
Materials and methods
We conducted a comparative study among 28 patients with type 2 diabetes mellitus with clinical manifestations of diabetic neuropathy. The average age of patients was 60.7 ± 10.0 years, the average duration of diabetes was 7.2 ± 5.4 years, the duration of Metformin intake was 5.5 ± 4.7 years, the average dose of Metformin was 1466.7 ± 544.9 mg, vitamin B12 deficiency was detected in 100% of patients (vitamin B12 level below 197 pg/ml, average level 103.0 ± 19.3 pg/ml). All patients were prescribed vitamin B12. 20 patients took the vitamin in a total course dose below 150 g (up to 1500 mg per day for 3 months). 8 patients received a total course dose above 150 g (maximum 190 g). NSS and NDSS, as well as vitamin B12 levels, were assessed 6 months after the treatment.
Results
Of the symptoms of the NSS and NDSS, a significant difference after treatment was obtained only for the criterion of "burning sensation" (1.46 ± 0.19 points vs 0.88 ± 0.13 points, $P = 0.022$) between the groups; a significantly greater reduction in paresthesia was noted in the group of patients who received a higher course dose of vitamin B12 (87.5% vs 15.0%, $P = 0.005$). No significant difference was found between the groups in terms of other symptoms of peripheral neuropathy.
Conclusion
To reduce neuropathic symptoms associated with vitamin B12 deficiency in patients with type 2 diabetes mellitus receiving long-term metformin, vitamin B12 supplementation at a dose of at least 150 g per course of therapy is necessary.
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EP900

JOINT3326

Hypoglycaemia in non-diabetic children – data from a paediatric endocrine center

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Objectives
Hypoglycaemia is a metabolic disorder which may be related to a heterogeneous group of disease in non-diabetic patients. The aim of the current study was to establish the frequency of hypoglycaemia observed in non-diabetic children aged 0-18 years, admitted to a tertiary paediatric endocrine center outside the intensive care or emergency unit and to analyze the associated clinical symptoms, underlying causes and treatment strategies.
Methods
We analyzed data for 2 years (2023-2024) from the clinical database of a tertiary paediatric endocrine center to identify all non-diabetic hypoglycaemic patients with blood glucose levels (BGLs) $\leq$3.9 mmol/l. The clinical notes of all enrolled patients were reviewed for demographic data, risk factors for hypoglycaemia, associated clinical symptoms including neurological symptoms and/or seizures during the hypoglycaemic episodes, registered developmental delay, relevant recorded morbidities or newly diagnosed conditions. We performed auxology and standard clinical examination of all participants. Blood glucose levels (BGLs), insulin and other hormones were measured and treatment with intravenous glucose administration and/or specific medications was evaluated. All patients with diabetes or prescribed diabetic medications were excluded from the analysis.
Results
We found 100 hypoglycaemic episodes among 3012 hospital admissions (3.32%). The mean age of the identified patients was 7.6 $\pm$ 5.3 years (ranged 0-17.9 years), 56.0% were boys. The mean BGL during the registered episodes was 3.49 $\pm$ 0.42 mmol/l (1.39-3.90 mmol/l) and the most commonly associated clinical symptoms were fatigue (15%), hypotony (14%), abdominal pain (6%), generalized seizures (3%) and vomiting (3%). Hypoglycaemia due to a newly diagnosed condition was recorded for 34.0% of children, while the other 66 patients had previously recorded disease which could explain the symptoms of low BGLs. Less than 1/3 of the participants had neurodevelopmental delay and 40% of these neurologically affected patients had been diagnosed with epilepsy or cerebral palsy. The most common morbidities associated with the development of hypoglycaemia were: fasting/starvation due to illness/anorexia (31.4%), genetic syndromes (16.2%), hypopituitarism with combined pituitary hormone or isolated growth hormone deficiency (14.1%) and congenital hyperinsulinism (12.1%). One-fifth of children needed glucose infusions to treat hypoglycaemia with none requiring glucagon administration. Almost 60% of the identified participants were commenced or continued on a specific therapy including rhGH (42.4%), long-acting somatostatin analog (13.6%), therapeutic diet/milk (11.9%) and diazoxide (8.5%).
Conclusion
Non-diabetic hypoglycaemia in paediatric patients is of a significant clinical importance and should be diagnosed and treated promptly.

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EP901

JOINT2782

Ketogenic diet fails to counteract western diet-induced damage in skeletal muscle

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The Western diet (WD), marked by elevated levels of sugars and saturated fats, significantly contributes to obesity and its related health complications. Its influence on insulin resistance and inflammation has been associated with several conditions, such as type 2 diabetes mellitus (T2DM), metabolic-associated steatotic liver disease (MASLD), and metabolic syndromes (MetS). Ketogenic diets (KDs) represent dietary approaches characterized by minimal carbohydrate intake, high fat, and adequate protein levels. Energy is sourced from ketone bodies (KBs), derived from fat oxidation and protein metabolism. Given the increasing evidence supporting the effectiveness of KDs in reducing inflammation, oxidative stress, and improving mitochondrial function, we hypothesized that KDs could hold promise in addressing obesity-related conditions, including sarcobesity. To test this hypothesis, we subjected mice to a Western diet (WD) for 16 weeks, followed by a transition to an *ad libitum* KD, or continued adherence to WD for an additional 4 or 8 weeks. Our finding demonstrated that within the muscle, a period in KD after WD is sufficient to influence the expression of genes associated with atrophy, autophagy and mitophagy. By exploring mechanisms implicated in muscle loss, we observed that KD leads to a significant reduction in branched-chain amino acids (BCAAs), whose levels are notably elevated in mice fed with WD, that apart their association with inflammation, could be used as primary source to produce ketone bodies in the liver. Finally, to further investigate the impact of fatty acids and KBs on muscle cells, we mimic *in vitro* WD and KD examining various doses of palmitate (PA) and butyrate (BU) on C2C12-derived myotubes. PA significantly reduced myotube diameter in a dose-dependent manner but also induces ROS production, and mitochondrial membrane depolarization. In contrast, low doses of BU protected against PA-induced atrophy in myotubes, while high doses appear to be ineffective or may even contribute to atrophy. Our findings suggest that KD could be detrimental on the muscle. Studies on tailored doses of ketone bodies are needed to understand if they really improve muscle performances.

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EP902

JOINT3651

Body mass index and nutrition-related risk among older people

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Introduction
BMI is a widely used indicator for assessing body weight in relation to height, commonly applied to evaluate the nutritional status of populations. The GNRI, a nutrition-related risk index, is specifically designed to identify elderly patients at risk of malnutrition-related complications and mortality.
Aim
This study aimed to compare BMI distributions based on the classification ranges defined by the World Health Organization (WHO) and the Committee on Diet and Health (CDH) and to evaluate their correlation with nutrition-related risk assessed through the Geriatric Nutritional Risk Index (GNRI) in older adults.
Material and Methods
The study included 185 patients hospitalized in a geriatric ward. Weight and height measurements were taken in the morning on the first day of admission for all participants using standardized methods and a validated scale. The Geriatric Nutritional Risk Index (GNRI) was calculated to evaluate nutrition-related risk. The study group was divided into two groups: no nutrition-related risk group (GNRI $>$ 98.0) and nutrition-related risk group (GNRI $\leq$ 98.0).
Results
137 individuals (74.1%) were categorized as having no nutrition-related risk. In the No Nutrition-Related Risk Group, the median BMI was 28.5 kg/m^2 (26.4-31.9 kg/m^2). In contrast, the Nutrition-Related Risk Group had a significantly ($P <$ 0.0001) lower median BMI of 22.8 kg/m^2 (20.7-24 kg/m^2). According to the CDH BMI criteria, 75.0% of participants classified as underweight were identified as having a nutrition-related risk, compared to only 6.3% under the WHO BMI criteria. Among patients with normal weight based on WHO criteria, 81.3% were classified as being at nutrition-related risk, whereas this applied to only 22.9% of those with normal weight under CDH criteria. In the excess body weight group, 12.5% diagnosed using WHO BMI criteria were found to be at nutrition-related risk, compared to just 2.1% when using CDH criteria.
Conclusion
This study highlights notable differences between the BMI classification systems recommended by the World Health Organization (WHO) and the Committee on Diet and Health (CDH) when applied to the elderly population. Consequently, it is crucial to create specific guidelines for this age group, especially for interpreting BMI, to ensure more precise health assessments and enhance care for older adults.

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EP903

JOINT1046

Postnatal overfeeding induces gut microbiota disturbances and impairs liver lipid metabolism through GPR43/FIAF/LPL pathway in the rat model of PCOS

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Background & Aims
In women with polycystic ovary syndrome (PCOS), the incidence of metabolic dysfunction-associated steatotic liver disease (MASLD) is high. The development of PCOS-associated MASLD is accelerated by prepubertal obesity, but the extent to which early-life weight gain exacerbates the metabolic features of PCOS is still under debate. To clarify this, we analyzed the impact of overfeeding in early postnatal period on metabolic features, gut microbiota profile and hepatic lipid metabolism in the rat model of PCOS.
Methods
Wistar rats were divided into 4 groups, in which treatment with 5α-dihydrotestosterone (5α-DHT) was used to mimic hyperandrogenemia, whereas litter size reduction was used to induce early postnatal overfeeding and prepubertal obesity. The composition of the intestinal bacterial community was determined by 16S rDNA sequencing. The level of short chain fatty acids was measured by mass spectrometry. Hematoxylin-eosin-stained sections, Western blots, and qRT-PCR were used to analyze hepatic lipid metabolism.
Results
Only postnatally overfed DHT-treated rats developed prominent obesity and glucose intolerance, which was not associated with altered Firmicutes/Bacteroidetes ratio. Postnatal overfeeding shifted the microbiota composition towards obesity-associated genera, while hyperandrogenemia led to reduced β-diversity and an increased abundance of androgen-regulated genera. Interaction of treatments reduced both α- and β-diversity and decreased the abundance of beneficial butyrate-producing genera Roseburia, Oscillospira, and Ruminococcus and plasma level of butyric acid. This shift in microbiota composition was accompanied by decreased expression of G-protein coupled receptor 43 (GPR43), fasting-induced adipocyte factor (FIAF), and increased expression of lipoprotein lipase (LPL). In accordance with the altered GPR43/FIAF/LPL pathway, increased expression of lipogenic transcription factors was observed in SL-DHT animals, but this did not result in hepatic lipid deposition.
Conclusions
Early postnatal overfeeding is important factor in the development of PCOS-related metabolic features, and it is associated with reduced α- and β-diversity and decreased abundance of beneficial butyrate-producing genera in the PCOS animal model. These changes impaired hepatic lipid metabolism via the GPR43/FIAF/LPL pathway. Although these changes are not associated with hepatic steatosis, they may pave the way for fatty liver disease in the long term.

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EP904

JOINT3223

Maternal obesity and gestational weight gain: impact on childhood obesity - a 12 year retrospective cohort study

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Introduction
Maternal obesity and excessive gestational weight gain are associated with childhood obesity through various mechanisms. According to international recommendations, weight gain during pregnancy for obese women (BMI ≥ 30 kg/m^2) should not exceed 9 kg. This study aims to analyze the weight evolution of children born to obese mothers and the association between preconception BMI and gestational weight gain with childhood BMI, based on WHO percentile curves.
Methods
This retrospective cohort study included 48 children whose mothers, diagnosed with obesity, were monitored during pregnancy in endocrinology/obstetrics consultations between 2010 and 2011. Maternal anthropometric data were collected during successive consultations, and children's growth data were recorded from birth to 12 years of age.
Results
The 48 women considered, had an average preconception BMI of 37.2 ($\pm$2.24) kg/m^2. A total of 64.6% of the women experienced excessive weight gain (>9 kg) during pregnancy. 12 of these women had been diagnosed with gestational diabetes, but were controlled with dietary measures. The average birth weight was 3,426.4 g ($\pm$388.325), with 22.9% ($n = 11$) classified as large for gestational age (weight above the 90th percentile). At 12 months, 37.5% of the children ($n = 19$) were above the 85th percentile for weight, and 20.8% ($n = 10$) were above the 97th percentile. By 3 years of age, 37.5% ($n = 19$) were classified as obese, and 27.1% ($n = 13$) were overweight. The prevalence of overweight and obesity continued to rise throughout childhood, reaching 66.7% at 6 years ($n = 33$), 83.3% at 10 years ($n = 40$), and 77.2% at 12 years ($n = 37$). Regarding gestational weight gain, a positive correlation was found between excessive maternal weight gain and higher degrees of childhood obesity ($P < 0.05$). Additionally, while higher pre-pregnancy obesity classes showed a trend toward increased childhood obesity, this association did not reach statistical significance ($P > 0.05$).
Conclusion
The prevalence of overweight and obesity in children born to obese mothers tends to increase throughout childhood. Excessive gestational weight gain is positively associated with a higher degree of childhood obesity. This association should encourage health professionals and caregivers the prompt adoption of healthy lifestyle measures in childhood and the implementation of early monitoring and surveillance of this children.

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EP905

JOINT778

Long-Term and short-term studies on metformin in obese children and adolescents: evaluating metabolic and cardiovascular outcomes

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Background
Obesity in children and adolescents is a global health challenge linked to metabolic and cardiovascular complications. Metformin, a drug primarily used for type 2 diabetes, has gained attention for its potential benefits in managing obesity-related cardiometabolic risks. This review synthesizes evidence on metformin's short- and long-term effects, including its impact on BMI, insulin sensitivity, inflammation, lipid profiles, and cardiovascular risk markers.
Methods
This review included 19 studies, comprising 10 randomized controlled trials (RCTs), observational studies, systematic reviews, and meta-analyses. Collectively, these studies evaluated 777 patients, with a focus on obese children and adolescents. Key outcomes examined included BMI changes, insulin sensitivity, inflammatory markers, lipid profiles, and vascular health indicators.
Results
This review analyzed 19 studies, including 10 randomized controlled trials (RCTs) with 657 patients, alongside observational studies, systematic reviews, and meta-analyses, encompassing a total of 777 patients. High-quality RCTs, such as those by Yanovski *et al*. (2011), Pastor-Villaescusa *et al*. (2017), and Masarwa *et al*. (2021), demonstrated metformin's consistent efficacy in reducing BMI and improving insulin sensitivity. Short-term studies showed significant improvements, including a **3-5% reduction in BMI**, **15-20% improvement in insulin sensitivity** (**HOMA-IR scores**), and **10-15% reduction in pro-inflammatory markers**. Lipid profile improvements included **5-8% enhancement in HDL and triglyceride ratios**, and cardiovascular markers, such as carotid intimal-medial thickness (CIMT) and blood pressure, showed modest improvements of approximately **5%**. Long-term impacts, while less pronounced, included sustained effects such as a **2-3% reduction in BMI**, **5-10% improvement in insulin sensitivity**, and **2-5% improvements in lipid profiles**. Notably, cardiovascular markers, such as CIMT and blood pressure, demonstrated **~10% sustained improvement** over time. While inflammation data were limited in long-term studies, a sustained effect of **~5% reduction in pro-inflammatory markers** was suggested. The findings highlight metformin's robust short-term effects in managing obesity-related metabolic risks, with evidence supporting its use in insulin-resistant and prepubertal populations. Across all studies, metformin demonstrated a favorable safety profile with no serious adverse events, making it a cost-effective and valuable intervention for pediatric obesity.
Conclusions
Metformin is a safe and effective intervention for short-term management of pediatric obesity and its cardiometabolic risks. Evidence supports its ability to modestly reduce

BMI, improve insulin sensitivity, and address key cardiovascular risk factors. Long-term benefits, particularly in preventing cardiovascular events, require further research. Its consistent safety and cost-effectiveness make metformin a valuable therapeutic option for managing obesity-related metabolic challenges in children and adolescents.

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EP906

JOINT1498

A rare case of hutchinson-gilford progeria syndrome

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Introduction
Progeria or Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare autosomal dominant syndrome that accelerates ageing and affects internal systems, affecting 1 in 18 million people. It is linked to lamin mutations and high hyaluronic acid levels, leading to cardiovascular and sclerodermatous changes. Bioinactive growth hormone and excess hyaluronic acid may stunt growth. While some endocrine aspects are studied, metabolism remains unclear. We report a case highlighting its complications.
Case report
A 12-year-old girl presented with progressively coarse skin, growth failure, and global alopecia. She appeared normal until age 2, when her parents first noticed these changes. Her prenatal history was unremarkable, intelligence average (IQ = 82), and no family history of similar conditions. She exhibited a senile appearance with prominent eyes, visible scalp veins, alopecia, peaked nose, and a small chin. Her hands were short and clawed, with thickened knuckle skin and racquet nails. The trunk and lower limbs showed mottled pigmentation and sclerodermatous changes. Ophthalmologic findings included bilateral lagophthalmos and left eye pterygium. ENT examination was normal. Chest auscultation revealed murmurs. Medical records show the patient weighs 11.5 kg ($<5^{th}$ percentile) and is 105,5 cm tall ($<5^{th}$ percentile), with BMI of 10.3 (Z score <-3). Progeria was diagnosed based on history and clinical findings. She has impaired glucose tolerance (fasting glucose 73 mg/dl, random glucose 136 mg/dl, HbA1c 5.7%), normal renal function, elevated liver enzymes (AST 183 U/l,ALT 187 U/L), and dyslipidemia (TC 207 mg/dl, TG 348 mg/dl, HDL 23 mg/dl, LDL 143 mg/dl). Electrolytes are normal, but blood gas analysis shows a mildly increased pH (7.46). Echocardiogram reveals severe mitral regurgitation, mild atrial regurgitation, severe mitral and atrial stenosis. Nutritional therapy includes 1500 kcal/day, primarily from carbohydrates 1356 kcal/day (90%), with protein 21.2 g/day (1.2 g/kg/day) and fat 900–1210 kcal/day (90–110 kcal/kg/day). Formula milk is administered in 5 servings/220 ml (6 scoops + 180 ml water), alongside three meals containing one egg per meal. Feeding occurs at scheduled intervals. She is prescribed lisinopril (1 mg/day) with echocardiograms every three months. For lagophthalmos, she receives Hyalub (3×1 ODS) and Cenfresh (6×1 ODS), with a two-week follow-up. scheduled. She continues outpatient follow-up in pediatric endocrinology, nutrition, cardiology, and ophthalmology.
Conclusion
Analysing indicators and identifying targetable deficits may offer potential for addressing cardiovascular disease and other significant phenotypes in HGPS, which have thus far been inadequately associated with these recognised endocrine changes.

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EP907

JOINT1550

Obesity-related metabolic dysfunction-associated steatotic liver disease: clinical characteristics and risk factors in children

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Background
Non-alcoholic fatty liver disease (NAFLD), now recognized as metabolic dysfunction-associated steatotic liver disease (MAFLD), is closely linked to obesity and its metabolic complications in adolescents. This cross-sectional study aims to assess the prevalence and characteristics of MAFLD in obese children and adolescents, examining the relationship between obesity, metabolic dysfunction, and liver health.
Methods
We retrospectively reviewed the clinical data of 487 obese children aged 7-14 years from the Department of Endocrine Genetic Metabolism at Jiangxi Children's Hospital between January 2020 and December 2022. Inclusion criteria were based on age and waist height ratio (WHtR), while exclusion criteria ruled out genetic obesity, diabetes mellitus, and other secondary causes of obesity. Clinical data included medical history, physical examination, laboratory tests, and insulin resistance assessment. The diagnosis of MAFLD was based on the presence of hepatic steatosis and at least one cardiometabolic risk criterion.
Results
The study cohort consisted of 479 children, with a median age of 10.6 years. The prevalence of MAFLD increased with age, affecting 45% of 7-9-year-olds and 68% of 10-14-year-olds. Males were more commonly affected, with a male-to-female ratio of 3.3:1. The MAFLD group had a higher average BMI, height, and weight compared to the non-MAFLD group. Liver enzymes were significantly elevated in the MAFLD group, indicating liver damage. The MAFLD group also exhibited higher insulin resistance, dyslipidemia, and lower kidney function. The binary logistic regression model identified alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) as significant positive predictors of MAFLD, while high-density lipoprotein (HDL) was a significant negative predictor.
Conclusion
MAFLD is prevalent in obese adolescents and is associated with insulin resistance, dyslipidemia, and liver dysfunction. The study highlights the importance of early identification and management of MAFLD in obese pediatric populations to prevent long-term complications.
Keywords
Metabolic dysfunction-associated steatotic liver disease (MAFLD), Adolescents, Obesity, Insulin resistance, Dyslipidemia, Liver enzymes.

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EP908

JOINT3395

Impact of family physicians' practice location and sector on the management of childhood obesity

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Introduction
Childhood obesity (CO) is a major public health concern, requiring early and appropriate management. As frontline healthcare providers, family physicians (FPs) play a crucial role in the screening, diagnosis, and treatment of this condition. However, their practices may be influenced by their location and sector of practice, potentially leading to disparities in care quality. This study aims to analyze these differences to identify potential areas for improvement and ensure more standardized and effective management of CO.
Methods
We conducted a cross-sectional descriptive and analytical study using a questionnaire assessing the practices of frontline FPs working in southern Tunisia. Data collection was carried out online or through direct interviews during 2024. Three main areas were evaluated: screening, diagnosis, and treatment of CO. Statistical analysis was performed using SPSS software.
Results
A total of 100 FPs participated, with a mean age of 48±11 years and a female predominance (64%). The majority worked in the public sector (59%) and urban areas (52%). Urban practice was associated with better screening practices (anthropometric assessment performed in 83% of cases, $P = 0.017$) and more thorough etiological investigations ($P = 0.03$). Dietary and pharmacological management approaches were similar, except for more personalized dietary counseling in urban settings ($P = 0.03$). Private-sector practice was significantly associated with better anthropometric and dietary assessment of CO patients ($P < 0.001$ and $P = 0.03$) and a more individualized management approach ($P = 0.04$). However, etiological assessment, evaluation of complications, and referral rates to specialist centers were comparable across groups.
Conclusion
Disparities in medical practice quality appear to be widening, particularly in favor of urban areas and the private sector. Our findings highlight more effective CO management in these settings, likely due to better financial resources, easier access to scientific training, greater proximity to specialized centers, and a reduced workload. Strengthening healthcare structures in rural areas and the public sector is essential to ensure equitable CO management.

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EP909

JOINT1712

Recurrent non-islet cell tumor hypoglycemia secondary to a large pulmonary tumor

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Introduction
Hypoglycemia in non-diabetic patients is a rare metabolic emergency that can arise from various causes. Non-islet cell tumor hypoglycemia is a rare but serious cause of hypoglycemia characterized by a paraneoplastic syndrome caused by a tumor that secretes high molecular weight IGF-2. Herein, we report a case of severe recurrent non-islet cell tumor hypoglycemia secondary to a large pulmonary tumor.
Observation
A 91-year-old woman was referred to the Endocrinology Department for hypoglycemia. Her medical history included hypertension, dyslipidemia, thyroid nodule, and a non-functional adrenal adenoma. In 2016, she presented with severe hypoglycemia and dyspnea. Laboratory investigations revealed low insulin and C-peptide levels during the hypoglycemic event. Although IGF1 and IGF2 levels were normal, the IGF2/IGF1 ratio was greater than 10, raising suspicion of a non-islet cell tumor secreting IGF2. A chest computed tomography (CT) scan showed a large right lung tumor measuring 150 mm. A PET-scan showed no significant hypermetabolism in the lung mass. The patient was treated with corticosteroids and subsequently underwent a right pulmonary lobectomy. Anatomopathological examination revealed a benign fibrous tumor. Long-term follow-up was marked by the resolution of hypoglycemia. Eight years later, the patient presented with recurrent severe hypoglycemia, asthenia, and weight loss. On physical examination, she had a good state of hydration, a body weight of 44.2 kg, a height of 147 cm, a body mass index of 20.45 kg/m^2, a blood pressure of 128/59 mmHg, a heart rate of 69 beats per minute. Biological investigations showed a fasting blood glucose level of 0.36 g/l,an insulin level of less than 7 nmol/l,a C-peptide level of 0.03 nmol/l,an IGF1 level of 27 ng/ml, an IGF2 level of 485 ng/ml, and an IGF2/IGF1 ratio of 18. The CT scan revealed a necrotic and heterogeneous lung parenchymal mass measuring 111 mm in the right upper lobe. The patient was treated with corticosteroids and referred to the department of Thoracic Surgery.
Discussion
In this case, hypoglycemia was secondary to a fibrous pulmonary tumor that secretes IGF-2. IGF-2 interacts with insulin receptors, leading to the inhibition of gluconeogenesis, glycogenolysis, and ketogenesis. Generally, the diagnosis of non-islet cell tumor hypoglycemia is suggested when low insulin and C-peptide levels are observed during a hypoglycemic episode, along with a high IGF2/IGF1 ratio (>3). Most fibrous tumors are benign. However, late tumor recurrence with aggressive features has been reported, even in the absence of prior evidence of malignancy.

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EP910

JOINT3566

Obesity associated with macroprolactinoma: a case report

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Introduction
Prolactin-secreting pituitary adenomas (prolactinoma) are generally benign tumors that appear following the monoclonal expansion of a cell line of the anterior pituitary (lactotropic cells). Prolactin (Prl) is a polypeptide hormone, primarily regulated by the inhibitory control of dopamine. This suppression has been proposed as a potential mechanism responsible for weight gain and metabolic abnormalities in patients. Elevated prolactin may promote obesity by disrupting lipid metabolism and influencing appetite. Prolactinomas are classified based on their size into microprolactinomas (<10 mm largest diameter) and macroprolactinomas (≥ 10 mm largest diameter) Treatment is primarily based on dopamine agonists, particularly cabergoline.
Case report
A 9 years old patient, diagnosed with a giant macroprolactinoma, who underwent surgery and experienced post-operative corticotropic deficiency, for which replacement therapy was started at a dose of 10 mg per day. The patient's progression was marked by significant weight gain associated with polyphagia, and the case is being closely monitored as part of our clinical care protocol On clinical examination, the patient had a BMI of 30 kg/m^2 and a waist circumference of 95 cm, which were indicative of pathological obesity.
Discussion
Hyperprolactinemia induces a functional blockade of dopaminergic tone, which may contribute to hyperphagia and weight gain observed in patients, thus playing a role in the pathogenesis of obesity, as demonstrated in our patient Expression of the Prl receptor (Prl-R) gene has previously been described in adipose tissue, and an increase in this expression during lactation has been documented in rats and humans. the study by Haji H *et al* demonstrated in Prl-R-deficient mice a reduction in abdominal fat and leptin concentration compared to controls. Studies have clearly shown that dopamine agonists significantly improve glucose homeostasis and insulin resistance and reduce body weight.
Conclusion
Hyperprolactinemia (HPL) promotes metabolic alterations, and controlling excess prolactin with dopamine agonists is essential for inducing weight loss and improving the metabolic profile.

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EP911

JOINT2613

Assessing body composition in individuals with obesity

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Introduction
Obesity is now recognized as a global pandemic and a major public health problem. It is characterized by an excessive accumulation of body fat, often associated with metabolic, cardiovascular and musculoskeletal complications. Beyond body mass index (BMI), which remains the most commonly used diagnostic tool, detailed assessment of body composition provides a better understanding of the imbalances between the various body compartments (fat, muscle, bone, water).
Methods
This is a retrospective observational study of patients living with obesity and hospitalized in the Endocrinology and Metabolic Diseases Department of the Mohammed VI University Hospital of Marrakesh. Data were collected from medical records. Body composition assessment was performed by an analyzer using bioelectrical impedanceanalysis (BIA) technology.
Results
Over two years, 70 patients were hospitalized in our center and benefited from impedance analysis. Their mean age was 46.9 ± 14.6 years (14-77 years), with a large female predominance (94.3%). The mean BMI in our series was 45.3 ± 6.9 kg/m^2 (30.1-60.5 Kg/m^2). Moderate obesity (BMI:30.0-34.9 kg/m^2) was found in 21.4% of patients; severe obesity (BMI:35.0-39.9 kg/m^2) in 37.1%; and morbid obesity (BMI>40 kg/m^2) was noted in 41.4%. The mean percentage of body fat mass was 43.8 ± 6.9%. The mean percentages of lean body mass and body muscle mass were 57 ± 6.3% and 52.5 ± 7% respectively. Mean percentages of total body water and bone mass were 41.1 ± 3.8% and 2.8 ± 0.3% respectively. The mean basal metabolic rate was 1711 ± 230.2 Kcal/day and the mean metabolic age was 61 ± 12.8 years. Forty-nine patients had a glucose metabolism disorder, i.e. 70% of our series, of whom 47.1% had diabetes and 22.9% pre-diabetes. Fourteen patients had a lipid metabolism disorder, i.e. 20% of our series, of whom 15.7% had pure hypercholesterolemia, 2.9% hypertriglyceridemia and 1.4% mixed dyslipidemia. Twenty two patients had arterial hypertension, i.e. 31.4% of our series. In our study, linear regression analysis showed that the increase in fat mass percentage correlated statistically significantly with the increase in BMI (P value < 0.001) and the decrease in muscle mass (P value $= 0.003$). On the other hand, we found no significant association between BMI or fat mass percentage with the presence of a glucolipid metabolic disorder or hypertension.
Conclusion
Individuals with obesity do not have the same body composition profile nor the same metabolic risks. A detailed analysis of these parameters would not only help to characterize obesity (type and metabolic status), but also to guide therapeutic strategies for tailored and personalized management.

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EP912

JOINT3301

Baseline morphofunctional characteristics of a sample of transgender individuals from a specialized transgender healthcare unit

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Introduction and Objective
Individuals experiencing gender incongruence with their sex assigned at birth may seek gender-affirming hormone therapy (GAHT) to align their gender

expression with their identity. GAHT is known to induce changes in body composition, and advanced morphofunctional assessment techniques could serve as valuable tools for evaluating these modifications. This study aims to analyze the morphofunctional characteristics of this population before the initiation of hormone therapy.
Materials and Methods
A descriptive observational study was conducted on individuals aged ≥18 years seeking GAHT at the Transgender Healthcare Unit (UAPT) of Hospital Universitario Clínico San Cecilio in Granada. Anthropometric variables, muscle strength (handgrip dynamometry), bioelectrical impedance parameters—including metabolically active cellular mass (BCM) and total body water (TBW)—as well as muscle and abdominal ultrasound measurements, were assessed.
Results
The study included 14 trans men and 7 trans women, with mean ages of 20.93 ± 3.36 and 22.85 ± 4.8 years, respectively, and BMI values of 23.83 ± 7.38 kg/m^2 vs. 22.51 ± 6.11 kg/m^2. Handgrip strength was higher in trans women (26.57 ± 10.32 kg vs. 25.02 ± 7.13 kg; $P > 0.05$). This finding aligns with a trend toward statistical significance in Y-axis thickness (1.79 ± 0.53 cm vs. 1.41 ± 0.32 cm, $P = 0.054$) and rectus femoris muscle area (5.87 ± 2.53 cm^2 vs. 3.84 ± 1.03 cm^2), as measured by ultrasound. These parameters correlate with total muscle mass and strength. Statistically significant differences were observed in BCM (x?;: 32.87 ± 7.34 kg/m^2 vs. 24.03 ± 4.28 kg/m^2, $P < 0.05$) and TBW (x?;: 43.62 ± 9.9 kg/m^2 vs. 31.38 ± 4.03 kg/m^2, $P < 0.05$), both higher in trans women. No significant differences were found in abdominal ultrasound measurements of superficial adipose tissue (0.57 ± 0.39 cm vs. 0.52 ± 0.45 cm, $P = 0.807$) or preperitoneal adipose tissue (0.57 ± 0.48 cm vs. 0.55 ± 0.29 cm, $P = 0.868$).
Conclusions
This study provides novel insights into the application of advanced morphofunctional assessment techniques for characterizing body composition and muscle strength changes in transgender individuals before GAHT. These findings establish a baseline for future research into the physiological effects of hormone therapy.

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EP913

JOINT1849

Efficacy on nutritional status of a nutritional support programme with specific supplementation for people with type 2 diabetes at risk of malnutrition in routine clinical practice

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Introduction and Objectives
Diabetes mellitus is a highly prevalent disease that can affect nutritional status as well as muscle mass and function. This study aims to evaluate the differences in nutritional status, through the analysis of morphofunctional and biochemical assessment parameters, of patients with diabetes and disease-related malnutrition (DRE) or high nutritional risk, at baseline and three months after starting specific nutritional supplementation.
Material and Methods
We selected 15 patients assessed in nutritional prehabilitation consultations, with a diagnosis of type 2 diabetes mellitus and digestive cancer, with DRE or high nutritional risk according to GLIM criteria, undergoing active cancer treatment (chemotherapy, surgery). A nutritional support programme was initiated with dietary recommendations, exercise and specific supplementation for people with type 2 diabetes. Anthropometric, biochemical and morphofunctional assessments were performed using vector bioimpedance (BIVA), at the first consultation and at a 3-month review. Differences were analysed using SSPS v.24 statistical software. A value of $P < 0.05$ was considered statistically significant and trend to statistical significance $P < 0.1$.
Results
Mean age 71.3 years (SDS 8.2). Three months after the start of nutritional supplementation, all morphofunctional parameters measured by BIVA (FFM, FFMI, FM, FMI, SM, SMI, SMI, ASM, ASMI) had increased. In particular, weight (69 vs 71kg; $P < 0.1$), BMI (26.5 vs 27.2 kg/m^2; $P < 0.1$) and appendicular skeletal mass (ASM) (17.8 vs 18.3 kg; $P < 0.1$) had improved with a trend towards statistical significance. At the biochemical level, three months after the start of nutritional supplementation (baseline vs 3 months): - Vitamin D (12.5 vs 29.7; $P < 0.05$), folic acid (13.8 vs 15.8; $P < 0.1$), albumin (4.19 vs 4.27; NS), pre-albumin (21.9 vs 24.1; NS) and glomerular filtration rate (78 vs 86; $P < 0.1$) levels improved. - Inflammation markers leucocytes (7909 vs 6298; $P < 0.1$), PCR (44.3 vs 22.7; NS) and ferritin (299 vs 206, $P < 0.036$), decreased. Glycaemic control showed no variation (HbA1c 6.5% vs 6.36%; NS), (haemoglobin 12.1 vs 12.4; NS).
Conclusions
The implementation of a nutritional support programme in routine medical practice, based on dietary recommendations, exercise and specific supplementation for people with type 2 diabetes with malnutrition or high nutritional risk, improved morphofunctional and biochemical outcomes in our cohort of oncology patients.

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EP914

JOINT1889

Evaluation of muscle strength in patients with type 1 diabetes mellitus: comparison of reference values

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Introduction
Handgrip strength is a widely used method to evaluate muscle strength, a key component of physical fitness. It is well known that low muscle strength is significantly related to early mortality from all causes and cardiovascular disease, as well as greater physical disability.
Objective
To compare the results obtained in the dynamometry of patients with type 1 diabetes mellitus followed at the Hospital de la Axarquía with different reference values (international, European Sarcopenia Consensus values, and reference values from a local study conducted in Pizarra).
Material and Methods
Descriptive cross-sectional observational study in patients with type 1 diabetes mellitus followed at the Hospital de la Axarquía. Clinical data were obtained from the medical history, and dynamometry data were obtained with a Jamar dynamometer. Statistical analysis was performed with the Jamovi program. A low dynamometry value was defined as.
Results
The sample of our study consisted of 134 patients, of which 78 were men (58.2%) and 56 were women (41.8%). The mean age was 45.6 years (±14.4) and the mean BMI was 26.4 kg/m^2 (±5.01). The mean duration of diabetes was 22.4 years (± 13.7 years) and the mean HbA1c was 7.75% (±1.06%). The mean dynamometry value was 41.2 kg (±10.4) in men and 24.9 kg (±6.29) in women. In men, a low dynamometry value was obtained in 7 (9%; with respect to international values), 13 (16.9%; with respect to values from the Pizarra study) or 4 (5.1%; with respect to dynapenia values of the European Consensus). In women, a low dynamometry value was obtained in 8 (14.3%; with respect to international values), 5 (9.1%; with respect to values from the Pizarra study) or 4 (7.1%; with respect to dynapenia values of the European Consensus).
Conclusions
The comparison between the three reference points (international, European Consensus, and Pizarra) reveals differences in the proportion of patients identified with low muscle strength. These differences highlight the importance of choosing appropriate reference points according to the population context.

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EP915

JOINT3993

Comparative analysis of morphofunctional parameters and clinical results in post-critical patients based on the definition of obesity used: body mass index or fat mass percentage

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Introduction
Obesity in adults is commonly classified using BMI, with values over 30 kg/m^2 indicating obesity. However, BMI has limitations as it doesn't accurately reflect body composition. Fat mass percentage (FM%) is a more precise measure, and can be estimated using various methods, with bioimpedancemetry being a cost-effective, accurate, and radiation-free option. According to the Consensus Statement of the European Society for Clinical Nutrition and Metabolism and the

European Association for the Study of Obesity (ESPEN and EASO) on sarcopenic obesity, obesity is defined as a body fat percentage (FM%) higher than 30% in men and 40% in women, respectively.

Objective

To compare body composition, complications, and need for aggressive therapies in post-critical obese patients, using two definitions of obesity: FM% > 30% in men and > 40% in women, vs BMI > 30 kg/m^2.

Methods

Prospective observational study including 75 patients admitted to the ICU for severe COVID-19 pneumonia. Demographic, clinical and analytical data were collected during admission, medical history and a complete morphofunctional assessment was performed 14 days after hospital discharge with bioimpedancemetry and phase angle, nutritional ultrasound, dynamometry and functional tests. Two mutually exclusive groups were established, one defined as BMI > 30kg/m^2 and the other as high FM% with normal BMI, and the differences between them were analyzed.

Results

Table 1.

	All	BM>30 kg/m^2	FM>30% (men); FM>40% (women)	p (t student)
	n = 75	*n* = 36	*n* = 10	
BMI(kg/m^2)	31.1±6.4	36.1±5.6	26.4±5.6	<0.001*
Diabetes mellitus(%)	34(45.3)	4(11.1)	6(60.0)	0.003*
PhA(º)	4.9±1.12	5.2±1.2	4.3±1.2	0.029*
SPhA	-1.00(1.1)	-0.45±0.9	-2.2±0.9	<0.001*
FFM(kg)	59.9±11.7	65.7±11.7	50.8±11.7	<0.001*
FM(kg)	30.6±13.4	39.2±13.9	27.7±13.9	0.010*
ASMM(kg)	23.6±5.9	26.8±6.0	19.3±6.0	<0.001*
SMI(cm^2/m^2)	9.84±1.8	10.8±1.7	7.9±1.7	<0.001*
BCM(kg)	28.9±8.6	32.4±9.0	22.1±4.0	0.001*
RF-CSA(cm^2)	4.21±1.5	4.8±1.7	3.0±1.7	0.011*
RF-Y axis(cm)	1.32±0.4	1.6±0.4	1.0±0.4	<0.001*
CRP	26.9±50.1	17.5±29.7	81.8±21.7	0.046*
HGS(kg)	24.7±12-3	28.6±13.1	18.8±13.1	0.021*
Hospital stay(-days)	48.3±44.9	41.6±20.1	73.8±71.0	0.037*

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Conclusions

Patients with BMI < 30 kg/m^2 but with FM > 30% (men) or > 40% (women) have differences in body composition parameters (BIA, nutritional ultrasound and dynamometry) and are also associated with a higher prevalence of diabetes mellitus and worse clinical outcomes during admission (longer hospital stay). In terms of body composition, there are differences especially in parameters related to muscle mass, but also in proinflammatory parameters.

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EP916

JOINT413

Dietary factors contributing to overweight and obesity in children

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Background

Childhood obesity and overweight have become pressing global health concerns, affecting an increasing number of children. These conditions have significant consequences on both physical and mental well-being, making them a crucial issue for society. Among the many contributing factors, dietary habits play a key role. This study aims to explore the dietary influences that contribute to childhood obesity and overweight.

Methods

This was a case-control cross-sectional study, conducted over a year in 2022, included 216 children from school health clinics in Tunis, Tunisia, excluding those with secondary obesity causes. Overweight was defined as a BMI > 1 standard deviation (SD) above the median of WHO growth standards, and obesity as a BMI > 2 SDs above the median. The children were categorized into groups: G1 of 54 overweight or obese children and G2 of 162 of normal weight children. We administred a questionnaire to children and their parents to evaluate the dietary risk factors of obesity.

Results

No significant association was found between overweight or obesity and age (P = 0.07), but the prevalence was significantly higher in male children (P = 0.038). No significant correlation was found between biscuit consumption and overweight or obesity in children (P = 0.72). However, the consumption of Cerelac was statistically associated with the presence of overweight or obesity (P = 0.03). A diet rich in fruits was more common in G1 (P = 0.62). G1 children had a lower fiber intake though this difference was not statistically significant (P = 0.72). Carbohydrate-rich diets were significantly more frequent among overweight or obese children (P = 0.038). A diet high in plant-derived fats was more common in the overweight or obese group (P = 0.439). No significant link was found between consumption of animal-derived fats and the presence of obesity or overweight (P = 0.254). Similarly, no significant relationship was found between night-time dessert consumption and obesity or overweight (P = 0.126). Snacking was reported by 17.7% of children in the normal weight group compared to 16.7% in the overweight/obese group, with no significant correlation with obesity or overweight (P = 0.867). The independent factors associated with the presence of overweight or obesity in children were male gender, Cerelac consumption, and a high intake of carbohydrates.

Conclusion

Tackling the underlying causes of childhood obesity and overweight, with a focus on understanding and addressing key contributing factors, is essential to reversing this escalating epidemic.

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EP917

JOINT2499

Nutrient intake in overweight patients with polycystic ovary syndrome (PCOS): a comparative study

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Background

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting women of reproductive age. The role of macronutrient and micronutrient intake, both in the development of PCOS and in managing its symptoms, is an area of increasing interest [1]. The aim of our study was to evaluate nutrient intake in overweight patients with PCOS.

Methods

This was a descriptive, cross-sectional and retrospective case-control study involving 61 overweight women, divided into two groups: 31 women with PCOS in the case group and 30 women without PCOS in the control group. The two groups were matched for age and body mass index. Data, including interview-based information and biological parameters were collected from the patients' medical records. Body composition was assessed using TANITA bioimpedance analysis. Dietary intake data were analyzed using Nutrisoft software.

Results

The mean age of the patients with PCOS and without PCOS was 31±8.6 years and 34.23±10.6 years, respectively. The mean age at diagnosis of PCOS was 23.4±7.3 years, with extremes ranging from 14 to 39 years. The majority of patients with PCOS had phenotype A (81%), while 19% had phenotype C. The dietary survey revealed a significantly higher intake of saturated fatty acids in patients with PCOS (10.2±2.8% TEI vs 8.2±2.9% TEI; P = 0.01) and a significantly higher insufficiency in omega-6 fatty acid intake (58% vs 5%; P = 0.001) compared to the control group. The average energy intake, as well as protein, carbohydrate, and lipid intakes, were similar between the two groups. Regarding micronutrients, PCOS patients had significantly lower intakes of vitamin C (91±69 mg/d vs 142±85 mg/d; P = 0.01) and vitamin B1 (1,03±0,32 mg/d vs 1,24±0,42 mg/d; P = 0.04). Micronutrient intake deficiencies were also more frequent in PCOS patients compared to the control group, primarily affecting vitamin C (64% vs 23%; P = 0.002), vitamin B1 (29% vs 0%; P = 0.03), vitamin B3 (29% vs 0%; P = 0.003), vitamin B6 (35% vs 12%; P = 0.03), calcium (87% vs 65%; P = 0.05), and iron (48% vs 19%; P = 0.02).

Conclusion

This study underscores the prevalence of micronutrient Intake deficiencies in overweight women with PCOS. These findings suggest the need for targeted dietary interventions to address nutrient intake imbalances in this population, contributing to a better management of PCOS symptoms and long-term health outcomes.

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EP918

JOINT1938

A study of interleukin-6 gene polymorphism in egyptian obese subjects

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Background
Polymorphisms in the interleukin 6 gene have been studied in various chronic diseases. Increased levels of IL-6 in humans have been associated with visceral fat accumulation and obesity. The aim of the work was to study interleukin-6 gene polymorphism in Egyptian obese patients.
Methods
A total of 100 people were enrolled in the study. They were divided into: Group A included 35 subjects of simple obesity, group B included 35 patients of complicated obesity, and group C included 30 healthy subjects. Laboratory investigations were done for all subjects including IL-6 gene snp rs1800796 polymorphism, uric acid, amylase, lipase, C reactive protein and lipid profile. Abdominal ultrasound was done to assess presence of fatty liver and/or fatty pancreas.
Results
Regarding the IL-6 gene polymorphism, there was no significant difference statistically between both obese groups, however there was a significant difference statistically among obese groups and healthy people. Employing an univariate regression; waist circumference, hip circumference, waist/hip ratio, uric acid, cholesterol, C reactive protein, GG allele of IL-6 ($P < 0.001$), fatty liver and/or fatty pancreas ($P < 0.001$) were statistically significant parameters for obesity. In multivariate analytical regression; uric acid ($P = 0.041$), and the GG allele of IL-6 polymorphism ($P = 0.028$) were statistically significant risk factors for obesity.
Conclusions
IL-6 gene snp rs1800796 polymorphism was associated with increased risk of obesity. The obesity traits were linked to G allele. Future studies on gene-environment interactions should be carried out to clarify the connection between the IL-6 polymorphism and obesity.

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EP919

JOINT3938

Mitraa: transforming patient care through ai-driven chatbot technology

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Aim
This study aims to evaluate the impact of Mitraa, an AI-based chatbot, on patient care, focusing on its effectiveness in improving medication adherence, patient engagement, and reducing unnecessary clinic visits.
Materials and Methods
A pilot study was conducted involving 100 patients with chronic conditions. Participants were provided access to Mitraa, which offers personalized, real-time health support, including medical information, medication reminders, lifestyle recommendations, and continuous monitoring. The chatbot leverages natural language processing (NLP) and machine learning algorithms to adapt to individual patient needs. Data on medication adherence, patient engagement, satisfaction, and clinic visit frequency were collected over a three-month period.
Results
Mitraa demonstrated significant improvements in patient outcomes. Medication adherence rates increased by 35%, and patient engagement rose by 40% during the study period. Additionally, 85% of users reported higher satisfaction with their healthcare experience, attributing this to Mitraa's accessibility and personalized guidance. The chatbot also contributed to a 25% reduction in unnecessary clinic visits, alleviating the burden on healthcare facilities.
Conclusion
Mitraa effectively enhances patient care by providing continuous, personalized support and bridging the gap between healthcare providers and patients. The observed improvements in adherence, engagement, and patient satisfaction highlight the chatbot's potential to foster proactive, patient-centered care. By reducing the strain on clinical resources and empowering patients to manage their health, Mitraa contributes to more efficient healthcare delivery and healthier communities.

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EP920

JOINT2272

Phenotyping in obesity: to whom are we prescribing semaglutide and tirzepatide?

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Introduction
Obesity is a chronic and relapsing disease that has been increasing in prevalence in the last decades. Two new drugs become available in Italy in the past year (July for Semaglutide and October for Tirzepatide) for the treatment of this condition. In clinical trials these molecules showed very promising efficacy and tolerability. However, clinical practice differs from clinical trials, especially when it comes to drugs that have a significant cost for the patient. As of today, no data exist on efficacy, tolerability and adherence of Semaglutide and Tirzepatide treatment in the Italian population.
Aim
To phenotype the patients that are willing to start a treatment with anti-obesity medication (Semaglutide or Tirzepatide) and follow them up to evaluate efficacy, tolerability and adherence to these molecules.
Methods
We collected anamnesis (including occupation), anthropometric measures, presence of obesity related comorbidities in 73 patients that were willing to start pharmacological treatment for obesity in our Division of Endocrinology and Diabetes Prevention and Care. Afterwards the pharmacological treatment was initiated and at 3-month follow-up was performed registering patients' weight, Hunger and Satiety VAS scales.
Results
The mean age was 51.9 years, the mean BMI 37.90 kg/m^2 and most patients were female 79% ($n = 57$). The most prevalent comorbidity was dyslipidemia, followed by hypertension and prediabetes. These were present respectively in 49,44 and 30% of the population. Even if these complications were common, end organ damage defined as myocardial infarction, ischemic stroke and kidney failure were rare (3% of the population). Analyzing the net income of our patients we were able to divide the population into three categories: below 20.000 €/year, between 20.000-30.000 € /year and more than 30.000 €/year. Almost all the population fit in the first and second categories (respectively 24 and 32 patients). When we performed the analysis, 37 patients reached the 3-month follow-up, with 3 patients that suspended the drug or did not start the therapy at all. Of the 34 patients still in therapy the average weight loss was 5%. Furthermore, the "hunger" scale was significantly reduced after 3 months, and the "satiety" scale was significantly increased.
Conclusions
Our study shows that, in a classic endocrinological setting, the population that starts Semaglutide or Tirzepatide is young, with multiple comorbidities but very few end organ damage. Furthermore, these drugs seem safe and effective also in clinical practice and used not only by the people of the highest socioeconomical status but by a heterogeneous population.

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EP921

JOINT3764

Real-life experience of semaglutide in the treatment of idiopathic intracranial hypertension: a case series

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Introduction
Idiopathic Intracranial Hypertension (IIH) is a disorder characterized by elevated intracranial pressure (ICP) without an identifiable cause. It primarily affects obese women and is associated with headaches, papilledema, and visual disturbances. The prevalence of IIH has increased with rising obesity rates. Weight loss remains the mainstay of treatment, and glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as semaglutide, have demonstrated effectiveness in metabolic control and weight reduction.
Methods
We retrospectively analyzed four female patients diagnosed with IIH who received semaglutide as part of their weight loss and ICP management strategy. The BMI before and after therapy, headache frequency and severity, and changes in visual symptoms were documented.
Results
Patient 1: A 38-year-old woman with BMI 28.7 kg/m^2 at baseline presented with perimenstrual migraines, visual impairment, and tinnitus. After 12 months of semaglutide therapy, her BMI reduced to 27.3 kg/m^2. Her monthly headache days (MHD) decreased from 30 to 15, with no visual disturbances. Patient 2: A 39-year-old woman with a history of gastric bypass and obesity (BMI 33.79 kg/m^2) experienced persistent holocephalic pressure and severe headaches. Following 10 months of semaglutide therapy, her BMI dropped to 27.3 kg/m^2, and MHD decreased from 30 to 15, with an intensity reduction from 7/10 to 3–5/10. Patient 3: A 48-year-old woman with hypertension and diabetes was diagnosed with IIH and papilledema (BMI 42 kg/m^2). After 6 months of semaglutide therapy, she lost 6 kg (BMI 40.4 kg/m^2), and her headaches completely resolved. Acetazolamide therapy was maintained, and no recurrence of symptoms was noted. Patient 4: A 34-year-old woman diagnosed with IIH in 2021 had a BMI of 35.3 kg/m^2 (96 kg, 165 cm). Due to polycystic ovary syndrome (PCOS), she was started on semaglutide, spironolactone, and metformin in 2022. After 18 months of therapy, she experienced significant weight loss (BMI reduced to 28.3 kg/m^2, 77 kg) and complete resolution of headaches. At her January 2025 follow-up, she was pregnant with recurrent headaches.
Discussion
All four patients demonstrated significant weight loss, headache reduction, and improved quality of life with semaglutide therapy. BMI reductions ranged from 6.3% to 25%. No patients exhibited progressive visual impairment, and two achieved complete headache resolution. GLP-1RAs promote weight loss and may directly affect intracranial pressure via GLP-1 receptors in the choroid plexus, supporting their potential role in IIH management.
Conclusion
Semaglutide represents a promising adjunct therapy for IIH, weight reduction and headache relief, potentially impacting intracranial pressure regulation.

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EP922

JOINT770

The role of continuous glucose monitoring systems (CGMS) in early detection of glycemic abnormalities in obese populations with normal or impaired fasting glucose

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Background
Continuous Glucose Monitoring Systems (CGMS) have revolutionized the detection of glycemic abnormalities, providing detailed insights into glucose variability, especially in obese populations.
Objective
To evaluate the benefits of CGMS in diagnosing and managing glycemic abnormalities in obese individuals with normal fasting glucose, impaired fasting glucose, or other glucose tolerance abnormalities.
Methods
A comprehensive review of CGMS studies from 2000 to 2024 was conducted. Studies were selected based on their focus on obese children, adolescents, and adults with normal or impaired fasting glucose. Outcomes assessed include the detection of postprandial hyperglycemia, glycemic variability, nocturnal hypoglycemia, and overall glucose profiles.
Results
CGMS has demonstrated significant benefits across multiple studies:.
1. **Enhanced Detection:** CGMS uncovered glycemic abnormalities in up to 30% of individuals with normal fasting glucose, including postprandial hyperglycemia and nocturnal-hypoglycemia, which were undetectable by fasting glucose or HbA1c measurements.
2. **Identification of Glycemic Variability:** Approximately 45% of subjects with normal glucose tolerance exhibited significant glycemic variability, highlighting the utility of CGMS in identifying transient glucose excursions.

Table 1.

Population	Key Findings	Benefits of CGMS
Obese children and adolescents	CGMS detected impaired glucose tolerance in 25% and early glycemic abnormalities in 30% of cases.	Early detection and intervention in pediatric populations.
Obese adults with normal fasting glucose	30% showed postprandial hyperglycemia and significant glucose fluctuations not detected by fasting glucose.	Identification of postprandial and nocturnal hyperglycemia.
Obese first-degree relatives of T2DM patients	40% exhibited abnormal glycemic profiles despite normal fasting glucose levels.	Improved risk stratification for genetically predisposed individuals.

3. **Early Diagnosis in High-Risk Groups:** CGMS identified abnormal glycemic profiles in 40% of obese first-degree relatives of type 2 diabetes patients, emphasizing its role in early detection among genetically predisposed individuals.
4. **Improved Screening in Pediatric Populations:** Among obese children and adolescents, CGMS detected impaired glucose tolerance in 25% of cases and revealed early glycemic abnormalities in up to 30%, many of which were missed by OGTT or fasting glucose tests.
5. **Dynamic Glycemic Profiles:** CGMS captured real-time data on glucose fluctuations, allowing clinicians to detect postprandial glucose excursions exceeding 7.8 mmol/lin 30% of participants with normal glucose tolerance.
Conclusion
CGMS offers unparalleled benefits in detecting and managing glycemic abnormalities in obese individuals, even those with normal FPG. By capturing real-time glucose fluctuations and variability, CGMS allows early identification of at-risk individuals and supports timely, personalized interventions. Future research should explore cost-effectiveness and long-term outcomes of CGMS-guided interventions in these populations.

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EP923

JOINT782

Comprehensive insights into metformin: evidence from *in vitro*, cellular, animal, and human studies on obesity and cardiovascular health"

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Background
Metformin, widely used for managing type 2 diabetes, has demonstrated significant benefits in addressing obesity-related metabolic and cardiovascular complications. Its anti-inflammatory, antioxidative, and lipid-modulating properties position it as a potential therapeutic option for reducing obesity-related cardiometabolic risks.
Methods
This review synthesizes evidence from cellular, animal, and clinical studies to explore metformin's mechanisms of action and its impact on metabolic and cardiovascular parameters in obese patients and adolescents. Key outcomes assessed include inflammation, oxidative stress, lipid profiles, vascular health, and cardioprotective effects.
Results
1. Mechanisms of Action: Metformin activates AMP-activated protein kinase (AMPK), reducing inflammation and oxidative stress in adipose tissue, the liver, and blood vessels. It decreases pro-inflammatory cytokines (e.g., TNF-α, IL-6) and inhibits the NF-κB pathway, shifting macrophages from pro-inflammatory (M1) to anti-inflammatory (m^2) states, thereby lowering metabolic and cardiovascular risks.
2. *in vitro* Findings: Metformin reduces inflammation, oxidative stress, and vascular smooth muscle cell proliferation in atheroma cells. It stabilizes plaques by enhancing autophagy and reducing reactive oxygen species (ROS) production, lowering the risk of rupture and atherosclerosis-related complications.
3. Animal Studies: In obese animal models, metformin improved endothelial function, reduced systemic inflammation, enhanced lipid metabolism, and demonstrated cardioprotective effects, including reduced myocardial ischemia and infarct size.
4. Clinical Impacts:.
• Blood Pressure and CIMT: Metformin lowered systolic and diastolic blood pressure by improving insulin sensitivity and reducing oxidative stress, also decreasing carotid intimal-medial thickness (CIMT), a marker of early atherosclerosis.
• Atherogenic Index: Metformin improved the ratio of triglycerides to HDL cholesterol, contributing to lower cardiovascular risk in obese patients and adolescents.

Table 1. Summary of Metformin's Effects.

***in vitro* Studies**	**Reduced inflammation and oxidative stress in atheroma cells; inhibited VSMC proliferation; stabilized plaques.**
Cellular Studies	Activated AMPK; reduced pro-inflammatory cytokines (TNF-α, IL-6); shifted macrophages from M1 to M2 state.
Animal Studies	Improved endothelial function; reduced systemic inflammation, oxidative stress, and myocardial ischemia; enhanced lipid profiles.
Human Studies	Lowered BMI (3-5%), blood pressure (~5%), CIMT (~10%); improved insulin sensitivity (~15-20%) and lipid profiles (~5-8%).

• Lipid and Metabolic Effects: It lowered triglycerides, LDL cholesterol, and BMI while increasing HDL cholesterol and insulin sensitivity, with modest improvements in BMI and metabolic markers in adolescents.

Conclusions

Through its multifaceted mechanisms of action, metformin demonstrates significant potential in managing obesity-related metabolic and cardiovascular risks. By improving insulin sensitivity, lipid metabolism, and vascular health while reducing inflammation and oxidative stress, metformin offers a promising strategy for mitigating obesity's cardiometabolic complications.

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EP924

JOINT623

Metformin in pediatric obesity: a safe and effective solution for lasting metabolic benefits

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Background

Pediatric obesity is a growing global health challenge, often linked to metabolic complications such as insulin resistance and type 2 diabetes mellitus (T2DM). Metformin, a staple medication for T2DM, has gained attention for its potential to manage obesity and associated cardiometabolic risks in children and adolescents. This review evaluates evidence from 19 studies to assess metformin's efficacy and safety in addressing pediatric obesity.

Methods

A total of 19 studies were analyzed, including 10 randomized controlled trials (RCTs) involving 657 patients, an open-label extension study with 42 participants, a retrospective review of 78 patients, a meta-analysis, and 5 narrative reviews. The studies spanned from 2008 to 2024 and investigated metformin's effects on body mass index (BMI), insulin sensitivity, and other metabolic parameters in obese pediatric populations.

Results

Efficacy:.

• Across the studies, metformin consistently reduced BMI and improved insulin sensitivity, with high-quality RCTs demonstrating significant metabolic benefits, particularly in prepubertal children and those with insulin resistance.

• Studies such as Yanovski *et al*. (2011) and Pastor-Villaescusa *et al*. (2017) reported modest yet meaningful BMI reductions and enhancements of metabolic markers.

• Observational studies and systematic reviews supported these findings, reinforcing metformin's role as a cost-effective intervention for managing pediatric obesity.

• The strongest benefits were observed in patients with baseline insulin resistance, with consistent improvements in BMI Z-scores, fasting insulin levels, and body composition.

Safety:.

• Metformin displayed a favorable safety profile across all studies. Common side effects, including mild gastrointestinal discomfort, were transient and self-limiting.

• No serious adverse events were reported, even in long-term studies.

Patient Impact:.

• The review included 777 patients across various study types. Prepubertal children and those with insulin resistance exhibited the most substantial benefits, with improved BMI Z-scores, metabolic health, and body composition.

Conclusions

Metformin is a safe and effective intervention for managing pediatric obesity, particularly for patients with insulin resistance. Robust evidence supports its use in reducing BMI and improving metabolic health, with the greatest benefits observed in prepubertal children. While its long-term effects require further investigation, current evidence positions metformin as a valuable tool for combating pediatric obesity and its cardiometabolic complications.

Keywords

Metformin, Pediatric Obesity, Insulin Resistance, Cardiometabolic Health, Randomized Controlled Trials.

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EP925

JOINT2030

Body composition and metabolic complications in a single-centre pilot cohort of adults with X-linked hypophosphatemia

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Background and Aim

X-linked hypophosphatemia (XLH) is a rare genetic disease hallmarked by hypophosphatemia and osteomalacia with skeletal deformities, caused by autonomous over-secretion of fibroblast growth factor 23 (FGF-23). Obesity is frequently observed in XLH patients, attributed to impaired mobility, but possibly also linked to direct negative metabolic effects of elevated circulating FGF23. Recent research suggests that adult XLH patients are obese with excess fat mass, but without increased prevalence of metabolic dysfunction.

Patients and Methods

Cross-sectional pilot study included a single-centre cohort of 9 adult XLH patients (8 female), 39.9 $\pm$ 4.6 years old, treated with active vitamin D and phosphate supplements. Anthropometric analysis included weight, height, BMI, and waist to hip circumference ratio (WHR). Body composition was analysed by DXA whole body scan - WBS (Hologic Discovery QDR). Total body fat percent (Fat%) was expressed as fraction of the upper limit of normal age and gender values (Fat%ULN). Fasting blood glucose and fasting insulin were used to calculate HOMA IR. Abdominal ultrasound was performed to screen for liver steatosis.

Results

The average body weight (60.33 $\pm$ 3.45kg) and BMI (29.24 $\pm$ 1.81 kg/m^2) were on the borderline of overweight and obesity. Four patients were obese (44.4%) and 3 (33.3%) overweight. Average WHR (0.79 $\pm$ 0.02) was below the threshold for abdominal obesity. DXA WBS revealed the average total body fat mass (FM) of 23.46 $\pm$ 2.6kg, the average total lean body mass (LMB) of 35.75 $\pm$ 1.93kg. The average Fat% of 37.73 $\pm$ 2.68%, translated to 0.89 $\pm$0.05 Fat%ULN. The average baseline insulin level was 16.30 $\pm$ 2.82 mIU/land the average HOMA IR was 3.56 $\pm$ 0.56. Seven patients (77.8%) had HOMA IR $>$ 2.4. Abdominal ultrasound revealed liver steatosis in 1 of 9 patients (11.1%).

Conclusions

Adult XLH patients in our pilot single centre cohort were predominantly overweight and obese but with average total body fat percent not exceeding upper limit of age and sex normal values and with average waist to hip ratio indicating low metabolic risk. Prevalence of liver steatosis upon sonography was low. However, average insulin resistance was higher than previously reported, possibly linked to factors beyond the obesity or body composition. Further research may elucidate correlation of insulin resistance with circulating FGF23 and the effects of anti-FGF23 antibody treatment on metabolic status in XLH patients.

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EP926

JOINT208

Long-term efficacy and safety of semaglutide in the treatment of syndromic obesity in prader willi syndrome - case series

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Introduction

Prader-Willi syndrome (PWS) is the most prevalent cause of syndromic obesity. Obesity development in PWS is driven by dysfunction in neural pathways

involved in satiety and reward, dysregulation in hormones regulating satiety and food intake, altered body composition and reduced energy expenditure, as well as the presence of various hormone deficiencies. As hyperphagia, satiety dysfunction and consequent food-seeking behaviors are intrinsic to PWS, obesity management can be challenging.
Case series
We present a long-term follow-up of treatment with GLP-1 receptor agonist (GLP-1 RA) semaglutide, up to 37 months, in three patients with PWS without diabetes. Patient 1 was a 28-year-old female with PWS, resulting from uniparental disomy, with BMI 50.8 kg/m^2. She was initially treated with a calorie-restricted diet and subsequently admitted to a specialized "group home center", however, her weight continued to progressively increase. Patient 2 was a 39-year-old female with PWS resulting from mosaic maternal uniparental disomy who underwent metabolic surgery at the age of 29, first a gastric band surgery and subsequently Roux-en-Y gastric bypass. Despite an initial weight loss of approximately 50 kg, she ultimately regained most of her lost weight. Before treatment with semaglutide she reached her maximum weight of 174 kg, her BMI was 82.8 kg/m^2. Patient 23 was a 25-year-old male with PWS, resulting from a uniparental maternal disomy, with body mass index (BMI) 41.3 kg/m^2. Semaglutide treatment at dosages from 0.5 mg to 2 mg weekly demonstrated variable efficacy, from preventing further weight gain in Patient 1 to achieving weight loss of up to 14.4% and 11% relative to baseline, in Patient 2 and Patient 3, respectively. All patients reported appetite suppression and increased satiety during semaglutide treatment, which was diminished during short term treatment interruptions due to drug unavailability. Mild transient gastrointestinal-related side effects were reported during dose escalation in the case of Patient 2, who had a history of metabolic surgery. No serious adverse events were reported during the observation period.
Conclusions
Following a personalized approach, GLP-1 RAs may have the potential to address the hallmark challenges of hyperphagia, obesity and metabolic dysfunction associated with syndromic obesity in PWS, with mild to moderate efficacy. Future research should prioritize long-term randomized placebo-controlled trials with larger sample sizes to provide stronger evidence on the long-term efficacy and safety of incretin therapies for obesity treatment in PWS as well as explore the potential synergistic effects combined with other therapeutic interventions.
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EP927

JOINT4030
Abdominal adipose tissue ultrasound characterization in patients living with excess body fat: experience from our Centre
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Background
Ultrasound measurement of abdominal fat is precise, reliable, inexpensive, with measurement accuracy equivalent to computed tomography and magnetic resonance imaging. Despite this, widespread adoption has been hampered by lack of experience or reliable standard operating procedures. The aim of our study was to characterize the adipose tissue layers of the abdominal wall trough ultrasound assessment in patients with excess body fat assess and compare our results with recent proposed guidelines.
Methods
Retrospective transversal study including 103 adult patients who underwent abdominal wall ultrasound at Clínica Universidad de Navarra. Exclusion criteria included BMI <25 kg/m^2 with normal fat mass. Fat mass was quantified by Clínica Universidad de Navarra-Body Adiposity Estimator. Ultrasound scan was performed in the midpoint between the xiphoid appendix and the navel (1-3 cm above the umbilicus) along the alba line.
Results
Mean age was 46.6 $\pm$ 14.4 years and 74.8% were women. Fifty patients (49%) were under GLP-1 analogs. After excluding patient treated with GLP-1 analogs, subcutaneous adipose tissue was moderately (P <0.05) correlated to preperitoneal adipose tissue (r = 0.41), BMI (r = 0.32), tryglicerides level (r = 0.32), the presence of diabetes (r = 0.34), dyslipidemia (r = 0.38) and with the number of metabolic abnormalities (r = 0.29). Preperitoneal adipose tissue was correlated with BMI (r = 0.36), ALT levels (r = 0.28) and triglycerides (r = 0.39). Patients with a subcutaneous adipose tissue measurement >1.8 cm (median value), had a strong correlation with the number of metabolic abnormalities (r = 0.49; P <0.01).
Conclusions
Ultrasound abdominal wall characterization must include the measurement of subcutaneous adipose tissue maximum thickness as it is associated with the presence of metabolic abnormalities, and therefore, metabolic risk. Identification and management/decrease of excess adiposity must be a target in a primary and secondary prevention setting. Abdominal wall ultrasound assessment may be an adequate target in the daily clinical setting.
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EP928

JOINT1363
Treatment of hypercholesterolemia with natural compounds
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Obesity is considered as an exceeding life style disorder notably in developing countries and it is prevailing at a frightful speed in new world countries as a result of fast food intake, causing raised blood cholesterol levels, which in turn can damage many systems in the body. The present study investigates the hypolipidemic effects of sulphated polysaccharide obtained from a green algae in induced obese subjects (High Fat Diet). The results showed an increase in body weight of HFD subjects by 27.09% as compared to control normal group. Moreover, serum lipase activity underwent an increase which led to an increase in the levels of total cholesterol (T-Ch), triglycerides (TG) and low density lipoprotein cholesterol (LDL-Ch) in serum associeted with a decrease in the level of high density lipoprotein cholesterol (HDL-Ch) in untreated HFD rats. This diet has disrupted the antioxidant status by decreasing the activities of antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX)) and subsequently an increase in thiobarbituric acid reactive substances (TBARS) level in liver and kidney of obese rats. All these disturbances are significantly corrected by extract administration with no fatty deposits in the liver and a protective effect against renal histological alteration. This confirms the important role of this polysaccharide in the fight against oxidative stress and the prevention of hyperlipidemia.
Keywords
Antioxidant, Hypercholéstérolémiae, Liver-kidney functions.
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EP929

JOINT908
F18 Choline PET-CT scan as single imaging modality for primary hyperparathyroidism
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Case History
We present a case of a 63-year-old female who presented with nausea, weight loss, constipation, low mood, and headache. The patient's past medical history included rheumatoid arthritis and a fractured ankle. There was no previous history of renal stones, nor a family history of hypercalcemia. Blood tests revealed normal renal function, low vitamin D levels (which were sufficiently replenished), elevated adjusted calcium at 2.96 mmol/l(reference range: 2.2–2.6 mmol/L), elevated parathyroid hormone at 26.4 pmol/l(reference range: 1.6–6.9 pmol/L), and a urinary calcium-creatinine ratio of 2.23. Primary hyperparathyroidism (PHPT) was diagnosed. Although Sestamibi scan and parathyroid ultrasound did not identify parathyroid adenoma. However, A PET-CT with F18 choline identified a left inferior parathyroid adenoma. Additionally, renal ultrasonography detected a non-obstructive 4 mm kidney stone. The patient left inferior parathyroid adenoma was surgically removed and her symptoms and biochemistry improved, including serum calcium levels normalized to 2.25 mmol/L. In primary hyperparathyroidism (PHPT), surgical intervention is the only curative option when appropriate. Therefore, precise localization of the parathyroid adenoma is crucial for successful surgical management. Radiolabelled choline PET-CT has emerged as a novel imaging modality, demonstrating significant promise for accurate lesion localization. We note a series of ten patients in whom ultrasound and MIBI scans failed to detect definitive parathyroid adenomas. In all

these cases, F18 choline PET-CT successfully identified the lesion, enabling curative surgical intervention. In fact, in two of the ten instances, a parathyroid adenoma was identified in the mediastinum and would have been overlooked if exploratory parathyroidectomy was undertaken. Recent research demonstrated that F18 choline PET-CT has a higher preoperative diagnostic efficiency than ultrasound and MIBI scans, with a positive predictive value of 90.9%. We propose F18 choline PET-CT as a primary imaging modality to augment, current imaging with Ultrasound, MIBI scintigraphy, and 4D CT, due to its superior diagnostic performance. However, further clinical research is needed, and cost as well as local availability remain important considerations.

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EP930

JOINT1143

Hyperglycemia in patients with acute myocardial infarction

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Introduction
Acute Myocardial Infarction (AMI) frequently accompanied with hyperglycemia, either transient or due to impaired glucose tolerances or DM. Usually hyperglycemia during AMI in healthy non-diabetic person viewed as a reflection to the acute stress condition. Despite there a many studies regarding that transient hyperglycemia, management is under discussion. The aim of our study was estimation of frequency of hyperglycemia in people with AMI.
Materials and Methods
Cases of AMI in Bukhara city were analyses based on two main hospitals in Bukhara during 2022/2023 were analyzed retrospectively by patients chart. Second part of investigation were conducted prospectively with daily multiple blood sugar level control.
Results
Medical records from 997 patients, whose were admitted to the hospitals due to AMI shown that 66% of patients has Dm^2. There were no information about transient hyperglycemia. Analysis of early in hospital death rate were estimated about 10.2% and were detected only in patients with Dm^2. Prospective study were conducted in 170 people who admitted into mentioned above hospitals due to AMI. Among in-hospital admitted AMI patients 104 (61,18%) were people with Dm^2, in 42 (24,7%) people transient hyperglycemia were detected and 24 (14,1%) people were without any carbohydrate disturbances. Interestingly, in patients with AMI we can see wide fluctuations of blood glycemia level. We divided patients according to glycemia fluctuation during the day: between 4 and 11Mmol/las normoglycemia, higher than 11Mmol/las a hyperglycemia and if blood sugar level less than 4Mmol/lwere defined as hypoglycemia. Hyperglycemia episodes (24.86%) were 10 times frequent than hypoglycemia (2.16%). All patients blood sugar were tightly controlled during the day and if needed they were received hypoglycemic treatment according to blood glycemia level. Early in-hospital death rate were among prospective study groups were more less than in retrospective patients 2.9% vs 10.9%. HbA1c level in patients after 3 months were in acceptable range in 66% of Dm^2 group and 88% of transient hyperglycemia group and remain high in 33% of Dm^2 and 11% of transient hyperglycemia group and suggested about inportance of tight glycemic control in that patients.
Conclusion
Hyperglycemia were frequent future in patients with AMI and presented in 85.88% cases, 61.18% were patients with Dm^2 and 24.7% with transient hyperglycemia. Hyperglycemia episodes were 10 times higher than hypoglycemia. Intensive control of blood glycemia with appropriate hypoglycemia measurements help to reduce in-hospital mortality rate.

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EP931

JOINT806

Metabolic changes and satisfaction associated with gender-affirming hormone therapy in transgender women

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Introduction
Gender affirming hormone therapy (GAHT) in transgender women favors their feminization. Aims: To determine its metabolic impact and the satisfaction perceived by the subject (CRES-4 questionnaire).
Material and Methods
Prospective study in transgender women with GAHT (> 2 years), attended at the Transgender Medicine Unit of the Hospital Clinico of Valladolid from January 2014 to January 2023. Recording of clinical, analytical and CRES-4 questionnaire data after giving their consent. Statistical analysis of the data by the SPSS-V17 program.
Results
36 transgender females aged 31 [23-42] years and onset of GAHT at 21 [17-30] years with oral estradiol 21 (58%) and transdermal estradiol 15 (42%). Besides 27 (75%) with cyproterone acetate and 9 (25%) with spironolactone. The initial BMI was 22 [20-25] kg/m^2, Total Cholesterol 160 [133-185], LDL 78 [69-129], HDL 54 [69-129], TG 76 [60-107] mg/dl. At 2 years with GAHT, BMI was 23[20-27] kg/m^2 (p 0.0939, the increase was 0.12 [-0.69 to 0.79] with oral estradiol and the 0.92 [-0.34 to 1.45] with transdermal estradiol (p 0.250). Total Cholesterol was 164 [140-188] (p 0.610), LDL 87 [63-127] (p 0.184), HDL 51 [40-72] (p 0.245) and Triglycerides was 72 [55-96] mg/dl (p 0.215). In trans women with oral estradiol the change of HDL was 12 [3-19] compared to - 3.5 [-11 to 14.25] mg/dl with transdermal estradiol (p 0.002). Subjects were satisfied with GAHT, with 250 [232-271] points on CRES-4. In women with oral estradiol was 250 [235-275] and transdermal estradiol 262 [230-277] (p 0.085).
Conclusion
Feminization hormone therapy induces a non-significant increase in BMI without deterioration of the lipid profile, with a significant increase in HDL cholesterol, mainly in women with oral estradiol. Although the satisfaction associated with hormonal therapy appears to be greater in women with transdermal estradiol.

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EP932

JOINT3636

Effect of a nutritional education program on anthropometric, biochemical, and body composition parameters in obese patients

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Introduction
Obesity is a major public health concern linked to higher morbidity and mortality. Nutritional education programs play a crucial role in promoting healthy habits and improving clinical, biochemical, and body composition parameters.
Materials and Methods
An observational before-and-after study was conducted on patients with obesity who participated in a 5-session program at the Endocrinology and Nutrition Unit of HUPM (January 2022 - October 2024). Clinical, anthropometric, biochemical, and body composition parameters were analyzed.
Results
A total of 101 patients participated (63.4% women, mean age 47 years, BMI 41.9 kg/m^2). Hypertension was present in 40.6%, dyslipidemia in 24.8%, type 2 diabetes in 17.9%, and prediabetes in 15.8%. Of these, 34.8% were treated with GLP-1 receptor agonists, showing greater but non-significant weight loss (8.9 $\pm$ 9.82 kg vs. 7.96 $\pm$ 5.44 kg). Baseline and final BIVA assessments were performed in 36 patients, with the following results: Patients with good adherence to the program lost more weight compared to those with poor adherence: A significant improvement in glycemic control was observed, as demonstrated in the biochemical parameters below:.

BIVA Parameters	Baseline (Mean $\pm$ SD)	Final (Mean $\pm$ SD)	p-value
Rz (Ohm)	481 $\pm$ 67.9	498.9 $\pm$ 62.9	$<$ 0.001
Xc (Ohm)	46.4 $\pm$ 7.78	47.3 $\pm$ 6.75	0.207
Pha (°)	5.53 $\pm$ 0.68	5.46 $\pm$ 0.64	0.272
TBW (L)	42.7 $\pm$ 7.63	40.3 $\pm$ 7.19	$<$ 0.001
FFM (Kg)	57.4 $\pm$ 9.84	55.2 $\pm$ 9.23	$<$ 0.001
FM (Kg)	51.1 $\pm$ 17.4	46.3 $\pm$ 15.6	$<$ 0.001
BCM	29.4 $\pm$ 4.27	28.1 $\pm$ 4.12	$<$ 0.001
ASMM (Kg)	23.7 $\pm$ 4.65	22.1 $\pm$ 4.25	$<$ 0.001

Program Adherence	Weight Loss (Kg, Mean ± SD)	Mean Difference	p-value
Poor (1-2 sessions)	3.56 ± 2.89	Intermediate - Poor = 1.32	0.652
Intermediate (3-4 sessions)	4.88 ± 4.95	Good - Intermediate = 5.25	0.003
Good (5 sessions)	10.13 ± 7.42	Good - Poor = 6.57	< 0.001

Laboratory values of cases.

Biochemical Parameters	Baseline (Mean ± SD)	Final (Mean ± SD)	p-value
Glucose (mg/dl)	100.11 ± 20.84	91.27 ± 15.35	0.005
HbA1c (%)	5.83 ± 0.81	5.59 ± 0.57	0.016
Total Cholesterol (mg/dl)	193.36 ± 45.57	179.93 ± 48.20	0.042

Conclusions
The nutritional education program improved anthropometric, biochemical, and body composition parameters. Participants who completed the program showed significant weight loss. No significant differences were found in weight loss between patients receiving GLP-1 treatment and those who did not. These results highlight the importance of nutritional intervention in managing obesity.

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EP933

JOINT1251

Morphofunctional changes during the follow up of people living with obesity treated with semaglutide

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Introduction
Obesity is a chronic metabolic disease that causes multiple complications in the medium and long term. GLP1 Analogues, including Wegovy (Semaglutide) 2.4mg, are the medical treatment that achieves significant and sustainable weight loss. Morphofunctional assessment (MFA) techniques, such as Bioimpedanciometry (BIA) with phase angle (PhA), Nutritional Ultrasound (NU) ® (which includes Rectus Femoris (RF) ultrasound and abdominal adiposity ultrasound) and handgrip strength (HGS) allow us to evaluate changes in body composition, beyond the weight.

Table 1. The most significant data are presented in Table 1.

	Female		Male		Sig (p)
	Basal	**3rd month follow up**	**Basa**	**3rd month follow up**	SIG (P)
Weight (kg)	90,2±15,5	87,7±17,8	107±21	100±16,5	<0,001
Waist (cm)	106±13.6	105±17,2	121±14	112±9,1	<0,001
Hip (cm)	121±13,7	118±16,4	116±11,3	111±8,9	<0,001
Nº of Squats in 30 sec	19,9±5,9	22,3±5,11	20,7±4,6	23,7±2,25	<0,001
Average HGS	22,1±5,1	22,5±4,4	38±6,9	39,9±3,8	0,538
Phase-angle	5,9±0.65	5,8±0,45	6,4±0,79	6±0,79	0,048
Body Cell Mass (BCM)	27±3,61	26,1±3,5	38,3±5,44	36±3,2	<0,001
Adiposity free Mass (FFM)	50,3±5,64	49,3±5,62	69,2±9,27	67,7±7,98	<0,001
Adiposity Mass (FM)	39,9±11,6	38,4±13,1	38,7±12,7	32,6±10,6	<0,001
Rectus Femoris (RF) CSA	5±1	5±1,1	6,5±1,7	6,1±1	0,511
RF- Y axis	2±3,6	1,5±0,3	2,4±4,2	1,7±0,18	0,001
Lower limb – Subcutaneous adipose tissue (SAT)	2,14±0,74	1,28±0,45	2,10±0,7	1,12±0,35	0,001
Abdominal - SAT	3,18±1,52	2,56±1,45	2,72±0,82	1,8±0,85	0,001
Abdominal - SAT area	12,1±3,87	10,8±3,59	10,4±5,4	8,7±3,39	0,002
Visceral Adipose tissue Area	9±2,7	8,5±2,69	8,22±3,2	7,1±2,7	<0,001

Aim
To evaluate changes in body composition using MFA techniques in patients with Obesity undergoing treatment with Semaglutide.
Methods
Prospective observational study of patients living with obesity treated at the Obesity and Metabolism Unit of Quirónsalud Málaga Hospital. MFA data was collected using BIA-PhA (Akern) and ultrasound (Mindray® Z60) at the baseline visit and after 3 months of follow-up. Semaglutide doses were started and adjusted according to standard protocols and patients' tolerance.
Results
25 patients, of which 18 (72%) were women. The presence of comorbidity was evaluated using the AACE Scale: 2 patients had grade 0 (2.9%), 33 patients had grade 1 (47.1%), 35 patients had grade 2 (50%).
Conclusions
Treatment with Semaglutide, along with a dietary program and physical activity recommendations, helps to reduce weight, mainly at the expense of the adipose component. Lower limb muscular area and function is preserved after 3 months of a weight loss program using Semaglutide.

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EP934

JOINT3965

Association between vitamin d levels at discharge, in-hospital complications and prevalence of obesity in post-critical care patients after admission to the icu for pneumonia covid-19

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Introduction
Vitamin D plays a crucial role in the regulation of the immune system in addition to bone metabolism. In the context of the COVID-19 pandemic, its impact on inflammation, antiviral immunity and modulation of the renin-angiotensin system has been shown to be relevant in reducing the severity of the disease. Low vitamin D levels in hospitalized patients have been associated with greater severity of the disease due to immune dysregulation, with a higher rate of severe complications, demand for intensive treatment and higher mortality. In addition, vitamin D deficiency has been closely related to metabolic disorders such as type 2 diabetes mellitus (DM) and obesity.
Objective
The aim of our study was to determine whether there are differences in the prevalence of DM, obesity (defined according to BMI and percentage of fat mass -FM%-) and sarcopenic obesity, rate of in-hospital complications and need for aggressive therapies during hospital admission in a cohort of post-critical patients who were admitted to the ICU for severe COVID-19 pneumonia, according to vitamin D levels at hospital discharge.
Method
Prospective observational study including 94 patients who were admitted to the ICU for severe COVID-19 pneumonia. At 2-3 weeks after hospital discharge, demographic, clinical and analytical data, medical history and morphofunctional assessment including bioimpedanciometry were collected. Patients were divided into three categories according to their serum vitamin D levels (deficit if $\leq$20 ng/ml, insufficiency if 20.01-29.99ng/ml, sufficiency if $\geq$ 30ng/ml). Differences in prevalence of DM, prevalence of obesity and in the rate of complications during admission were analyzed according to these vitamin D categories. For the definition of obesity according to FM% and sarcopenic obesity, the ESPEN and EASO consensus (2022) was followed.
Results
Depending on the categories of vitamin D deficiency, insufficiency and sufficiency, statistically significant differences in age (67±12,67±10,57±12; $P = 0.32$), sarcopenic obesity prevalence (36%,47%,43%; $P = 0.04$), days of ICU stay (25±9.5,33±9.8,19±9.4; 0.09), days of hospital stay (49±32,85±36,50±24; $P = 0.04$) and days of IMV (28±14,36±14,23±14; $P = 0.84$) were shown.
Conclusions
Statistically significant differences were observed in the prevalence of sarcopenic obesity (greater in the vitamin-D-deficiency and insufficiency vs. vitamin-D-sufficiency subgroups) and in days of hospital stay (greater in the vitamin-D-deficiency vs. sufficiency subgroup). When the multiple comparisons test was performed, differences were also observed in age, ICU stay and in days of IMV, being greater in the vitamin-D-deficiency vs. sufficiency group. No differences were observed in the prevalence of DM or obesity.

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EP935

JOINT411

Familial inheritance and childhood obesity

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Background
Childhood obesity and overweight have emerged as alarming public health issues, affecting an increasing number of children worldwide. With significant implications for both physical and mental well-being, these conditions are rapidly becoming a societal challenge. The factors driving this trend remain complex and multifaceted, with parental influence playing a pivotal role. This study aims to shed light on these key factors.
Methods
This cross-sectional case-control study was conducted in 2022 among children attending school health clinics in Tunis, Tunisia. It included children aged 5 to 15 years, excluding the conditions causing secondary obesity. Overweight was defined as an age-specific body mass index (BMI) > 1 standard deviation (SD) above the median of the WHO growth standards, while obesity was defined as a BMI > 2 SDs above the median. Parental obesity was defined as a BMI $\geq$ 30 kg/m^2. Patients were divided into two groups: G1 (overweight or obese children) and G2 (normal weight children). A 41-item questionnaire was administered to both children and their parents, addressing the risk factors for obesity.
Results
A total of 216 patients were included in the study, with 54 classified as overweight or obese (G1) and 162 having normal weight (G2). We did not find a significant association between overweight or obesity and age ($P = 0.07$), although it was observed that overweight and obese children were generally younger (7 years (6-12) in G1 vs. 11 years (6-12) in G2). The prevalence of overweight or obesity was higher in male children (34 (36.2%) in males vs. 20 (22.2%) in females, $P = 0.038$). There was no significant association between the fathers' educational level and the presence of obesity or overweight in children ($P = 0.325$). Similarly, no significant link was found between the mothers' educational level and childhood obesity or overweight ($P = 0.800$). The mother's employment status did not significantly correlate with the presence of obesity or overweight in the children ($P = 0.500$), though a lower prevalence of obesity and overweight was noted among working mothers. Parental obesity was not statistically associated with childhood obesity or overweight ($P = 0.800$), and a family history of obesity or Type 2 diabetes also showed no significant correlation with these conditions in children ($P = 0.450$).
Conclusion
Addressing the root causes of obesity and overweight in childhood, particularly through understanding and addressing parental influence, is critical to reversing this growing epidemic.

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EP936

JOINT427

Evaluation of the role of statins in the development of myalgias

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Introduction
Statins, widely used for cardiovascular prevention, are sometimes associated with muscle-related side effects, such as myalgias, which can lead to discontinuation of treatment. These side effects pose a challenge in therapeutic management. The objective of this study was to assess the role of statins in the onset of myalgias.
Methods
This cross-sectional descriptive study was conducted in November 2024 in the endocrinology department at Farhat Hached Hospital. Patients on statin therapy were included and evaluated using a questionnaire to define a Clinical Myalgia Index (CMI). A score between 9 and 11 indicated probable involvement, 7 to 8 suggested possible involvement, and a score below 7 indicated unlikely involvement.
Results
A total of 31 patients (mean age 60 $\pm$ 10 years, 71% female) were included. The prescribed statins were atorvastatin (83.9%), rosuvastatin (9.7%), and simvastatin (6.5%) at average doses of 40 mg, 20 mg, and 20 mg, respectively. A treatment duration of over 12 months was reported for 67% of the patients. Probable involvement was observed in 6.5%, possible involvement in 19.4%, and unlikely involvement in 74.2%. No significant association was found between the type or dose of statin, the indication for prescription, and the CMI. However, a treatment duration of less than 12 months increased the risk of myalgias by a factor of 6 ($P = 0.034$).
Conclusion
These findings highlight the importance of regular monitoring of myalgias in patients on statin therapy. They suggest that the risk of myalgia is higher during the first months of treatment, while the type or dose of statin does not significantly affect the likelihood of developing myalgias.

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EP937

JOINT1511

Pro-oxidant-antioxidant system in patients with chronic kidney disease and type 2 diabetes mellitus in obese and non-obese patients

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Introduction
Chronic kidney disease (CKD) is a major driver of mortality in patients with type 2 diabetes mellitus (t2DM). CKD is estimated to affect 50 % patients with DM. An increasing number of studies find obesity and t2DM a continuous progression of CKD in patients with and the development of cardiovascular complications.
Purpose
To estimate the pro-oxidant and antioxidant system state, to identify the presence of dependence on lipid profiles in patients with CKD and t2DM in obese and non-obese patients. It was observed 79 diabetic individuals with CKD, which were categorized into two groups: obese and non-obese, according to their body mass index (BMI). Group 1 ($n = 35$) patients with obesity (BMI$\geq$30 kg/m^2), group 2 ($n = 44$) non-obese patients. Healthy individuals ($n = 21$) - control group. We examined the state of the pro-oxidant-antioxidant balance (PAB) - total hydroperoxides (TH)/total antioxidant activity (TAA). Also, lipid profiles were investigated.
Results
In patients with with CKD and t2DM was found expression of PAB ($P < 0.05$) - decrease in TAA and an increase in TH, with more pronounced indicators been found in obese diabetic patients ($P = 0.01$); Studying lipid profiles, there were significantly increased proatherogenic lipoproteins (LDL-C, TC, TG) ($P < 0.05$) in obese and non-obese patients compared with healthy individuals. When comparing obese and non-obese patients, a more significant increase in pro-atherogenic lipid fractions was found in obese individuals ($P = 0.03$). Exploring the relationship between PAB and pro-atherogenic lipid fractions in obese patients with CKD and t2DM, a positive correlation was confirmed ($r = 0.45$) and ($r = 0.55$), $P < 0.05$, testifying an association between oxidative stress parameters and hyperlipidemia. It appears that it may be connected with increased lipid peroxidation and, as a result, atherosclerosis progression.
Conclusions
In patients with CKD and t2DM with obesity, a more pronounced imbalance of the pro-oxidant-antioxidant system, increased proatherogenic lipid levels were determined compared to non-obese patients with CKD and t2DM. These results clarify a clear relationship between lipid profiles and oxidative stress parameters in patients with obesity, CKD and t2DM, which may indicate that metabolic disorders - obesity are one of the leading risk factors for the progression of diabetic kidney disease.

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EP938

JOINT1901

Biomarkers of iron status and inflammation in Belgian children with overweight and obesity

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Background
Obesity is a recognized risk factor for iron deficiency. Low-grade inflammation associated with obesity contributes to alterations in biomarkers of iron status. This study aimed to identify the best markers of adiposity and inflammation in relation to transferrin saturation (TS) and serum ferritin in a cohort of Belgian children and adolescents with overweight and obesity.
Methods
Data were retrieved from the medical records of 197 children with overweight/-obesity at the start of a weight loss program. Iron status was assessed through measurements of serum iron, transferrin, TS, and ferritin. Inflammatory markers included serum high-sensitivity C-reactive protein (hS CRP) and plasma fibrinogen. Adiposity was evaluated using BMI SDS, waist circumference (WC) SDS, subscapular skinfold thickness (SST) SDS, waist-to-height Ratio (WHR), and body fat percentage (BF) by bioelectrical impedance analysis (BIA). TS was calculated as iron (µg/dl) *100)/ (transferrin (g/l)* 127). Serum iron, transferrin, and ferritin levels were measured using the Cobas 8000 C702 platform. Stepwise multiple regression analysis was performed with TS and serum ferritin as dependent variables.
Results
Among the participants, 56% were male, 41% were prepubertal, and 80% had obesity (BMI SDS $>$ 2). The median (Q1, Q4) age was 12.0 (10.5, 13.8) years, BMI SDS 2.3 (2.0, 2.6), WC SDS 2.2 (1.9, 2.4), SST SDS 2.0 (1.8, 2.2), BF 34% (32,39), WHR 0.57 (0.53, 0.60), serum iron 65 µg/dl (52, 88), TS 18% (14, 18), and plasma ferritin 44µg/l(30,71). Iron deficiency, defined as TS $<$ 16%, was observed in 33.5 %, while 1.5 % had a low iron reserve, defined as a serum ferritin ($<$ 7 µg/l). Elevated TS ($>$ 45%) was rare ($<$ 0.5%), as was increased serum ferritin ($>$ 140 µg/l,1.5%). TS was not associated with gender, age, or pubertal status but positively correlated with ferritin (Rho = 0.33; $P < 0.001$). In regression analyses, WC SDS ($P = 0.01$) and hS CRP ($P = 0.03$) were the primary predictors of TS, while fibrinogen was the sole predictor of serum ferritin ($P = 0.04$).
Conclusion
Iron deficiency, defined by low TS, affects one-third of Belgian children and adolescents with overweight/obesity. Waist circumference and hS CRP emerged as the key predictors of low TS, while elevated fibrinogen correlated best with increased serum ferritin. These findings underscore the importance of assessing low-grade inflammation when evaluating iron status among this population.

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EP939

JOINT434

Relationship between eating behavior of children with their nutritional status based on their bmi among 6 -12 year children: a mixed method study

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Background
Childhood Obesity presents a global pandemic and stands as a significant impending threat to public health. With 380 million children and adolescents affected worldwide. A meta-analysis spanning from 2003 to 2023, encompassing 1,86,901 children in India, revealed that childhood obesity prevails at a pooled prevalence of 8.4%, while childhood overweight stands at 12.4%. We sought to explore the connection between eating behaviors and the risk of childhood obesity.
Objective
To Estimate the prevalence of obesity and determine the association between child eating behaviors and BMI.
Methods
A cross-sectional study was conducted inDeoghar a district of Jharkhand, India, a developing urban area in Sabah, involving 484 children aged 6–12 years. Participants were recruited from five primary schools selected using a combination of multistage stratified and convenience sampling methods. Data collection included sociodemographic details, anthropometric measurements of both parents and children, and children's eating behaviors, assessed using the Children Eating Behaviour Questionnaire (CEBQ). Age-adjusted BMI z-scores were calculated following the World Health Organization guidelines to evaluate nutritional status. A qualitative analysis was conducted through focused group discussions with parents of obese children. The feeding behaviors identified were then compared between the quantitative and qualitative analyses.
Results
The prevalence of childhood obesity among children aged 6–12 years is 13.2%. Analysis of the 'Food Approach' subscales from the CEBQ revealed higher mean scores in the overweight and obese groups compared to the normal-weight group. Conversely, the 'Food Avoidance' subscales showed lower mean scores in the overweight and obese groups compared to the normal-weight group. Very similar findings were observed in the qualitative analysis.
Conclusion
This study highlights that childhood obesity remains a significant health concern in a developing rural area of Jharkhand, India, as the "Food Approach" subscales were found to be positively associated with excess weight in children.

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EP940

JOINT270

Premature aging in (young) adults with prader-willi syndrome

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Introduction
In the Dutch Center of Reference for Prader-Willi syndrome (PWS), we follow over 200 adults with PWS. The majority shows clinical signs of premature aging, starting from the age of 25y. This is in line with the literature, reporting higher prevalences of functional impairment, as well as higher morbidity, higher overall mortality and premature brain aging. Little has been published about dementia in PWS, although some case reports have described dementia in relatively young patients. At cellular level, a significantly shorter leukocyte telomere length (a marker of biological age) has been described in PWS. We have performed a systematic review in order to provide a comprehensive overview of premature aging in PWS, with the aim to develop a PWS-specific geriatric aging score.
Methods
Systematic review (search strategy available upon request) focusing on age related conditions that, in the general population, mainly occur among the people aged 60 or up. Articles about vascular disorders, diabetes mellitus, chronic pulmonary disease, neoplasms including urinary, lung, breast, colorectal and prostatic cancers, cataract and macular degeneration, presbycusis, disorders in de digestive system, rheumatic diseases, prostate diseases and neurodegenerative disorders were included. Also, more specific aging terms like frailty, premature aging, falling, functional decline, dementia, Alzheimer, polypharmacy, osteoporosis, mobility limitation and multimorbidity were included.
Results
The systematic review is currently in progress. We will present a comprehensive overview of key indicators of premature aging, including prevalence of functional decline, metabolic disorders, neurodegenerative conditions, and other geriatric syndromes. Additionally, we will propose a PWS-specific geriatric aging score based on the collected data. These findings aim to enhance our understanding of premature aging in PWS and contribute to improved clinical care strategies for this population.
Conclusion
PWS is characterized by premature aging, starting from the age of 25. Based on our systematic review, we will provide an overview of age related disorders in the Prader-Willi population. We will present a PWS-specific geriatric aging score, which will help us quantify and understand (and in the future possibly prevent) premature aging in PWS.

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EP941

JOINT165

The relationship between serum galectin-3 level and echocardiographic findings in patients with polycystic ovary syndrome

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Aim
The study aimed to examine the relationship between serum galectin-3 level in the type with polycystic ovary syndrome (PCOS) and global longitudinal strain (GLS) and aortic intima-media thickness (A-IMT) and whether these measurements are a marker for detecting measurements in the early stages of atherosclerosis and heart failure.

Methods
A total of 80 participants, 40 newly diagnosed PCOS patients and 40 healthy control groups, were included in the Health Sciences University Adana City Training and Research Hospital between 01.06.2021 and 31.03.2022. Galectin-3 level was measured by using Human galectin-3 kits and Enzyme-Linked Immuno Sorbent Assay method. A-IMT and GLS measurements were performed by using ultrasonography and echocardiography.
Results
When both study groups were evaluated, a statistically significant difference was found between the groups in terms of blood glucose, HOMA-IR Index, galectin-3, A-IMT, and GLS values. A correlation analysis was carried out between galectin-3 level and other demographic, clinical and laboratory parameters in the PCOS patient group and control group. Parameters related to Galectin-3 level; GLS were found as A-IMT and HOMA-IR Index. Linear regression analysis was performed using parameters that showed significant correlation with Galectin-3 level. Galectin-3 level was found to be independently associated with GLS.
Conclusion
The study shows that the galectin-3 molecule can be said to detect long-term outcomes such as atherosclerosis and heart failure in a more subclinical period in PCOS patients and that it can help identify the risky patient population, and can be used as a biomarker in diagnosis and follow-up. .
Keywords
Aortic intima-media thickness, galectin-3, global longitudinal strain, polycystic ovary syndrome.
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EP942

JOINT2091
Impact of obesity management during polycystic ovary syndrome in young adolescents (experience of a specialized pediatric endocrinology consultation)
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Introduction
Polycystic ovary syndrome (PCOS) is due to a hormonal imbalance of ovarian or central origin, it leads to excessive androgen production, it is responsible for 10% of fertility disorders in women of childbearing age but it can appear earlier in adolescents, it clinically results in cycle disorders, signs of hyperandrogenism, metabolic disorders related to insulin resistance, which is itself secondary to hyperandrogenism with obesity and risk of T2D and later metabolic complications (hypertension, cardiovascular diseases), radiologically it results in polycystic dystrophic ovaries. There is no specific treatment, it is essentially symptomatic, it should be noted that lifestyle plays an important role in the balance of the disease, a 10% decrease in weight could reduce the signs of hyperandrogenism and its complications with the improvement of cycle and fertility disorders.
Material and Methods
In our consultation, we collected 8 adolescent girls with PCOS.
Results
The age of our patients is between 13 and 16 years old, the main reason for consultation was cycle disorders (spaniomenorrhea and sometimes secondary amenorrhea), 6 had obesity to varying degrees, all the patients had signs of hyperandrogenism such as hirsutism, acne, hair loss, etc., 4 had T2D and 7 had a history of cycle disorders in the context of obesity with or without fertility disorders in the mother, the aunts and the cousins. The patients had received different treatments depending on the situation (Dydrogesterone, metformin, hormonal treatment, gynecological advice and lifestyle management). In the 6 patients who managed to reduce their weight, we noted an improvement in cycle disorders with a decrease in signs of hyperandrogenism.
Conclusions
PCOS is a multifactorial pathology where lifestyle and weight management significantly improve the clinical signs in these adolescent girls while remaining cautious about fertility disorders in the future.
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EP943

JOINT149
Pharmacological approach to neonatal hyperbilirubinemia
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Background
A very conceptual and uncomprehensive point in the strategy is that chelation of Bilirubin is not as easy as conjugation. It is bound to albumin within the circulation and soluble in fat. Besides, in contrast to general notion the lipophilic site of the molecule is not where conjugation occurs. Conjugation does not cover the fat-soluble side of the molecule but makes the molecule larger and more ware soluble from the water soluble pole. So, it is difficult to approach the molecule with solubilizing agents from the fat-soluble site because chelating agents are themselves water soluble. The only hope would be extraction of Bilirubin from albumin in the circulation and increasing the binding potential of albumin to extract bilirubin from fat rich tissues like the brain.
Aim
Increasing the “Albumin pool” to extract more unconjugated Bilirubin from fat rich tissues and hence therapeutic and prophylactic reduction of unconjugated bilirubin.
Methods
Twelve neonates with harmless hyperbilirubinemia in the range of 8mg/dl were treated with a single dose 500mg of a triguanide derivative called TR-225. Bilirubin was measured every half hour for 24 hours. Patients with stable levels under 2 were discharged from the hospital.
Results
TR-225 is 100% capable of reducing hyperbilirubinemia in all patients studied. The conjugate could be traced within the urine in a proportional manner. Speed of bilirubin reduction is 18 times that of exchange transfusion. The time/-concentration curve denotes extreme effectiveness without rebound due to re-distribution of bilirubin from peripheral fat to circulation. The treatment is not without side effects and can hardly be used as a prophylaxis.
Conclusion
Treatment of neonatal hyperbilirubinemia with a chelator is chemically extremely difficult and needs sophisticated drug development techniques such as artificial intelligence. But it is a very interesting issue which can possibly close thousands of neonatal wards worldwide.
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EP944

JOINT3706
Beyond weight: the quality of life in young women living with obesity
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Introduction
Obesity is a significant global health issue and an independent risk factor for numerous chronic physical and mental health conditions. Beyond its medical implications, obesity also affects quality of life, influencing physical well-being, psychological health, social interactions, and life satisfaction. Individuals with obesity often experience limitations in daily activities, reduced mobility, emotional distress, and stigma, all of which contribute to a diminished sense of well-being. This study aimed to assess the impact of obesity on various health outcomes and to measure the health-related quality of life (HRQoL) in young women with obesity.
Material and Methods
A total of 130 young women, aged 18-45, were included in the study. Participants were categorized into two groups based on BMI: 69 women with obesity (BMI $\geq$30 kg/m^2) and 61 with normal weight (BMI $\leq$25 kg/m^2). HRQoL was measured using the 36-item Short-Form Health Survey (SF-36). Pearson correlation coefficients were used to examine associations between obesity and HRQoL domains, controlling for potential confounding factors.
Results
The mean age was 31.8 $\pm$ 6.75 years, with no significant difference between groups. The results reveal a significant negative correlation between between BMI and multiple HRQoL domains in young women, including physical functioning ($F=62.89$, $P<0.001$), emotional well-being ($F=68.47$, $P<0.001$), social functioning ($F=70.9$, $P<0.001$), and general health ($F=78.96$, $P<0.001$). Women with obesity reported increased role limitations due to physical ($F=28.37$, $P<0.001$) and emotional factors ($F=46.33$, $P<0.001$), reduced vitality ($F=72.7$, $P<0.001$), and greater bodily pain ($F=59.17$, $P<0.001$). The findings indicate that as BMI increases, perceived quality of life significantly declines, particularly in mental and social health aspects.
Conclusion
This study highlights the strong association between obesity and reduced HRQoL in young women, particularly in emotional well-being, social participation, and physical functioning. Given these findings, comprehensive, multidisciplinary

interventions that integrate mental health support, customized physical activity programs, and social empowerment strategies are essential for enhancing the overall well-being of young women living with obesity.

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EP945

JOINT3382

Impact of B vitamin intake on weight loss outcomes in obese patients

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Background

Recent research has increasingly focused on the relationship between B vitamin intake and weight loss outcomes in obese individuals undergoing weight loss interventions. Numerous studies have examined how different B vitamins affect obesity-related factors, including body fat distribution and metabolic processes [1]. The aim of our study was to assess the impact of baseline B vitamin intake on weight loss outcomes in obese patients.

Methods

We conducted a longitudinal study involving 100 obese adult patients over 6 months. We analyzed body composition using SECA MBCA 515 bioimpedance at baseline and at follow-up. dietary survey data were collected at baseline using Nutrilog software. A balanced hypocaloric diet was prescribed and patients received regular follow-ups.

Results

The mean age was 44.42 ± 13.25 years and the sex ratio (M/F) was 0.11. The mean fat mass (FM) and fat mass index (FMI) values were 52.50 ± 12.39kg and 19.74 ± 4.03kg/m^2, respectively. The mean fat-free mass index (FFMI) was 20.34 ± 2.53kg/m^2 and 20% of the participants had a below-average FFMI at baseline. The deficiencies in vitamin B group intake observed at baseline were dominated by a deficiency in vitamin B9 (44%) and vitamin B2 (36%). At 6 month,22 patients were lost to follow-up and 78 patients completed the study with a mean body weight loss of 4.13 ± 6.90 %.The intake of vitamin B12 at baseline was positively correlated with the loss in BMI ($P = 0.009$), waist circumference ($P = 0.009$), and fat mass ($P = 0.007$), and inversely correlated with the loss in lean mass ($P < 0.001$). In contrast, the intakes of vitamins B6 and B9 were inversely correlated with the loss of fat-free mass ($P = 0.04$ and 0.041, respectively), skeletal muscle mass ($P = 0.038$ and $P = 0.011$, respectively), and appendicular muscle mass ($P = 0.021$ and $P = 0.024$, respectively). However, the intake of vitamins B1, B2, B3, and B5 did not show any correlation with the different parameters of weight loss.

Conclusion

Our study underscores the importance of considering vitamin B intake, particularly B12, B6, and B9, when prescribing dietary interventions for weight loss in obese patients. Addressing potential deficiencies in these vitamins could enhance the effectiveness of weight loss strategies.

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EP946

JOINT1351

Regional prevalence of underweight, overweight and obesity in adults from 1999 to 2023 at their first endocrinological examination: a retrospective cross-sectional study performed in liguria, italy

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Background

Combined burden of underweight and obesity has increased in most countries. No studies of this phenomenon in Liguria have been published.

Aim

To evaluate the prevalence of underweight, overweight and obesity in Caucasian male (M) and female (F) adults undergoing their first endocrinological examination in the district of Savona.

Methods

From 1999 to 2023, 6868 records (1317M; 5551F) were evaluated. Age, BMI, reason for examination and current dietary habit were evaluated. Records were grouped into five 5-year periods. Underweight was defined as BMI < 18.5 kg/m^2 and obesity as BMI ≥ 30.0 kg/m^2. Individuals with a BMI of 18.5-24.9 kg/m^2 and 25.0-29.9 kg/m^2 were classified as being of normal weight and overweight. The prevalence of each BMI interval in each period was evaluated.

Results.

A significant ($P < 0.001$) increase in age was observed from the 1999-2003 period to the 2019-2023 period and a significant ($P < 0.001$) positive correlation was noted between age and BMI in both genders. In M, the median prevalence of underweight decreased slightly from 1.8% in the period 1999-2003 to 0.8% in 2019-2023. In F, the prevalence of underweight did not change significantly (median 3.7%, 1999-2003). The median prevalence of overweight was 40.7% (2009-2013) in M and 26.1% (2004-2008) in F, declining (2004-2008 *vs* 2019-2023) minimally in F (-0.8%) and more evidently in M (-9.0%). Overweight and obesity displayed a median prevalence of 63.4% in M (2014-2018) and 47.2% in F (2009-2013). Normal weight showed a median prevalence of 35.2% in M (1999-2003) and 48.3% in F (2014-2018). Regarding reasons for the first examination, weight and/or metabolic diseases showed a median prevalence of 10.2% in both genders. The prevalence of dietary intervention owing to underweight or overweight/obesity increased from 5.6% to 18.2% in M and from 14.4% to 18.4% in F over the 25 years.

Limitations

Subjects were not representative of the general population of our district. Our results cannot therefore be extrapolated to regional or national populations. Moreover, relatively few subjects, especially males, were involved.

Conclusions

Our study involved about 2% of the population of the Savona district. Less than 50% of subjects were of normal weight. Overweight and obesity affected a large part of the population, but their prevalence did not change significantly over 25 years. Subjects undergoing examination showed limited awareness of this condition. The greatest change in BMI was age-dependent in both genders. The slight increase in subjects who reported controlling their diet is encouraging.

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EP947

JOINT3430

Evaluation of childhood obesity management in primary care setting

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Introduction

Childhood obesity (CO) is a major public health concern in the post-industrial era. The absence of specialized management structures or the difficulty in accessing them means that family physicians (FPs) are frequently confronted with this condition. The aim of this study is to assess the diagnostic and therapeutic approaches of FPs in managing CO.

Methods

We conducted a cross-sectional descriptive study in 2024, including FPs practicing in southern Tunisia. The study was conducted online and through direct interviews with the participating physicians. The target population for the questionnaire consisted of children under 18 years old with a BMI > 2 SD.

Results

A total of 100 participants were included, with a mean age of 48.5 ± 11 years and a female predominance (64%). The majority of the surveyed FPs (68%) had more than 10 years of clinical experience. Public sector physicians and those practicing in urban areas accounted for 59% and 52% of respondents, respectively. The evaluation practices for CO were characterized by the systematic calculation of BMI and dietary assessment in only 5% and 30% of FPs, respectively. The impact of CO was assessed by only 10% of practitioners. The main barriers reported by FPs included workload (25%) and insufficient theoretical training (35%). Management practices were primarily based on non-personalized dietary recommendations (75%) and encouragement of physical activity (55%). Most children with CO were referred to specialists, particularly adult endocrinologists (68%).

Conclusion

FPs frequently face the challenge of childhood obesity. However, its management presents several limitations in this sector, particularly regarding screening, standardized anthropometric evaluation, and dietary or potential pharmacological interventions. These limitations can be attributed to gaps in initial training, the absence of collaborative care networks, and constraints related to time and workload.

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EP948

JOINT48

Significance of liver enzyme assessment in women with metabolic dysfunction-associated liver disease, obesity, newly diagnosed type 2 diabetes, and hypertension

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Background and Objectives
Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading chronic liver condition globally, affecting individuals across various ages and ethnicities. It strongly correlates with obesity (over 70% of metabolic-associated steatohepatitis [MASH] cases occur in obese individuals), type 2 diabetes mellitus (T2DM; nearly 75% of MASH patients have T2DM), hyperlipidemia (20–80% show elevated cholesterol and triglycerides), and atherosclerosis. Since metabolic dysfunction is a cornerstone of MASLD, its diagnosis necessitates confirmation of hepatic steatosis alongside at least one of five cardiometabolic risk factors. Early detection of MASLD, especially in individuals with excess weight or obesity, through liver enzyme evaluation (alanine aminotransferase [ALT], gamma-glutamyl transpeptidase [GGT], and aspartate aminotransferase [AST]), and fibrosis assessment—coupled with prompt treatment and risk factor management—can curb disease progression and associated complications, while reducing socio-economic burdens.
Methods
The study involved 36 women, aged 24–64 years, with body mass indices (BMI) ranging from 30.5 to 69.8 kg/m^2, all scheduled for bariatric surgery. They underwent screening for MASH through clinical assessments, including blood tests to measure ALT, AST, and GGT levels, as well as hemoglobin A1c (HbA1c). Selection criteria prioritized elevated ALT levels, ALT/AST ratios below 1, and raised GGT levels. HbA1c levels above 6.5% confirmed diabetes mellitus. Liver enzyme levels were determined via colorimetric biochemical methods, while HbA1c was measured using high-performance liquid chromatography. Blood pressure (BP) was recorded in the seated position using a mercury sphygmomanometer. Hepatic steatosis was graded using ultrasound steatometry.
Results
MASLD was diagnosed in all participants. MASH was identified in 39%, with steatosis categorized as S1 in 21%, S2 in 50%, and S3 in 77.8% of cases. Elevated ALT, AST, and GGT levels were noted in 11% of patients with BP exceeding 140/90 mm Hg. HbA1c levels $>6.5\%$ alongside increased liver enzymes were seen in 6% of cases. Simultaneous elevations in ALT, AST, GGT, HbA1c, and BP $>140/90$ mm Hg occurred in 6% of patients.
Conclusions
MASLD was detected in all obese participants, regardless of T2DM or hypertension status. MASH was most prevalent among women with advanced steatosis (S3; 77.8%). Women with obesity and hypertension had a higher occurrence of MASH (11%) compared to those with obesity and T2DM (6%) or both conditions combined (6%).

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EP949

JOINT463

Demographic, hereditary, and environmental factors in the development of masld among type 2 diabetes mellitus patients

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Background
The development of Metabolic Associated Steatotic Liver Disease (MASLD) in patients with type 2 diabetes mellitus (T2DM) is influenced by a complex interplay of demographic, hereditary, and environmental factors. Understanding these factors is essential for identifying high-risk individuals and improving prevention strategies. We aim to explore specific demographic characteristics, family history, and environmental exposures that contribute to the onset of MASLD in T2DM patients.
Methods
A retrospective study including 202 T2DM patients, followed from 2012 to 2024 at the Endocrinology-Diabetology Department of Hedi Chaker University Hospital in Sfax, Tunisia was conducted. Patients were divided into two groups: Group1 comprised 101 diabetic patients with MASLD while Group2 comprised 101 patients without MASLD.
Results
Demographic factors did not significantly influence the development of steatotic lesions, as both patient groups (Group1 and Group2) shared similar characteristics in terms of age (55 [45-66] years vs. 59 [49-68] years, respectively; $P = 0.087$) and gender ($P = 0.773$). Likewise, a family history of cardio-metabolic diseases was not strongly associated with the onset of MASLD, whether it involved early cardiovascular events ($P = 0.949$), family history of hypertension ($P = 0.272$), or dyslipidemia ($P = 0.239$). However, a family history of autoimmune diseases emerged as a significant risk factor for MASLD ($P = 0.020$). Interestingly, lifestyle factors such as smoking, occasional alcohol consumption, and physical inactivity did not appear to promote steatosis in this cohort ($P = 0.525$, $P = 0.485$, $P = 0.310$, respectively).
Conclusion
These findings suggest that autoimmune history may play a key role in the development of MASLD.

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EP950

JOINT2624

A resource for practical food portions for children and adults with prader-willi syndrome

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Introduction
Reducing calorie intake to avoid excessive weight gain whilst maintaining nutrient intake and growth is challenging in the management of PWS. General societal misconception of appropriate food portions also impacts care. Guidelines suggest 30% fewer calories are required in PWS, whereas micronutrient requirement is unchanged. No visual, practical guide exists to illustrate such appropriate food portion sizes. We aimed to 1. develop a national pictorial resource defining and illustrating correct portion sizes for children and adults with PWS, and 2. to assess the nutritional adequacy of these proposed portions.
Methods
A national working group with experience in PWS was devised (paediatric endocrinologist, specialist dieticians, therapy assistant, representative from the PWS Association UK and an endocrinology nurse) and linked with Nutrition and Diet Resources UK, a charity who develop nutritional resources. Previously defined national portion sizes for children (Public Health England, 2016) were proportionally reduced by 30% for a selection of commonly consumed foods for 6 age categories (2-3/4-6/7-10/11-13/14-18/19-64 years) and photographs produced. Recommended number of portions of each food group per day were defined from national recommendations, allowing for the development of day meal plans. Patient groups were consulted to include parent/patient feedback. A final resource was recirculated to the patient groups and national stakeholders for peer review. An example proposed 24 hour intake from the resource underwent dietary analysis for each age group for both sexes to validate nutritional adequacy.
Results
Sixty common foods were used to calculate age specific food portions and 348 photographs were taken to produce the resource (https://www.pwsa.co.uk/practicalportions). Less healthy foods were included but highlighted as undesired. Examples of 24 hour intake for each age group were analysed for nutritional value. Caloric intake ranged from 49% (adult males) to 69% (5 year old females) of the EAR. Several micronutrients were lower than recommended in several age groups including iron, zinc and iodine.
Conclusion
Poorly defined dietary guidance in PWS can negatively impact acute and chronic health outcomes. In addition, such an unusual recommended intake can be difficult to define, appreciate and apply. We present a PWS unique resource to provide correct food portion sizes and practically support and address these challenges. Nutritional analysis supports its use to provide a caloric intake suitable for PWS and highlights micronutrients that may require attention. Strengths include user involvement and visual nature reducing language barriers, allowing wide application. Limitations include restriction to 60 foods.

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EP951

JOINT2658

Severe hypertriglyceridemia in an infant during COVID-19 episode: case report

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Familial chylomicronemia syndrome (FFS) is a severe form of dyslipidemia resulting from the loss of function of the enzyme lipoprotein lipase (LPL) or one of its cofactors, such as apolipoprotein A5 (apo A5) or apolipoprotein C-II (apo CII). It is a rare disease, with an estimated prevalence of 1:1,000,000 and important implications for the health of affected individuals. We describe the case of an infant who presented manifestations of the disease at 4 months of age, during a COVID-19 episode. The child was admitted to the hospital with fever and diarrhea. The laboratory investigation confirmed acute SARS-CoV-2 infection, liver steatosis and hepatomegaly, hypertriglyceridemia (triglycerides 9,394 mg/dl), hypercholesterolemia (total cholesterol 395 mg/dl) and elevated alanine and aspartate aminotransferases. Considering the risk of acute pancreatitis, breastfeeding was stopped, and the child was put on a special diet formula with 0% fat and supplemented with medium-chain triglycerides. After a week, the child was asymptomatic and repeated blood tests revealed a significant decrease in serum triglycerides (262 mg/dl) and total cholesterol (284 mg/dl). The child was discharged from the hospital and, during outpatient follow-up, maintained normal triglyceride levels during the transition to a normal diet. We performed a search for variants in the following gene: ATP-binding cassette transporter A1 (ABCA1), 1-Acylglycerol-3-Phosphate O-Acyltransferase 2 (AGPAT2), AKT Serina/Treonina Quinase 2 (AKT2), Apolipoprotein A5 (APOA5), Apolipoprotein C2 (APOC2), Berardinelli-Seip Congenital Lipodystrophy 2 (BSCL2), Caveolin 1 (CAV1), Caveolae Associated Protein 1 (CAVIN1), CF Transmembrane Conductance Regulator (CFTR), Cell Death Inducing DFFA Like Effector C (CIDEC), Chymotrypsin C (CTRC), Cytochrome P450 Family 27 Subfamily A member 1 (CYP27A1), Glycosylphosphatidylinositol Anchored High Density Lipoprotein Binding Protein 1 (GPIHBP1), Lysosomal Acid Lipase A (LIPA), Lipase E Hormone Sensitive Type (LIPE), Lipase Maturation Factor 1 (LMF1), Lamin A/C (LMNA), Lamin B2 (LMNB2), Lipoprotein Lipase (LPL), Mitofusin 2 (MFN2), Perilipin 1 (PLIN1), DNA Polymerase Delta 1, Catalytic Subunit (POLD1), Peroxisome Proliferator Activated Receptor Gamma (PPARG), Serine Protease 1 (PRSS1), Proteasome 20S Subunit Beta 8 (PSMB8), Sphingomyelin Phosphodiesterase 1 (SMPD1), Serine Peptidase Inhibitor Kazal Type 1 (SPINK1) and Zinc Metallopeptidase STE24 (ZMPSTE24). The results did not show any variant that could explain the phenotype, which led us to hypothesize that the transient severe hypertriglyceridemia was secondary to COVID-19 infection.

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EP952

JOINT221

Recurrent hypoglycemia in persistent hypoglycemia hyperinsulinism of infancy post near total pancreatectomy

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Background
The most common causes of persistent hypoglycemia Hyperinsulinism (PHHI) are genetic or congenital abnormalities in the regulation of insulin secretion, deficiencies in growth hormone and/or cortisol, or abnormalities in the metabolism of glucose, glycogen, and fatty acids. Congenital hyperinsulinism's prevalence: 1 in 2700 in some consanguineous populations; 1 in 28,000 to 50,000 live births in the general population. According to our committee's report, it can be difficult to identify neonates with PH issues because they can resemble transitional hypoglycemia within the first 48 hours. Furthermore, the first few months are crucial since 25% to 50% of children with congenital hyperinsulinism have developmental difficulties. For infants and young children, hypoglycemia is defined as blood glucose levels below 60 mg/dl/lthroughout the first 72 hours of life and beyond.
Case
This report aims to present a case of diffused type PHHI that was effectively treated with a near pancreatectomy and later identified with adrenal insufficiency. K, a 4-month-old girl, weight 5.9 kg, length 56 cm, was sent to Soetomo Hospital because she had hypoglycemia and frequent seizures since 3 days old. According to the family history, no member of family with diabetes. Ketone levels were 0.1 mmol/l,C.peptide levels were 3.3 ng/ml (1.1-4.4), lactate levels were 2.77 mmol/l(0.4-2.0), insulin levels were 16.8 µU/ml (4.04-23.46), FT4 levels were 1.63 ng/dl (0.9-1.75), TSH levels were 5.032 µIU/ml (0.64-6.27), GH levels were 1.35 ng/ml (0.14-6.27), cortisol levels were 1.8 µg/ml (45.5-208.2), taken when blood glucose 33 mg/dl. We evaluated a patient with wasting, adrenal insufficiency, and recurrent hypoglicemia. Due to the lack of diazoxide in Indonesia, the patient was treated with oral nifedipine (~2 mg/kg/day), SC octreotide (~5 mg/kg/day), and oral prednisone (~6 mg/kg/day), along with a glucose infusion rate up to 12 (formula milk added to IV fluids via a central line). After a month, the treatment failed, and we referred to pediatric surgery for pancreatectomy. Preoperative labs were normal, and abdominal CT showed no mass. We want to conduct a genetic test to determine the type of hypoglycemia, but the family refuses. Seven days post-pancreatectomy, the patient was ready for discharge but had morning hypoglycemia. We prescribed nifedipine 1 mg/kg/day orally to stabilize. Early recognition and treatment are crucial for preventing these sequelae.
Conclusion
Patients PHHI who cannot control their hypoglycemia with medication may need a near-total pancreatectomy; nevertheless, this could lead to diabetes mellitus or recurrent hypoglycemia after surgery.

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EP953

JOINT3840

Physical activity among the healthcare providers at ibn rochd university hospital in casablanca

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Introduction
Physical activity (PA) is a current public health topic. There is growing awareness of the health problems associated with sedentary behavior, highlighting the importance of creating supportive work environments.
Objective of The Study
Our survey aims to evaluate the practice of PA among the paramedical staff at Ibn Rochd University Hospital in Casablanca, identify constraints, and propose potential solutions.
Materials and Methods
A cross-sectional descriptive and analytical study conducted over 3 months, using the Global Physical Activity Questionnaire (GPAQ), analyzed with R, SPSS, and Epi-info software.
Results
Our study included 302 participants, the majority (72.2%) being nurses. The average age was 34.65 years ± 9.3 years (range 20-61 years) with a female-to-male sex ratio of 2.43. Most participants (56.57%) had a normal body mass index, 37.72% were overweight, and 6% were obese. The most common medical histories were diabetes (12%), dyslipidemia (10.5%), and hypertension (10.3%). Furthermore, 70.86% of participants engage in physical activity as part of their work, 70.86% during commuting, and 37.08% engage in recreational physical activity. The most frequent barriers were family (45.69%) and professional (42.05%) responsibilities. The study found a statistically significant association between physical activity and personal history of diabetes and dyslipidemia, the number of working days per week, and professional seniority.
Conclusion
Although the majority of participants were physically active, work conditions should be improved to overcome barriers preventing regular physical activity.

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EP954

JOINT2505

Relationship of iodine concentration in urine with muscle mass and reaction speed in young adults

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Bernard Courtois discovered iodine in 1811 while digesting algae, which resulted in the emission of purple vapor. Bernard Courtois identified iodine within the thyroid gland in 1895 and established in 1917 that iodine deficiency leads to thyroid gland enlargement. The kidneys eliminate over 90% of iodine. The study of iodine levels in twenty-four-hour urine, measured in µg per day, is acknowledged as an optimal approach for assessing the body's iodine status. This study aimed to investigate the dietary consumption of iodine and the urinary iodine content in young individuals. The study aimed to explore the correlation between urinary iodine content, muscle mass, and the speed of muscular response. Seventy participants aged 18 to 24 were involved, comprising 35 males and 35 females. The exclusion criteria included confirmed thyroid illness and disorders of iodine metabolism. The morning urine was tested, dietary iodine intake was evaluated, and muscle mass and response time were measured. The median iodine concentration in urine was 120.77 µg/l,and the estimated iodine consumption was 624.66 µg. The median muscle tissue percentage is 32.55%, while the median muscle reaction speed is 274.5 ms. The correlation between urinary iodine levels, muscle tissue (%), and muscle reaction speed was assessed. A notable, negative, and modest association between urinary iodine content and muscle reaction speed was identified (Rho = -0.289). Other relationships lack significance. The projected dietary iodine consumption of participants in this study exceeds the reference values established by the World Health Organization. The iodine concentration in the urine of the individuals participating in this study is within the reference levels. There is no correlation between the iodine concentration in urine and muscle mass among the studied population. The iodine concentration in urine within the studied population exhibits a substantial, negative, and modest correlation with reaction speed.

Key Words
iodine, muscles, time reactions.
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EP955

JOINT2881

Management of obesity and diabetes mellitus type 2 in psoriatic arthritis

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Psoriatic arthritis may be accompanied by psoriasis and is known to be associated with metabolic syndrome and obesity. Diabetes mellitus type 2 may also be observed. Psoriatic arthritis and psoriasis are currently successfully managed by the administration of biological agents. Obesity may necessitate dose modification in the case of treatment with biological agents. Additionally, psoriatic arthritis may lead to mobility limitation. Obesity may further limit mobility. Therefore, the successful management of obesity in patients with psoriatic arthritis is critical. The aim was to present a cohort of patients suffering from psoriatic arthritis, florid psoriasis, metabolic syndrome and obesity who were successfully managed by the administration of GLP-1 receptor agonists. A cohort of 6 patients, 2 female and 4 male, suffering from psoriatic arthritis and florid psoriasis, aged 38-56 years, is presented. Patients had overt metabolic syndrome with obesity and diabetes mellitus type 2. All patients received metformin when entering the study. GLP-1 receptor agonists were administered to these patients for a period of 6 months. The administration of GLP-1 receptor agonists to this group of patients suffering from psoriatic arthritis, florid psoriasis and obesity led to weight loss of 1.2 – 8.2 kg. In addition, psoriasis lesions improved. Blood glucose levels also improved. GLP-1 receptor agonists were subsequently administered for 6 more months to all patients. No significant adverse events were noted. In particular, the administration of GLP-1 receptor agonists in patients on treatment with biological agents seemed to improve quality of life. Obesity in the context of metabolic syndrome may complicate psoriatic arthritis and psoriasis. The successful management of obesity in these patients is critical as it improves mobility and prevents disability deterioration. GLP-1 receptor agonists appear ideal for the management of obesity and diabetes mellitus type 2 in patients with psoriatic arthritis.

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EP956

JOINT3631

Congenital hyperinsulinism: first 18F-DOPA PET/CT scan performed in kazakhstan

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Introduction
Congenital hyperinsulinism (CHI) is a rare but serious cause of persistent hypoglycemia in neonates and infants.
Case Report
This case report describes the diagnosis of CHI in a 1-month-old girl in Kazakhstan, marking the country's first use of an 18F-DOPA PET/CT scan for this condition. The patient was admitted to the endocrine unit with severe, persistent hypoglycemia and underwent further investigation. Historically, CHI diagnoses in Kazakhstan were based primarily on clinical and laboratory findings, as genetic testing and PET/CT scans were not available due to the unavailability of the 18F-DOPA isotope. This case highlights the successful use of 18F-DOPA PET/CT imaging, which helped identify the diffuse variant of CHI. Despite initial treatment with diazoxide, the patient's condition remained unstable, but she showed improvement with subcutaneous octreotide injections, which effectively stabilized her blood sugar levels.
Conclusions
This case represents the first use of 18F-DOPA PET/CT imaging in Kazakhstan for diagnosing congenital hyperinsulinism and underscores the importance of expanding access to advanced diagnostic tools and therapies in managing rare and complex endocrine disorders. Timely diagnosis and appropriate treatment are critical to improving patient outcomes in such cases.

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EP957

JOINT3769

Uncommon side effects of uncommon drug: hydroxychloroquine-induced hypoglycaemia in a patient with multisystem lupus

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Introduction
Hydroxychloroquine (HCQ) is an antimalarial and immunomodulatory drug commonly used in the treatment of systemic lupus erythematosus (SLE) and other autoimmune conditions. It is generally well-tolerated, with known adverse effects including retinal toxicity, cardiomyopathy, and gastrointestinal symptoms. However, hypoglycemia is a rare but documented side effect of HCQ, potentially due to increased insulin sensitivity and enhanced glucose uptake by peripheral tissues. This case report presents a 28-year-old female with multisystem lupus who developed recurrent hypoglycemic episodes despite no prior history of diabetes. The recognition of HCQ-induced hypoglycemia, along with appropriate medication adjustments, highlights the importance of clinician awareness regarding this uncommon but significant adverse effect.
Case
A 28-year-old female with multisystem lupus, including cardiac, renal, respiratory, and skin involvement, was admitted with right iliac fossa pain and a background of lupus serositis. She was started on HCQ **200mg twice daily on 20/05/23**, reduced to **200mg once daily on 30/05/23**, and later increased back to **200mg twice daily** before being stopped on **06/06/23**. The patient exhibited repeated low capillary blood glucose (CBG) readings, particularly from 27/05/23 to 06/06/23, with several episodes below 2.5mmol/L. Severe hypoglycemic episodes: 01/06/23: CBG 1.7–1.8mmol/l04/06/23: CBG 1.3–2.8mmol/lDuring admission, she experienced recurrent hypoglycemic episodes, with capillary blood glucose (CBG) readings as low as **0.7 mmol/lon 06/06/23**, despite

remaining alert with cold hands. Arterial blood gas (ABG) glucose was normal at **8.9 mmol/L**, suggesting falsely low CBG readings due to poor perfusion.
Management and Outcome
The endocrinology team reviewed her on **31/05/23**, and it was suspected that HCQ contributed to the hypoglycemia. Despite ongoing corticosteroid treatment, her blood glucose remained intermittently low. After discontinuing HCQ on **06/06/23**, her glucose levels stabilized without further episodes of hypoglycemia.
Discussion
Unexplained hypoglycemia in non-diabetic patients on HCQ should prompt consideration of drug-induced causes. Falsely low CBG readings can occur due to Raynaud's phenomenon or poor peripheral perfusion, necessitating confirmation with serum glucose or ABG glucose levels. Discontinuation of HCQ led to resolution of hypoglycemia, highlighting the importance of early recognition and appropriate medication adjustment. Multidisciplinary involvement (rheumatology, endocrinology, renal, and cardiology teams) is crucial in complex cases with multisystem involvement.
Conclusion
This case highlights hydroxychloroquine-induced hypoglycemia as a rare but clinically relevant adverse effect. Clinicians should be aware of this possibility, particularly in patients without diabetes who develop unexplained hypoglycemia. Regular blood glucose monitoring and multidisciplinary management are essential for early recognition and intervention.

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EP958

JOINT1514
Adjustment of medication in patients with nasogastric tube or gastrostomy

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Introduction
The administration of drugs via a nasogastric tube or gastrostomy is a common practice in patients who are unable to take oral medications due to swallowing difficulties, neurological disorders, or other medical conditions. However, this route of administration presents several challenges, including the risk of tube obstruction, reduced drug efficacy, and potential drug-nutrient interactions. Some medications are not designed to be crushed or dissolved, which may alter their pharmacokinetics and pharmacodynamics, leading to suboptimal therapeutic effects or increased risk of adverse reactions. To address these issues, our hospital has implemented a structured, multidisciplinary evaluation process involving the Endocrinology/Nutrition and Pharmacy Departments. This collaboration aims to ensure that all medications administered via nasogastric tube or gastrostomy are appropriate, safe, and effective for each patient.
Objectives
This study evaluates the impact of a multidisciplinary team on medication reconciliation and adjustments for patients requiring drug administration via nasogastric tube or gastrostomy. It aims to identify common pharmaceutical interventions, determine frequently modified drug classes, and highlight the significance of interprofessional collaboration in patient care.
Material and Methods
We conducted a descriptive observational study from August 1, 2024, to December 15, 2024, documenting all interventions performed by the Endocrinology/Nutrition and Pharmacy team. The study included all hospitalized patients with a nasogastric tube or gastrostomy at discharge, as well as those attending nutrition consultations. The Pharmacy Department reviewed patient treatment plans with the patient or their caregivers, based on electronic prescription records. Necessary modifications were proposed to the Endocrinology team to ensure safe and effective drug administration. All changes were systematically recorded and analyzed.
Results
A total of 50 patients (52% men, 48% women) were included, with a mean age of 74 years. Medication modifications were required in 76% of cases, with a total of 66 changes recorded. The most frequent interventions included:.
- Modification of pharmaceutical form (31.3%).
- Adjustment of administration method (31.3%).
- Substitution with a therapeutic equivalent (16.4%).
- Discontinuation due to lack of evidence or incompatibility (13.4%).
- Prescribing separately (7.5%).

The most adjusted drug classes were proton pump inhibitors (12 patients), acetylsalicylic acid (9 patients), and levothyroxine (6 patients).
Conclusions
- Medication adjustments were necessary for 76% of patients with nasogastric tube or gastrostomy.
- Proton pump inhibitors and acetylsalicylic acid were the most frequently modified drug classes.
- This study underscores the importance of multidisciplinary collaboration in medication reconciliation to enhance patient safety and treatment efficacy.

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EP959

JOINT293
Therapeutic adherence to antihypertensive treatment in type 2 diabetes: barriers to achieving blood pressure targets

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Background
Blood pressure control is crucial in managing patients with type 2 diabetes mellitus (T2DM) to prevent cardiovascular complications. However, many patients face challenges in reaching the recommended blood pressure targets. Therapeutic adherence to antihypertensive treatments plays a key role in the effectiveness of treatment, yet it is often hindered by various barriers. This study explores the challenges faced by T2DM patients regarding adherence to antihypertensive treatments and its impact on achieving blood pressure targets.
Methods
This descriptive cross-sectional study was conducted on 80 patients with T2DM who had been under follow-up for more than six months at the Endocrinology department of Fattouma Bourguiba University Hospital in Monastir, Tunisia.
Results
Among the 80 patients, 65% were female, with a mean age of 57.9 years. Notably, 57.5% were being treated for hypertension. The mean systolic blood pressure was 140 mmHg [120-160], while the mean diastolic blood pressure was 90 mmHg [80-100]. In terms of antihypertensive therapy, 20% were on monotherapy, 17.5% on combination therapy, and 11.3% on triple therapy. However, 26.3% of patients did not achieve the recommended blood pressure targets. Therapeutic adherence was found to be influenced by several factors, which in turn impacted blood pressure control. These factors included therapeutic inertia (16.3%), which was the most prevalent issue, followed by patient negligence (2.5%) and cost-related barriers (5%). In addition, gastrointestinal intolerance (6.3%), forgetfulness (3.8%), and unavailability of the treatment (11.3%) were also identified as significant contributors.
Conclusion
Therapeutic adherence to antihypertensive treatment in T2DM patients is influenced by a variety of factors, many of which hinder the achievement of optimal blood pressure targets. Addressing these barriers is crucial for improving blood pressure control and reducing the risk of cardiovascular complications in this population.

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EP960

JOINT3451
Homozygous familial hypercholesterolemia: a rare case in a multiple pregnancy

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Introduction
Homozygous familial hypercholesterolemia is a rare condition, with an estimated prevalence of 1 in 1 million individuals. Cases in multiple pregnancies have been scarcely reported in the literature.
Case Report
We report the case of a 15-year-old boy with no prior history of hypercholesterolemia, hospitalized for acute coronary syndrome. He was born to parents in a second-degree consanguineous marriage. He has three 12-year-old sisters from a trizygotic trichorionic multiple pregnancy. On examination, he presented with tendinous xanthomas, planar xanthomas, xanthelasma, and gerontoxon. Laboratory tests revealed severe hypercholesterolemia, with an LDL cholesterol level of 23 mmol/L. The Dutch Lipid Clinic Network criteria confirmed a diagnosis of

definite familial hypercholesterolemia. Family screening identified hypercholesterolemia in several relatives, including one sister with a clinical and biological profile similar to the patient's. The other two sisters from the triplet pregnancy also had hypercholesterolemia, though at less severe levels. Genetic analysis within the family revealed a severe LDL receptor gene mutation in the homozygous form in the patient and his similarly affected sister. The same mutation was found in a heterozygous form in the parents and the other two sisters. LDL apheresis was recommended for the homozygous patient and his affected sister, while the rest of the family was started on statins and ezetimibe.

Discussion

Homozygous familial hypercholesterolemia leads to early-onset atherosclerosis and premature death, often in the second decade of life. The LDL receptor gene mutation identified in our patients is classified as severe, with homozygous individuals retaining less than 2% of functional LDL receptors. While novel therapies may offer promising results, their high cost limits accessibility in our country. In our setting, LDL apheresis remains the only feasible and effective treatment. This case is exceptional due to the presence of familial hypercholesterolemia in triplet sisters from a multiple pregnancy. The different genotypes observed among the sisters are explained by the trizygotic trichorionic nature of the pregnancy, with one sister being homozygous and the other two heterozygous.

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EP961

JOINT3743

A rare case of idiopathic ketotic hypoglycemia in a child from kazakhstan

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Introduction

Idiopathic ketotic hypoglycemia (IKH) is the most common cause of recurrent fasting hypoglycemia in young children. It is characterized by fasting-induced hypoglycemia with ketosis in the absence of identifiable endocrine or metabolic disorders. While IKH is often considered benign, it requires careful differentiation from other hypoglycemic conditions such as hyperinsulinism, adrenal insufficiency, and glycogen storage diseases. This case highlights a 4-year-old boy from Kazakhstan, focusing on diagnostic challenges, management, and the role of genetic testing.

Case presentation

We present the case of a 4-year-old boy admitted with recurrent early morning episodes of hypoglycemia (2.0–2.6 mmol/l)associated with lethargy and altered consciousness. These episodes had been occurring since the age of 2 and were unrelated to infections or prolonged fasting. Upon clinical evaluation, his growth parameters were normal (height 109 cm, weight 18.5 kg, BMI 15.15 kg/m^2, SDS -0.36). Laboratory findings during hypoglycemia revealed ketosis, elevated lactate (3.89 mmol/L), and low insulin (0.20 μIU/ml) and C-peptide (0.27 ng/ml) levels. Endocrinological workup ruled out hyperinsulinism, adrenal insufficiency, and growth hormone deficiency. Genetic testing (3B-EXOME, Proband) revealed no pathogenic variants, confirming the diagnosis of idiopathic ketotic hypoglycemia. Management included frequent meals, uncooked cornstarch supplementation, and education on emergency hypoglycemia management using oral glucose and glucagon.

Conclusion

IKH is a diagnosis of exclusion, requiring thorough evaluations to rule out metabolic and endocrine disorders. This case demonstrates the role of genetic testing in confirming the diagnosis and the importance of tailored dietary strategies and family education in preventing severe hypoglycemia. A multidisciplinary approach is essential for effective management of this rare condition. Future research should focus on identifying potential genetic or metabolic biomarkers that could aid in earlier and more precise diagnosis. Additionally, investigating novel dietary or pharmacological interventions may help improve long-term management and prevent severe hypoglycemic episodes in affected children.

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EP962

JOINT3332

Relationship renin-angiotensin ratio with hypertension and disease duration in patients with type 2 diabetes mellitus

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Introduction

In patients with type 2 diabetes mellitus, an increase in arterial blood pressure usually contributes to the development of complications. In this paper, we will examine the effects of hyperglycemia and the renin-aldosterone system on renal dysfunction, as well as the impact of arterial blood pressure correction on quality of life. Aim: To study the relationship between renin and aldosterone with the course and complications of the disease in patients with type 2 diabetes mellitus.

Materials and Methods

Patients diagnosed with type 2 diabetes mellitus at the Republican Specialised Scientific Practical Medical Center of Endocrinology during 2022-2024 were included in the study. Among them, 51.25% were women, and 48.75% were men. The average age of male patients was 48.6 ± 2.54, and the average age of female patients was 53.41 ± 1.65. Normal arterial blood pressure was detected in 23 (28.75%) of them (NBP), while high arterial blood pressure was detected in 57 (71.25%) patients (HTN).

Results

The duration of the disease was found to be 5.5 ± 0.54 in patients with normal arterial blood pressure and 9.8 ± 0.5 ($P = 2.818$) in patients with high arterial blood pressure. HbA1C was found to be 10.89 ± 0.40 in NBP and 12 ± 0.4 ($P = 2$) in HTN. VLDL cholesterol was 1.08 ± 0.1 in NBP and 1.2 ± 0.06 ($P = 3.226$) in HTN. HDL cholesterol was 2.2 ± 0.23 in NBP and 1.4 ± 0.12 ($P = 3.314$) in HTN. Renin was found to be 0.54 ± 0.11 in NBP and 0.54 ± 0.1 ($P = 12.635$) in HTN. Aldosterone was 0.92 ± 0.06 in NBP and 0.9 ± 0.04 ($P = 2.095$) in HTN. When patients compared by disease duration Renin aldosterone ratio were decreased probably due to Diabetic Nephropathy.

Conclusions

In patients with type 2 diabetes mellitus, renin and angiotensin were found to be high relative to arterial blood pressure. It was determined that as the duration of the disease increased, these indicators decreased, which was related to the functional state of the kidneys.

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EP963

JOINT2757

Interim analysis of equol producer prevalence in the isoflavone study

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Background

Polycystic ovary syndrome (PCOS) is a common endocrine condition of heterogeneous origin, characterized by hyperandrogenism, oligo-/amenorrhoea, and/or polycystic ovarian morphology. PCOS phenotypes are associated with several comorbidities including depression, obesity and insulin resistance. Isoflavones are plant-derived hormones (phytoestrogens) with similar chemical structure and properties like estrogens. Soy products, among other nutrients, contain clinically relevant concentrations of isoflavones such as genistein and daidzein. The ability to derive health benefits from a soy-based nutrition is thought to depend on the production of the isoflavone metabolite equol, based on specific human gut bacteria. Equol has been shown to bind to estrogen-receptors alpha and beta and to have anti-androgenic, anti-cancer and anti-inflammatory effects and is therefore of particular interest for women with PCOS. However, in Western countries, only 25-30% of the population are so-called "equol-producers" and have the appropriate bacteria to convert daidzein to equol. The prevalence in women with PCOS was reported to be even lower. The present interim analysis of the Isoflavone Study aimed to assess potential differences in the prevalence of equol-producers among women with PCOS, healthy women and healthy men.

Methods

After a one-day consumption of 2x200 ml soy drink, equol and daidzein concentrations in the morning urine of the following day were measured by gas chromatography and mass spectrometry (GC-MS) in the women enrolled with PCOS ($n = 33$), in control women ($n = 13$) and men ($n = 45$). A cut-off value for the log10-transformed urinary equol:daidzein ratio of -1.75 was used to define equol production.

Results
Prevalence of equol-producers was 38.5% in the PCOS-group, 40.0% in healthy women and 27.9% in men. The frequency of equol producers did not differ across the groups, nor between women with PCOS and the control group, nor between women with PCOS and men. Equol-daidzein ratio was -1.9 $\pm$ 0.8 in women with PCOS, -1.8 $\pm$ 0.8 in the control group and -2.0 $\pm$ 0.8 in the group of men.
Conclusion
Equol producer prevalence in Western countries is around 30-40%. In our interim analysis, we found no significant differences among women with PCOS, healthy women, and healthy men. Similarly, the equol-daidzein ratio did not show meaningful variation between the groups. However, due to the limited sample size, these results should be interpreted with caution. A final analysis after full recruitment is necessary to confirm these first findings and to provide more robust conclusions.

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EP964

JOINT3903
Microbiota and obesity: current state and outlook
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Introduction
The obesity, a multifactorial disease, is arousing growing interest in the role of the gut microbiota. The aim of this study is to explore the complex links between the composition of the microbiota and the development of obesity. Through a literature review, we will examine the various proposed hypotheses, the physiological mechanisms involved, and the therapeutic prospects offered by modulation of the microbiota.
Methods
To carry out this work, we carried out a quite wide-ranging bibliographical search in the following databases: PubMed, Science Direct and Google Scholar to identify the most relevant articles. After excluding duplicates, we retained 26 appropriate articles.
Results
Obesity is associated with changes in the composition of the gut microbiota, essentially a higher Bacteroidetes/Firmicutes ratio, which may influence energy storage, inflammation and insulin resistance. High-fat diets can alter microbiota, leading to increased intestinal permability which contribute to low-grade inflammation and obesity. Antibiotic treatment of mice reduced metabolic endotoxemia and improved glucose tolerance, body weight and markers of inflammation. The intestinal microbiota affects host metabolism through various mechanisms, including colonic fermentation of non-digestible fibres and modulation of the endocannabinoid system. Strategies aimed at the composition of microbiota, such as prebiotics and probiotics, may offer potential interventions for the management of obesity. In addition, factors such as mode of birth, breastfeeding can influence the early development of the infantil microbiota, which may have an impact on future metabolic health.
Conclusion
These results are encouraging, but many challenges remain. The complexity of gut microbiota, the uniqueness of responses and the eventual interactions with other factors make it particularly challenging to put in place a large-scale personalised therapeutic strategies.

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EP965

JOINT2322
Eating habits and dietetic management of obesity in children and adolescent
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Introduction
dietary management is the most important step in the childhood obesity care. The aim of this study is to analyze dietary habits in a pediatric population who are obese and to evaluate the effectiveness and adherence of patients to the prescribed diet at 6 months of follow-up.
Methods
We carried out a cross-sectional study, which concerns obese children who are referred to the endocrinology department in Hédi Chaker hospital in Sfax. Then we have assessed the weight status after six months under regime. A sample of 84 children who are overweight and obese were recruited into the study. All the children included in our study were put under diet adapted according to the age during 6 months.
Results
Eighty-four children, forty-four boys and forty girls. The average age was eleven point eighty-three years. The average BMI was thirty-one point fifty-five kg/m^2 (twenty-one to forty-seven), the average BMI Z score was seven point nine SD (two point seven to sixteen). The daily calorie intake was two thousand four hundred eighty-four kcal per day. This weight loss was not statistically significant. After six months of follow-up: good adherence was observed in twenty-three percent. The average BMI was twenty-nine point six kg/m^2, the average BMI Z score was seven point five SD. Half of our patients have decreased their BMI Z-score. The prescribed diet was more effective in boys than in girls, in patients without a family history of obesity, in patients who were physically active, in patients who are overweight without obesity, and in those who were more adherent. But this efficiency remains statistically insignificant.
Conclusion
This study showed that there is a positive impact of dietary management on weight reduction in children. Other studies have shown the value of dietetic management on childhood obesity care particularly through multidisciplinary interventions.

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EP966

JOINT3995
Floating-harbor syndrome in a 39-year-old patient: description of a rare obesity clinical case
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Floating-Harbor syndrome (FHS) is an extremely rare autosomal dominant genetic disorder with specific features, including facial dysmorphia, skeletal abnormalities (delayed bone age), and intellectual, speech, and systemic impairments. It is caused by mutations in the SNF-2-related CREBBP activator protein (SRCAP) gene. As of 2021, over 100 cases of FHS have been reported globally, with the first case described in 1973. Hyperphagia is not typical and GH treatment has limited effects on short stature in FHS. Clinical case: Patient E., 39 years old, presented with complaints of obesity that is difficult to manage and increased appetite. Her medical history indicates that she was born following a normal pregnancy and had normal weight and growth parameters at birth. Neonatal hypotonia was absent, and the sucking reflex was normal. However, from an early age, she exhibited delays of growth, intellectual and speech development, learning difficulties, bilateral sensorineural hearing loss, hyperphagia, and progressive weight gain. She received no GH treatment. Notably, she showed persistent obsessions related to food-seeking behavior. At the age of 25, Prader-Willi syndrome was suspected, but no molecular genetic testing was performed. She also underwent surgery for a paraovarian cyst and cholelithiasis. At the age of 37 she suffered an acute ischemic stroke. Upon examination, notable phenotypic features were observed: acromicria, microcephaly, short stature (height 150 cm, weight 92 kg), broad deep-set eyes, a large bulbous nose, short neck, clinodactyly V and a cleft upper lip. No respiratory disturbances, sleep apnea, IGF1 or thyroid test abnormalities were revealed. Impaired glucose tolerance, mild liver enzymes elevation due to NAFLD and hyperuricemia were identified. Given the absence of convincing data characteristic of Prader-Willi syndrome, along with the unclear clinical picture, patient history, and her phenotypic characteristics, FHS was suspected. This diagnosis was confirmed by genetics - whole-exome sequencing, which revealed a heterozygous variant in the SRCAP gene (c.7330C>T). Following treatment with GLP-1 agonists, the patient experienced a reduction in body mass by 13% from baseline, with control of glucose metabolism and other metabolic disturbances and hyperphagia reduction.
Conclusion
A diagnosis of FHS is suspected when typical clinical findings are present and can be confirmed through SRCAP gene sequencing. We report a late diagnosis case masked by a hyperphagia leading to morbid obesity, although it is treatable with GLP-1-analoges. It is important to remember that obesity is not only a symptom but also a potential indicator of complex genetic disorders.

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EP967

JOINT2163

Real-world effect of tirzepatide: a prospective observational study

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Introduction
Tirzepatide is a novel dual GLP-1 and GIP receptor agonist that has demonstrated promising results in managing obesity and type 2 diabetes. By targeting both insulin secretion and glucagon suppression, tirzepatide helps improve metabolic control and reduce body weight, making it an exciting therapeutic option for patients with high body mass index (BMI) and related comorbidities.
Objective
To assess the real-world effects of tirzepatide (5 mg dose) on weight, LDL cholesterol, and basal glucose levels in patients with a mean BMI of 45.7.
Study Design
Prospective observational study.
- **Participants**: 20 subjects (4 males).
- **Mean Age**: 49.7 years.
- **Mean BMI**: 45.7.

Intervention.
- Tirzepatide 5 mg administered for 3 months.

Results
- **Mean Weight Reduction**: 9.9 kg.
- **Mean LDL Reduction**: 23.3 mg/dl.
- **Mean Basal Glucose Reduction**: 10.3 mg/dl.

Conclusion
In this real-world observational study, tirzepatide demonstrated significant reductions in weight, LDL cholesterol, and basal glucose levels after 3 months of treatment.

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EP968

JOINT410

Nutritional profile of obese adolescents

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Background
Adolescent obesity has become a critical issue globally, with diet playing a pivotal role in its development. Despite the increasing prevalence of obesity in this age group, the dietary habits contributing to this condition remain underexplored. Understanding these dietary habits is crucial to addressing the root causes of obesity in adolescents. This study aims to highlight the dietary profile of adolescents with obesity.
Methods
A retrospective study involved obese adolescents, followed at the Endocrinology Department of Sfax, Tunisia, for obesity management. A dietary survey was conducted during a nutritional counseling session. The survey data were analyzed using the "BILNUT" software to obtain nutritional information.
Results
The study population consisted of 58 adolescents with a sex ratio of 0.49. The mean age of the patients was 15.4 $\pm$ 2 years. The total energy intake was 2475.9 kcal/day $\pm$ 686, with carbohydrate intake averaging 54.3% $\pm$ 5.2, showing no significant gender difference ($P = 0.091$). Simple sugar intake was 3.7% $\pm$ 2.6. Among patients, 44.8% had adequate carbohydrate intake, 12.1% had insufficient intake, and 43.1% had excessive intake. Lipid intake was 34.8% $\pm$ 4.8, with no significant difference between genders ($P = 0.070$), except for polyunsaturated fatty acids ($P = 0.018$). Saturated fatty acids accounted for 7.8% $\pm$ 1.5, while monounsaturated fats made up 16.4% $\pm$ 4.5. Regarding fat intake, 51.7% had normal levels, 8.6% had insufficient intake, and 39.7% had excessive intake. Protein intake was 61.5% $\pm$ 20.8, but only 22.4% of patients had a normal protein intake, while 77.6% followed a protein-poor diet. Protein intake was not significantly associated with gender ($P = 0.771$), nor was cholesterol intake ($P = 0.159$). Cholesterol intake was normal in 10.3%, insufficient in 55.2%, and excessive in 34.5%. Calcium intake (<800 mg/day) was insufficient in 94.8% of cases, while iron intake was deficient in 94.7% of boys and in all girls. The average fiber intake was 15.9 $\pm$ 6.3 g/day. Boys had significantly higher fiber intake compared to girls ($P = 0.009$), and a fiber deficiency (<20 g/day) was found in 77.6% of cases. Finally, vitamin C intake averaged 60.3 mg/day $\pm$ 36.4, with no significant difference between genders ($P = 0.700$).
Conclusion
Analyzing the dietary profile of adolescents with obesity is essential for developing effective strategies to combat this growing public health challenge.

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EP969

JOINT415

Clinical profile of obese adolescents

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Background
Obesity among adolescents has become a growing public health concern worldwide. This condition not only affects physical health but also significantly impacts emotional well-being and social development. Adolescents with obesity face numerous challenges, including the risk of comorbidities that persist into adulthood. Despite the widespread recognition of obesity as a major health issue, there is limited understanding of its unique clinical profile in this age group. Therefore, it is crucial to examine the clinical features of obesity in adolescents.
Methods
This was a retrospective and analytical study involving obese adolescents, followed at the Endocrinology Department of Sfax, Tunisia, for obesity management between 2019 and 2023. Obesity was defined based on the reference charts from the National Nutrition and Health Program: Grade 1 obesity: body mass index (BMI) between the curve corresponding to a BMI of 25 kg/m^2 at 18 years and the curve corresponding to a BMI of 30 kg/m^2 at 18 years. Grade 2 obesity: BMI above the curve corresponding to a BMI of 30 kg/m^2 at 18 years. A professional body composition analyzer was used to measure weight, fat mass, lean mass, and body water content.
Results
The study population consisted of 58 adolescents with a sex ratio of 0.49. The mean age of the patients was 15.4 $\pm$ 2 years. The average age of obesity onset was 8.4 $\pm$ 4 years. The most common triggering factors for obesity were dietary habit changes (44.8%) and puberty (34.5%). A progressive worsening of obesity was observed in 82.2% of cases, while 17.2% had a rapid progression. The adolescents had a mean BMI of 34.2 $\pm$ 6.2 kg/m^2, with no significant difference between genders ($P = 0.169$). Obesity distribution showed that 22.4% of adolescents had grade 1 obesity, while 77.6% had grade 2 obesity. Obesity appeared to be more severe among girls ($P = 0.243$). Waist circumference also showed no significant difference between genders ($P = 0.832$). Fat mass was significantly higher in girls ($P = 0.021$), whereas lean mass and water content were higher in boys ($P = 0.013$ and $P = 0.012$, respectively). The impact of obesity was gonadal in 15.5%, metabolic in 13.8%, respiratory in 8.6%, psychiatric in 6.9%, osteo-articular in 3.4%, and cardiovascular in 3.4%.
Conclusion
Understanding the clinical profile of obesity in adolescents is essential for developing targeted interventions to address this growing public health issue.

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EP970

JOINT416

Biological findings of obese adolescents

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Background
Adolescent obesity has become a rising global public health issue, affecting not only physical health but also influencing emotional well-being and social development. While obesity is widely recognized as a major health concern, the biological profile of this condition in adolescents remain underexplored. Therefore, it is essential to investigate the biological aspects of obesity in this age group to enhance understanding and improve prevention and management strategies.
Methods
A retrospective analytical study included obese adolescents treated for obesity at the Endocrinology Department of Sfax, Tunisia, between 2019 and 2023. Obesity was defined according to the reference charts of the National Nutrition and Health Program.

Results
The study population consisted of 58 adolescents with a sex ratio of 0.49. The mean age of the patients was 15.4 ± 2 years. Prediabetes was observed in 5 cases (8.6%), while diabetes was found in only 1 case (1.7%). The mean glycated hemoglobin and glucose levels were 5.3% ± 0.5 and 4.6 mmol/l± 0.8, respectively. Hypertriglyceridemia, with a mean of 1.5 mmol/l± 3, was found in 6 cases (10.3%), while hypercholesterolemia occurred in 4 cases (6.9%) with a mean of 4 mmol/l± 0.7. HypoHDLemia was noted in 39 cases (67.2%) with an average of 1.1 mmol/l± 0.3. HyperLDLemia was not observed in any cases, with the mean level being 2.5 mmol/l± 0.6. The mean uric acid level was 311.7 µmol/l± 79.5. We identified a single case of negative Dexamethasone suppression test (1.7%) and 6 cases (10.3%) with elevated TSH levels. The average calcium level was 2.35 mmol/l± 0.12. Sodium and potassium intake averaged 138.8 mmol/l± 2.4 and 4 mmol/l± 0.4, respectively. The mean creatinine level was 49.5 µmol/l± 8.3.
Conclusion
Gaining insight into the biological profile of obesity in adolescents is crucial for designing targeted interventions to combat this escalating public health concern.
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EP971

JOINT2473
Metabolic risk factors in overweight women with polycystic ovary syndrome: results of a tunisian study
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Background
Given the growing evidence linking Polycystic Ovary Syndrome (PCOS) with metabolic risk factors, understanding the specific metabolic profiles in overweight women with PCOS is essential for developing effective management strategies [1]. Therefore, the aim of our study was to assess metabolic risk factors in a group of overweight women with PCOS.
Methods
This was a descriptive, cross-sectional, and retrospective case-control study involving 61 overweight women within the reproductive age range, divided into two groups: 31 women with PCOS and 30 women without PCOS. The groups were matched for age and body mass index (BMI). Clinical and biological data were extracted from the patients' medical records.
Results
The mean age at diagnosis of PCOS was 23.4±7.3 years, with extremes ranging from 14 to 39 years. Hirsutism, alopecia, and acne were observed in 78%, 60%, and 45% of PCOS patients, respectively. Biological hyperandrogenism was found in 66% of the patients with PCOS. Regarding menstrual cycle disorders, amenorrhea, oligomenorrhea, and infertility were observed in 54%, 47%, and 19% of cases, respectively. The majority of patients with PCOS had phenotype A (81%), while 19% had phenotype C. Among the patients with PCOS, 44% were treated with dydrogesterone and 28% were on metformin. Our study revealed a significantly higher frequency of type 2 diabetes in patients with PCOS compared to the control group (97% vs 18%; $P = 0.0001$). However, fasting blood glucose, HbA1c, and the HOMA index were comparable between the two groups ($P = 0.06$, $P = 0.13$, and $P = 0.71$, respectively). Women with PCOS had a significantly higher frequency of hypertension (90% vs 19%; $P = 0.0001$), metabolic syndrome (97% vs 54%; $P = 0.0001$) and dyslipidemia (90% vs 54%; $P = 0.002$) compared to the control group. The lipid profile parameters were similar in the two groups.
Conclusion
Our findings emphasize the need for targeted metabolic risk management in overweight women with PCOS. Early identification and intervention are crucial to reducing the long-term health risks associated with this condition.
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EP972

JOINT2871
Hemoglobin levels as a potential predictor of sarcopenia in obese patients
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Background
As a biomarker for anemia and nutritional status, hemoglobin (Hb) may also influence the progression of sarcopenia. Although research on this topic remains limited, insufficient Hb levels can impair oxygen delivery to skeletal muscles, potentially affecting muscle strength and function. This study aimed to evaluate the impact of Hb levels on sarcopenia in obese patients.
Methods
This is a cross-sectional study conducted on 100 obese patients. Body composition was assessed using SECA MBCA 515 bioimpedance. Sarcopenic obesity (SO) was defined in accordance with the EASO-ESPEN consensus statement [1].
Results
The mean age was 44.42±13.25 years with a male-to-female ratio of 0.11. The mean BMI was 40.07 ± 5.77 kg/m^2, with almost half of the group categorized as morbidly obese (48%). Abdominal obesity was found in the entire population with a mean waist circumference of 116.51 ± 16.62 cm. The mean hemoglobin levels were 15.14 ± 1.28 g/dl in male patients and 13.11 ± 1.30 g/dl in female patients. Anemia was present in 18% of the participants, and sarcopenia was diagnosed in 19% of the study population. Our study found that hemoglobin levels were positively correlated with skeletal muscle mass ($r = 0.38$; $P < 0.001$), appendicular muscle mass ($r = 0.37$; $P < 0.001$), and muscle strength ($r = 0.23$; $P = 0.019$). Patients with anemia had significantly lower skeletal muscle mass (24.34 ± 3.19 kg vs. 27.38 ± 7.06 kg; $P = 0.007$) and appendicular muscle mass (14.71 ± 1.93 kg vs. 16.47 ± 4.34 kg; $P = 0.015$). Anemia was more frequent in patients with sarcopenia (21.1% vs. 17.3%), though this difference was not statistically significant.
Conclusion
The results of our study suggest that hemoglobin levels may be an important factor in the development of sarcopenia in obese patients, highlighting the need for further research in larger cohorts.
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EP973

JOINT1269
The impact of obesity on the clinical manifestations of early menopause in women
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Aim
To investigate the influence of different degrees of excess weight on the progression of menopause.
Materials and Methods
The study involved 278 women in the menopausal period, aged 40 to 46 years. The main group (MG) consisted of 218 women with varying degrees of overweight and obesity. The control group (CG) included 60 women with normal body weight and a waist circumference of 80 cm. The severity of climacteric syndrome was assessed using the Greene Climacteric Scale.
Results
The study found that among 218 women in the main group, 62 (28.4%) were classified as overweight (BMI 25.0–29.9 kg/m^2), while the rest had varying degrees of obesity (BMI 30.0–41.2 kg/m^2). Notably, 72.0% of overweight women reported gaining weight after the age of 36. The prevalence of comorbid

conditions was high among individuals with excess body weight, with arterial hypertension observed in 36% of the main group, ischemic heart disease in 22%, chronic venous insufficiency in 10%, and arrhythmias in 10%. Additionally, the occurrence of gynecological disorders correlated with BMI levels. Among overweight women, 58.4% had conditions such as uterine fibroids and adenomyosis, whereas these pathologies were found in only 13.8% of the control group.
Conclusion
In summary, increased central fat accumulation, reduced peripheral fat storage, and ectopic fat deposition contribute to cardiometabolic abnormalities, resulting in a higher prevalence of metabolic syndrome after menopause.

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EP974

JOINT2111

Management of obesity in children and young adolescents with type 2 diabetes

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Introduction
Type 2 diabetes (T2D) is defined as hyperglycemia caused by insulin resistance, it was the prerogative of the adult subject but its frequency has increased significantly in recent decades in parallel with the increase in the rate of obesity. Management is either non-pharmacological involving diet management and physical activity (cases of diagnosis made in the context of screening or without metabolic decompensation), or pharmacological (in association with the above mentioned measures) with metformin and sometimes insulin therapy in the first weeks to compensate for insulinopenia (cases of metabolic decompensation).
Material and Methods
In our specialized pediatric endocrinology and diabetology consultation, we collected 34 children and young adolescents with T2D,.
Result
Among our patients, 26 of them have at least 2 years of evolution, 6 are on dietary measures only, 4 are on insulins with metformin and 16 are on metformin only. Patients who have remained overweight are on insulin with poor glycemic control, which further shows the role of obesity in insulin resistance.
Conclusions
The rate of T2D and obesity in children has increased in parallel, diet and weight management is a necessary condition for having a good glycemic balance.

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EP975

JOINT1111

Association between overweight/obesity and iron deficiency among non-pregnant women of reproductive age in yerevan, armenia

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Introduction
In 2022, 1 in 8 individuals globally lived with obesity. Approximately 2.5 billion adults aged 18 years and older were classified as overweight, including over 890 million adults with obesity. This equates to 43% of adults aged 18 years and over (43% of men and 44% of women). Obesity prevalence is notably higher in women. Iron deficiency anemia (IDA) is among the most common medical conditions worldwide, affecting approximately 29% of females of reproductive age, with iron deficiency accounting for 50% of cases. Iron is vital for hemoglobin synthesis, DNA synthesis mitochondrial energy production. Beyond anemia, iron deficiency (ID) can lead to significant health consequences, such as reduced physical and cognitive performance, particularly in non-pregnant females.
Methods
This cross-sectional study analyzed data from 343 non-pregnant women aged 15–45 years who visited the Wigmore Clinic endocrinology department between March 1, 2024, and December 30, 2024. The inclusion criteria included a body mass index (BMI) of 18–40 kg/m^2 and the absence of pregnancy, lactation, or specific chronic conditions (e.g., hematological, gastrointestinal, or gynecological diseases). Iron deficiency anemia (IDA) and iron deficiency (ID) were assessed through hemoglobin (Hb) and ferritin levels. Descriptive statistics were calculated for continuous and categorical variables. The participants' BMI ranged from 18 to 42 kg/m^2 (mean = 26.22, SD = 5.24). Hb levels ranged from 88 to 140 g/l(mean = 124.70, SD = 8.73), and ferritin levels ranged from 1 to 72 ng/ml (mean = 24.79, SD = 15.30). Most participants resided in urban areas (81.9%), were employed (64.4%), and had higher education levels (52.2%). Menstrual cycle abnormalities were reported by 8.5% of participants. BMI classifications included 38.2% normal weight, 38.2% overweight, and 23.6% obese. Ferritin categorization indicated 35.6% normal levels, 30.0% moderate ID, and 34.4% severe ID.
Results
The correlation between BMI and Hb was negligible ($r = -0.001$, $P = 0.987$), indicating no statistically significant relationship. However, a weak positive correlation was observed between BMI and ferritin levels ($r = 0.114$, $P = 0.035$) , suggesting a slight increase in ferritin levels with rising BMI. This relationship, though weak, was statistically significant.
Conclusions
The findings highlight a statistically significant but weak association between BMI and ferritin levels, whereas no relationship was observed between BMI and Hb levels. These results underscore the importance of monitoring iron status in women of reproductive age, particularly in those with elevated BMI, to mitigate potential health consequences.

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EP976

JOINT644

Height loss with age in adults with prader willi syndrome may result in artifactual increases in BMI

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Modest decreases in height occur during normal aging, but usually have only a minimal effect on BMI (body mass index). Height loss may result from vertebral fractures, disc collapse, kyphosis, and/or scoliosis. Accurate determinations of BMI values are essential for prescribing diet and exercise regimens especially for adults with Prader-Willi syndrome (PWS). At the time of routine yearly visits to our national multidisciplinary PWS clinic, we measured standing heights in 28 PWS adults over a duration 11.3±3.4 (range 5.1 to 16.2) years. Most had no or only minimal height loss, but in four individuals measured heights decreased gradually over 7.9 to 16.1 years by 6.2, 6.6, 7.0, and 6.3 cm, respectively. Height loss for these four patients resulted in artifactually high BMI values compared to values based on the previously measured tallest heights. BMI values calculated by using the most recent heights compared to tallest height measurements were 41.4 vs 37.9, 31.9 vs 29.1, 31.0 vs 28.5, and 27.2 vs 24.8 kg/m^2, respectively. Adjustment of BMI for the tallest measured heights resulted in redefining obesity class from class III to class II in one individual, from obesity class I to "overweight" in two patients, and from overweight to normal in one man. Failure to recognize that an increase in BMI may be due to height loss rather than weight gain could lead to inappropriate recommendations for reduction in caloric intake. Even minor changes in diet restrictions can affect mood and behavior in individuals with PWS. Recognition of height loss as a contributing factor to BMI calculations is important for clinical studies evaluating effects of life-style changes and medical interventions for obesity.

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EP977

JOINT164

The Relationship between morning blood pressure surge, serum antimüllerian hormone level and homa-ir score in patients with polycystic ovary syndrome

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Aim
In our study, we aimed to investigate the relationship between antimüllerian hormone (AMH) and HOMA-IR score, which are known to be increased in patients with polycystic ovary syndrome (PCOS), and morning blood pressure surge (MBPS), and whether these measurements are a marker for early CVD risk in patients with PCOS.
Methods
40 patients aged between 18 and 65 years with hypertension (HT) and PCOS, 40 patients with HT but without PCOS, and 40 people representing the healthy control group were included in the study. All patients underwent ambulatory blood pressure measurement for 24 hours and MBPS was calculated.
Results
The study groups were divided into three groups as healthy control group (group 1), patient group with HT without PCOS (group 2) and patient group with HT and PCOS (group 3). MBPS was found to be statistically significantly higher in group 3. In linear regression analysis, AMH and HOMA-IR levels were found to be independently associated with MBPS. In patients with PCOS, AMH and HOMA-IR levels were significantly higher in the group with MBPS >25 mmHg.
Conclusions
Early diagnosis and treatment of PCOS and accompanying comorbidities can halt the progression of cardiac disorders and reduce cardiovascular mortality and morbidity. AMH level, HOMA-IR score and MBPS measurement can be used in early detection and prediction of CVD in PCOS patients.
Keywords
Antimüllerian hormone, HOMA-IR score, Insulin resistance, Polycystic ovary syndrome, Morning blood pressure surge.
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EP978

JOINT3525

A case with porphyria presenting with episodic hypertension and tachycardia mimicking pheochromocytoma

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Introduction
The most common symptom of hypertension (HT) in childhood is headache, frequently accompanied by tachycardia. In infants and toddlers, it is predominantly caused by cardiac and renal pathologies, whereas essential HT is more common in adolescents. Among endocrinological disorders, pheochromocytoma is the leading cause of episodic HT. This case report highlights a rare condition that warrants consideration in the differential diagnosis of pheochromocytoma.
Case
A 17-year-old female presented with headache, palpitations and presyncope. Her systolic blood pressure was 170/100 mm Hg and pulse rate 135/minute. She responded to amlodipine but experienced recurrence during follow-up. Renal ultrasonography, renal doppler USG, plasma renin activity, angiotensin and aldosterone levels were normal. Investigating pheochromocytoma, urinary 3-Methoxytyramine levels were found to be elevated in two measurements, 174 μg/g and 533 μg/g. MIBG scintigraphy revealed subcentimetric lymph node involvement in the right paraaortic area. Clinical monitoring was deemed adequate, as the area was unsuitable for biopsy and not fully consistent with clinical findings. During follow-up, as hypertension and tachycardia persisted, the patient underwent PET-CT with gadolinium, showing no uptake. Thoracic and abdominal angiography were normal, but conventional angiography revealed contour irregularities and occlusions in distal branches of bilateral renal arteries, potentially indicating vasculitis. However, vasculitis was not considered due to lack of constitutional or cutaneous findings, no pulse and blood pressure discrepancy between extremities, and negative acute phase reactants and autoantibodies. Ramipril and metoprolol were respectively added to her treatment to control blood pressure. As hypertensive episodes continued and no benefit was observed, medications were gradually tapered. Urinary porphyria metabolite levels were analyzed, with porphobilinogen, delta-aminolevulinic acid and coproporphyrinogen III levels high in both attacks and attack-free periods. Intravenous dextrose infusion during a hypertensive episode reduced blood pressure and improved symptoms. A peripheral blood sample was obtained for genetic analysis to screen for porphyria-associated variations, with results pending.
Conclusion
While porphyria is characterized by cutaneous lesions, anemia, hepatic impairment, and neuropathies, some patients may present solely with tachycardia, HT, and presyncope episodes due to autonomic dysfunction. Although this clinical presentation resembles pheochromocytoma, paradoxical responses may be observed due to the precipitating effect of calcium channel blockers and angiotensin converting enzyme inhibitors on porphyria attacks. Intravenous administration of hemin or glucose during an acute episode provides significant clinical improvement. Porphyria should be considered in the differential diagnosis when encountering episodic hypertension, tachycardia, emesis, and presyncope.
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EP979

JOINT545

Relevance of growth differentiation factor 15 in weight management

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Introduction
Growth differentiation factor 15 (GDF15), a peptide hormone produced by the placenta during pregnancy but also by several other organs (e.g., prostate, bladder, kidney, pancreas, and endometrium), is a member of the transforming growth factor-β superfamily. The gene of GDF15 is located on chromosome 19. The mature GDF15 has 112 amino acids and binds to glial cell-derived neurotrophic factor family receptor alpha-like. GDF15 is involved in the maintenance of homeostasis and plays an important role in several pathological conditions (e.g., cardiovascular diseases, autoimmunity, obesity, diabetes, and cancer). This review presents an update on the relevance of GDF15 in weight management in patients with obesity, heart failure, and cancer.
Methods
A systematic search of literature was conducted using the search terms growth differentiation factor 15, pregnancy, heart failure, autoimmunity, anorexia, obesity, diabetes, cancer, and weight management.
Results
The median serum GDF15 level in control subjects is around 680 pg/ml and increases with aging. There is an increase in GDF15 secretion under stressful conditions (e.g., pregnancy, inflammation, myocardial ischemia, pulmonary diseases, diabetes, and cancer). GDF15 plays an important role in the maintenance of cell and tissue homeostasis. It has anti-inflammatory and immunomodulatory properties. GDF15 regulates appetite and body weight by inducing anorexia which results in reduction of food intake. In a study of non-obese monozygotic twin pairs, serum GDF15 levels were negatively correlated with body mass index (BMI) within twin pairs, meaning that subjects with lower serum GDF15 levels had a higher BMI than their corresponding twin. In metformin-treated patients with or without type 2 diabetes, metformin stimulates GDF15 production, contributing to the weight-loss property of metformin. The increased serum GDF15 levels in patients with heart failure or cancer contribute to cachexia (anorexia and weight loss). In view of the above GDF15 properties, GDF15 analogs and antagonists can be used in the weight management of obesity (reduction of body weight by inducing anorexia using GDF15 analogs) and heart failure or cancer (reduction of cachexia by improving appetite and increasing body weight using GDF15 antagonists).
Conclusion
GDF15, a hormone synthesized by the placenta during pregnancy and several other organs, is involved in multiple physiological and pathological conditions. It contributes to the regulation of appetite and body weight. GDF15 induces anorexia and this property can be used in the weight management of obesity and cardiac or cancer cachexia with its analogs and antagonists.
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EP980

JOINT2167

Impact of neurodegeneration on GLUT4 activity in experimental dm rats brain hyppocampus

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Introduction
.Cell membrane function abnormalities were seen in type 2 Diabetes Mellitus (DM) and leads to abnormal insulin signaling transduction followed decreased activity of GLUT4. Neurodegeneration also affects brain function by affecting GLUT4 activity. We studied GLUT4 activity in rats brain hyppocampus in rats with experimental streptozotocine induced DM in compare with additional neurodegeneration state.
Material and Methods
Adult 12 week aged rats were divided into 3 groups, experimental streptozotocine induced DM fed standard chow (DM) and fed with high fat diet and neurotoxin (DM+N), also control group without DM. Experimental DM development were evaluated in blood samples taken from tail vien by glucometer. After 12 weeks experiments rats were sacrificed and brain samples were flash frozen for further measure of GLUT4 acitity in extracted hyppocampus by ELISA.
Results
DM rats blood glucose level were increased 2.1 times in compare with control rats and confirm streptozotocin induced DM model. Blood glucose level were higher by 2.7 times in DM+N group and suggested about worsening of glycemia by accompanied neurodegeneration. Activity of GLUT4 in brain hyppocampus were decreased by 15% in DM and 19% in DM+N group in compare with control rats suggesting about poor insulin signaling in brain hyppocampus and were more worsen in combination of neurodegeneration.
Conclusion
Insulin signaling transduction were affected in experimental DM and accompanied with decreasing of GLUT4 activity in brain hyppocampus. Neurodegeneration more worsen insulin signaling transduction and more affects GLUT4 activity in rats brain hyppocampus.

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EP981

JOINT3497

Influence of vitamin d deficiency in patients with obesity on thyroid gland and liver function

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Background and aims
Obesity is one of the most common medical and social issues influencing the onset and progression of type 2 diabetes mellitus, metabolic-associated fatty liver disease, arterial hypertension, polycystic ovary syndrome, obstructive sleep apnea, and certain types of cancer. Currently, the role of vitamin D (VD) in the course of obesity is being investigated, and the influence of VD supplementation on this pathology is being analyzed. Additionally, a correlation has been observed between VD deficiency and thyroid gland and liver function. Our research aimed to study correlation between VD insufficiency/deficiency and insulin resistance in patients with obesity, depending on body mass index (BMI) and waist circumference (WC), and to determine their association with thyroid gland and liver function.
Materials and Methods
Our study included 30 individuals aged 22 to 64 years, including 23 individuals with alimentary-constitutional obesity (BMI 35.3 ± 5.2 kg/m^2) and 7 overweight individuals (BMI 27.1 ± 2.3 kg/m^2) and no history of prediabetes or diabetes mellitus. HOMA index, vitamin D (25(OH)D), thyrotropin-stimulating hormone (TSH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels were obtained as well as anthropometric parameters, including body weight, height, and waist circumference (WC).
Results
The study results indicated that VD deficiency was more pronounced in patients with obesity. Levels of 25(OH)D, HOMA index, TSH, and ALT achieved statistical significance in obese patients (24.6 ± 13.6 ng/ml; 6.9 ± 4.69; 4.2 ± 3.5 μIU/ml; 47.0 ± 28.1 U/l,respectively) compared to overweight individuals (27.0 ± 7.8 ng/ml; 5.89 ± 4.1; 2.77 ± 1.87 μIU/ml; 43.7 ± 27.7 U/l,respectively). Additionally, WC was significantly higher in obese patients (107 ± 24 cm) compared to the overweight group (82.5 ± 8.5 cm) ($P < 0.05$). Serum 25(OH)D negatively correlated with BMI ($r = -0.17$, $P < 0.05$), whereas HOMA index positively correlated with BMI ($r = 0.31$, $P < 0.05$). Serum 25(OH)D negatively correlated with HOMA index ($r = -0.19$, $P < 0.05$) and with WC ($r = -0.11$, $P < 0.05$). Serum 25(OH)D negatively correlated with TSH ($r = -0.23$, $P < 0.05$), as well as ALT negatively correlated with 25(OH)D ($r = -0.22$, $P < 0.05$).
Conclusion
Our study demonstrates a high prevalence of vitamin D deficiency in patients with obesity and it is also correlated with thyroid gland and liver dysfunction. The intensity of hypovitaminosis of vitamin D is aggravated with higher levels of HOMA index and higher degrees of obesity. Effective treatment of VD deficiency can improve clinical outcomes of obesity and metabolic disorders associated with it.

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EP982

JOINT3067

Psychological profile of the obese diabetic patient

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Introduction
Obesity is a chronic disease defined by excessive adipose tissue deposition that can be detrimental to health. The "diabetes-obesity" association is very frequent, resulting in an exacerbation of psychological complications.
Objective
Compare psychological profiles in a population of type 2 diabetics according to their weight status.
Methods
This was a cross-sectional study of 254 diabetic patients. Data were collected on the basis of a pre-established questionnaire, anthropometric measurements, the PSS4 Score to assess stress levels, and HAD scales assessing anxiety and depression.
Results
The population was divided into two groups: 179 obese patients (obese group) and 75 with a normal BMI (non-obese group). Obesity was present in 46.2% of male patients and 78.8% of female patients. The mean age was 58.66 ± 8.7 years for the obese group vs 59.04 ± 8.7 years for the non-obese group. Diabetes duration was 13.94 ± 8.4 years in the obese group and 13.05 ± 7.7 years in the non-obese group. Patients in the obese group perceived more stress than those in the non-obese group (mean PSS4 scores were 7.65 ± 4.08 and 6.64 ± 4.25 respectively). The mean HAD anxiety score was 9.6 ± 4.9 in the obese group vs 8.63 ± 5.1 in the non-obese group ($P = 0.16$). For the HAD depression score, the mean was 9.3 ± 5.1 in the obese group vs 7.9 ± 5.3 in the non-obese group ($P = 0.06$).
Conclusion
Given the psychological impact of obesity and diabetes as two chronic diseases, psychosocial support is needed to help obese diabetics live better with their disease and improve their quality of life.

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EP983

JOINT2015

Success rates of pre-pregnancy and gestational obesity interventions in preventing childhood obesity: a comprehensive review

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Background
Childhood obesity is a global epidemic with roots in maternal health during and before pregnancy. Interventions targeting pre-pregnancy obesity, gestational weight gain (GWG), and related maternal factors have been explored to mitigate risks and break the intergenerational cycle of obesity.
Objective
To review evidence on the success rates and benefits of interventions addressing pre-pregnancy and gestational obesity in preventing childhood obesity, focusing on their outcomes and effectiveness.
Methods
A review of 20 studies (2000–2024) including randomized controlled trials, observational studies, and systematic reviews was conducted. These studies examined lifestyle, behavioral, and system-level interventions during the prepregnancy, pregnancy, and postpartum periods. Success rates were calculated based on study outcomes.

Results
Lifestyle Interventions: Achieved an average success rate of 65%, effectively reducing GWG, gestational diabetes mellitus (GDM), and improving maternal metabolic health. Examples include the RADIEL Study (728 women) and the Maternal Obesity Management (MOM) Trial (60 women). Behavioral and mHealth Interventions: Demonstrated an average success rate of 60%, promoting healthy behaviors and improving glucose tolerance during pregnancy. The VACOPP study (185 participants) and the "mami-educ" mHealth program showed promising outcomes. Early-Life Interventions: Multifactorial strategies during the first 1,000 days had an average success rate of 45%, mitigating childhood obesity risks through integrated care. However, these interventions required sustained postpartum support for long-term effectiveness. Childhood Obesity Prevention: Interventions focusing on both prenatal and early-life factors showed a success rate of 40% in reducing childhood obesity prevalence, highlighting the need for continuous care.
Conclusions
Interventions targeting maternal prepregnancy and gestational health demonstrate moderate to high success rates, with the greatest effectiveness observed in structured lifestyle programs. Sustained efforts into the postpartum period and scalable, personalized interventions are critical for long-term success in reducing childhood obesity.

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EP984

JOINT237

Lactic acidosis secondary to metformin toxicity :a case report

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Introduction
Metformin is an oral antidiabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes. The most common symptoms following overdose appear to include vomiting, diarrhea, abdominal pain, tachycardia, drowsiness, and, rarely, hypoglycemia. The major potentially life-threatening complication of Metformin overdose is metabolic acidosis. We report a case of fatal Metformin toxicity following an acute intentional Metformin intoxication.
Case report
18 years old female presented to the emergency department three hours after a suicide attempt with 30 grams of metformin, severely agitated, confused. With severe abdominal pain associated with persistent vomiting Examination Pulse: 120/minute, BP: 80/60mmHg, Temprature was 37.0°C. and respiratory rate of 28. cardio-respiratory system was normal; her abdomen was soft and non-tender. Arterial blood gas analysis on admission showed a profound lactic acidosis:pH 6.8 (7.38 to 7.42); pCO2 :27 (35-45Mmhg), pO2:99 bicarbonate 4.2 (22-28 mmol/L)and lactate >15 (<1 mmol/l)Blood test results at presentation HB: 11.2g, platelet 131 (150-450) Creatinine 1.8mg (0.74 to 1.35) family members took her to toxicology emergency unit where gastric lavage was done, oral charcoal and intravenous fluids were given. During her ICU stay Day 1 The patient had severe lactic acidosis, for which she received sodium bicarbonate (200 ml) infusion. She was resuscitated by intra-venous fluids (Ringer acetate) and put on noradrenaline with no response so adrenaline was added Day 2 Lactic acidosis was persistent and severe so she received one hemodialysis session after nephrology consultation. Day 3 The patient was off adrenaline but withdrawl of nor-adrenaline failed so dobutamine infusion was added supported by the data detected in echocardiography EF 20%, akinetic whole septum, hypokinetic other whole segments sparing apical segments (apical segments contract better than basal segments). Day 4 The patient developed one attack of convulsions generalized tonic seizures followed by post-ictal confusion. Neurology consultation revealed unremarkable MRI with diffusion and EEG levetiracetam 500 was given twice daily Day 5 The patient was off nor-adrenaline then off dobutamine with intact peripheral pulsations and normal blood pressure echocardiography was normal. EF 60%.
Conclusions
metformin overdose, diagnosis and timely intervention in the form of hemodialysis for metabolic acidosis, coupled with sufficient hemodynamic resuscitation. Hence, emergency clinicians and toxicologists must maintain a high level of suspicion for drug poisoning in any patient presenting with marked metabolic acidosis or displaying symptoms related to the gastrointestinal and respiratory systems.

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EP985

JOINT3668

Prevalence and associated factors of obesity among smokers

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Introduction
The association between obesity and smoking is gaining increasing interest in public health. The aim of our study was to investigate the factors associated with obesity among smokers.
Materials and Methods
A cross-sectional analytical study was conducted at the smoking cessation clinic of CHU Fattouma Bourguiba in Monastir, including 253 male smokers who attended consultations in 2023. Anthropometric measurements were recorded, and spirometry was performed for each participant.
Results
The mean age was 48.62 $\pm$ 16.69 years. More than a quarter of the participants were sedentary (27.6%), and 19% consumed alcohol. The average cigarette consumption was 34.61 $\pm$ 32.13 pack-years. The mean age at first cigarette use was 17.16 $\pm$ 9.82 years, while the mean age at the onset of regular smoking was 19.92 $\pm$ 7.23 years. The average pulmonary age, as measured by spirometry, was 65.27 $\pm$ 21.24 years, with only 42.3% of participants having normal spirometry results. The mean body mass index (BMI) was 24.71 $\pm$ 4.46 kg/m^2. Overweight and obesity were observed in 30% and 13.8% of cases, respectively. Obesity was more prevalent among sedentary individuals (22.4% vs. 9.7%, $P = 0.009$) and alcohol consumers (26.1% vs. 10.7%, $P = 0.006$). Higher BMI was correlated with a later onset of smoking ($P = 0.04$) and an increased pulmonary age ($P = 0.001$).
Conclusion
The coexistence of obesity and smoking is common, highlighting the need for a holistic health approach that addresses both issues in an integrated manner.

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EP986

JOINT3857

Assessment of anthropometric and body composition parameters of diabetologists pan india

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Aim
This study aims to evaluate the anthropometric and body composition parameters of diabetologists across India, focusing on gender-based variations and their potential health implications. The research hypothesizes that professional demands and lifestyle factors may influence these parameters, affecting overall health and metabolic risk.
Materials and Methods
A total of 100 practising diabetologists, equally distributed by gender (50 males and 50 females), were recruited for this cross-sectional study. Anthropometric and body composition measurements were obtained using the InBody380 bioelectrical impedance analysis device. The parameters assessed included height, weight, Body Mass Index (BMI), Percent Body Fat (PBF), and Skeletal Muscle Index (SMI). To ensure consistency and accuracy in data collection, participants adhered to standardized pre-measurement protocols, which included fasting for at least two hours and abstaining from exercise or alcohol consumption before the assessment.
Results
The study revealed significant gender-based differences in anthropometric and body composition parameters: Males: Average height: 168.9 cm Average weight: 78.08 kg BMI: 27.4 kg/m^2 PBF: 31.7% SMI: 7.5 Females: Average height: 159.8 cm Average weight: 68.29 kg BMI: 26.8 kg/m^2 PBF: 40.11% SMI: 6.28 Both male and female diabetologists presented BMI values within the overweight category. The elevated PBF observed in females suggests a higher predisposition to metabolic complications, while the lower SMI reflects physiological differences that may necessitate targeted interventions.
Conclusion
This study underscores the importance of regular health assessments and personalized lifestyle modifications for healthcare professionals, particularly diabetologists. The sedentary and demanding nature of their professional roles contributes to increased health risks, necessitating proactive measures such as dietary adjustments and structured exercise regimens. Addressing these health challenges is

crucial not only for the well-being of the healthcare providers themselves but also for reinforcing their role as exemplars of healthy living for their patients. A holistic approach to health management among diabetologists is essential to mitigate risks and promote overall well-being.

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EP987

JOINT971

Metabolic disorders in patients with polyvascular disease according to the KAMMA register

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Aim
To investigate the characteristics of metabolic status in individuals with polyvascular disease (PVD).
Materials and Methods
KAMMA (NCT05189847) is an international register of real clinical practice, comprising 28 centres across the Russian Federation, the Republic of Kazakhstan, the Republic of Uzbekistan and the Republic of Belarus. The register includes 3059 individuals over the age of 18 with confirmed atherosclerosis in two or more arterial basins, as well as one or more atherosclerosis risk factors. The ankle-brachial index (ABI) was measured for all the patients in the study, either manually or automatically. The level was considered to be low if it was $\leq$0.9, normal if it was between 0.9 and 1.4, and high if it was $\geq$1.4.
Results
The mean age of the people included in the study was 66 years [59-72], and 60.3% of them were men. The most common comorbidities were hypertension in 96%, coronary heart disease in 94.8%, history of myocardial infarction in 47%, heart failure in 81%, chronic kidney disease (CKD) $\geq$C3A stage in 24.2%, and chronic lower-extremity arterial insufficiency in 21%. In the whole population, the mean body mass index was 29.4 [26.0;32.5] kg/m^2, corresponding to overweight; waist circumference was 97 [88;105] cm, corresponding to abdominal obesity. 27% of patients had dyslipidemia with low-density lipoproteins (LDL) elevation $>$ 4.9 mmol/l,3.4% of patients had familial hypercholesterolemia. In most cases, LDL target levels were not achieved despite treatment with statins (92.8%). Alternative hypolipidemic drugs (omega-3 polyunsaturated fatty acids 11.2%, ezetimibe 8.4%, fibrates 2.9%, antibodies to PCSK9 1.4%) were used less frequently. 10.2% of patients had prediabetes, while 32.2% had type 2 diabetes mellitus (DM), with a mean glycated hemoglobin level of 6.4 [5.7;7.2] %. Patients with type 2 DM had lowered ABI more often than patients without type 2 DM (47.6% vs 36.1%, $P <$ 0.001). In 7% of patients with type 2 DM, the course of the disease was complicated by the development of diabetic foot. Among them, lowered ABI (76.8% vs 38.9%, $P <$0.001), CKD C3 (14.5% vs 4.8%, $P <$0.001) and C4 (5.8% vs 0.6%, $P <$0.001) stages were significantly more common.
Conclusion
The complex of identified metabolic disorders, together with inadequate control of key risk factors (presence of overweight, abdominal obesity, dyslipidemia, type 2 DM, prediabetes), may contribute to the development and accelerated progression of PVD and potentially have a negative impact on its outcome.

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EP988

JOINT995

Risk factors for metabolic disorders in patients with polycystic ovary syndrome

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Background
Polycystic ovary syndrome (PCOS) is a common endocrine disorder often associated with various metabolic disturbances. The presence of metabolic disorders, such as diabetes, dyslipidemia, and hyperuricemia, may complicate the clinical management of PCOS patients. This study aims to compare the clinical and metabolic profiles of PCOS patients with and without these metabolic complications, providing insights into their potential impact on the disease.
Methods
A retrospective comparative study was conducted on 49 patients followed for PCOS in the Endocrinology Department at Hedi Chaker University Hospital, Sfax, Tunisia. The patients were classified into two groups: Group 1 included 13 patients with PCOS and metabolic disorders (diabetes, dyslipidemia, hyperuricemia), while Group 2 consisted of 36 patients without such disorders.
Results
The mean BMI was 29.4 in Group 1 (G1) vs 25.2 in Group 2 (G2); $P = 0.001$. Obesity or overweight was observed in 77% of G1 patients vs 47% of G2 patients; $P = 0.06$, with an android type distribution in 54% of cases. Acanthosis nigricans was found in 46% of G1 patients vs 3% of G2 patients; $P = 0.001$. Menstrual cycle disorders were reported by 77% of G1 patients and 83% of G2 patients; $P =$ 0.9, including amenorrhea in 18 cases and oligomenorrhea in 22 cases. Infertility or subfertility was found in 22% of G1 patients vs 26% of G2 patients; $P = 0.7$. Hirsutism was present in 38% of G1 patients vs 47% of G2 patients; $P = 0.5$. Hormonal analysis revealed an average LH of 12 IU/ml and an average FSH of 7 IU/ml, with no significant differences between the two groups. The average estradiol level was 38 pg/ml, while the average testosterone level was 1.11 ng/ml. Hyperprolactinemia was detected in 14 patients (28%), with 12 cases in G1.
Conclusion
Aside from abnormalities related to insulin resistance, there were no statistically significant differences in the clinical and hormonal profile of this syndrome in the presence or absence of metabolic disorders.

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EP989

JOINT658

Role of spermidine in longevity

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Introduction
Aging is a natural universal and irreversible phenomenon. It is associated with decreased autophagic activity. Spermidine is a naturally occurring polyamine that was discovered in human semen in 1678. Its sources are endogenous (e.g., synthesis by gut microbiome) and exogenous (e.g., dietary intake and supplements). Spermidine is involved in various physiological processes including regulation of autophagy and maintenance of cellular homeostasis. Spermidine administration may be beneficial in the fight against aging. This review presents an update on the role of spermidine in longevity.
Methods
A systematic search of literature was conducted using the search terms spermidine, autophagy, aging, and longevity.
Results
Aging is associated with a progressive deterioration of the cell and organ functioning and the occurrence of several age-related diseases responsible for increased mortality. Autophagy, a major protein turnover pathway that maintains cellular homeostasis under stress conditions, decreases in aging individuals, impacting the longevity. Spermidine plays an important role in cellular growth, regeneration, and regulation. It stimulates autophagy through the inhibition of several acetyltransferases, has anti-inflammatory and antioxidant properties, and positively affects the cell cycle. Stimulation of autophagy is the main mechanism of action of spermidine at the molecular level. Spermidine has the potential to prevent or postpone the occurrence and severity of various age-related diseases (e.g., ischemic heart disease, stroke, chronic obstructive pulmonary disease, cancer, respiratory infection, type 2 diabetes, osteoporosis, and dementia), decrease mortality, and increase longevity. An association between high dietary spermidine intake and reduced mortality has been reported in a cohort of 1,770 healthy subjects aged 39-67 years with a medium follow-up of 13 years. The median of serum spermidine level in normal subjects is around 25 ng/ml and the level declines with aging. Considering the physiological properties of spermidine, foods with high contents of spermidine (e.g., plant-derived products and aged cheese), the Mediterranean diet, and spermidine supplements (spermidine in capsule) may potentially be beneficial for healthy aging and increased longevity. However, the safety of chronic spermidine administration should be further investigated before clinical guidelines are established.

Conclusion
Spermidine regulates a wide range of biochemical and physiological aging processes. Its anti-aging properties is mainly through the stimulation of autophagy. Spermidine can prevent or postpone the occurrence and severity of several age-related diseases. Diet rich in spermidine and spermidine supplements can be beneficial for healthy aging and increased longevity. However, more investigations are necessary to better define the risks and benefits of long-term spermidine administration.

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EP990

JOINT2489

Metabolic syndrome and cancer metabolic syndrome and cancer

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Introduction
Cancer is currently one of the leading causes of mortality worldwide. The aim of our study was to describe the epidemiological and clinical profile of cancer in patients with metabolic syndrome.
Methods
This was a retrospective study that included 16 patients with metabolic syndrome and cancer, collected between 2012 and 2021 in the Endocrinology Department of Sfax.
Results
Our study included 16 patients with a sex ratio of 0.45. The mean age at cancer diagnosis was 58.8 $\pm$ 14.8 years (range: 28–82). None of the patients had a family history of cancer. Hypertension was present in 81.3% of cases, diabetes in 62.5%, and established cardiovascular disease in 12.5%. The mean BMI was 29.25 $\pm$ 7.4 kg/m^2 (range: 20.48–54), with obesity found in 31.3% of patients. Android obesity was present in 81.8% of women vs only 20% of men. The mean systolic blood pressure was 139 $\pm$ 22.52 mmHg (range: 120–190), and the mean diastolic blood pressure was 82 $\pm$ 12.9 mmHg (range: 60–110). Mean fasting blood glucose was 12.23 mmol/l,mean HDL cholesterol was 0.97 $\pm$ 0.34 mmol/l,and mean triglycerides were 2.03 $\pm$ 1.13 mmol/L. Among the 16 patients: 6 had breast cancer, 2 prostate cancer,2 adrenocortical carcinoma, lung cancer, 1 renal cancer, 1testicular cancer, 1 thyroid cancer, 1 colorectal cancer and 1 lymphoma.
Discussion
The pathophysiological link between cancer and metabolic syndrome remains poorly understood. However, some studies implicate excessive caloric intake as a trigger for reactive oxygen species, which exert mutagenic effects.

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EP991

JOINT2818

Severe form of lipoedema and obesity, therapeutic challenge: report of a rare case

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Objective
Lipoedema is a systemic disease with disssarenged accumulation and distribution of fat tissue, due to disturbed fat metabolism. It was first introduced as a separate clinical entity in the United States in 1940. The cause is unknown, but is bealieved genetic factors to be involved. Mostly clinically misdiagnosed, it presents as lipoedema, lipolymphedema, or combined with obesity.
Case
We present a case of a 42-year-old woman introduced in the endocrinology department due to overweight with a BMI of 93.6kg/m^2 and disproportionate accumulation on fat tissue on both legs. It was reported present parental and twin sister obesity. All efforts for hygiene-dietary modalities were insufficient. According to the clinical findings, it is combined type 2 and 3 of lobular lipoedema in stage IV, with obesity and comorbidities. Treatment with low-calorie diet, medicines and bariatric surgery was implemented. After that therapeutic and reconstructive plastic surgery was approached. Due to a weight regain, GLP1-RA was started, resulting with reduction of body weight. The overall treatment resulted with a weight loss of 91kg and a significant improvement health condition and quality of life.
Conclusion
The etiology and pathophysiology of lipedema remain unclear. The case at hand shows that there are huge therapeutic challenges for such a complex case. We show that this kind of multidisciplinary approach is necessary and it was effective, improved the quality of life and prevented comorbidities.
Key words
lipoedema stage 4, obesity, Bariatric surgery, plastic surgery, GLP1-RA.

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EP992

JOINT1608

Clinical case of hypothalamic obesity following craniopharyngioma removal

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Introduction
Hypothalamic damage resulting from craniopharyngiomas (CP) and their treatment has been widely associated with hyperinsulinemia, increased appetite due to leptin resistance, and reduced energy expenditure, leading to diminished physical activity. Dysfunction of the hypothalamus, often accompanied by pituitary hormone deficiencies, predisposes up to 50% of affected patients to the development of hypothalamic obesity (HO), typically characterized by rapid and significant weight gain.
Materials and Methods
In May 2020, an 18-year-old female patient S. with a body mass index (BMI) of 25.7 kg/m^2 underwent stalk CP resection at the N.N. Burdenko National Medical Research Center of Neurosurgery. Postoperatively, she was diagnosed with panhypopituitarism, including central diabetes insipidus, secondary hypocortisolism, hypothyroidism and hypogonadism. Hormone replacement therapy was initiated with desmopressin 0.1 mg three times daily, hydrocortisone 20 mg/day, levothyroxine 100 mg/day, and estradiol gel + dydrogesterone (1/10mg/day). In December 2020, the patient experienced a decline in health, presenting with nausea, vomiting and a decrease in sodium to 105 mmol/l(136-145mmol/L). She was urgently admitted to the intensive care unit, where rapid correction of hyponatremia led to central pontine and extrapontine myelinolysis in the context of panhypopituitarism. The patient developed bilateral supranuclear paresis of the facial, masticatory and bulbar muscles along with tetraplegia. One year later, the patient reported increased appetite and a 19 kg weight gain. Metformin therapy (1000mg/day) was prescribed. In 2022, during hospitalization at the Endocrinology Research Centre, insulin resistance was confirmed (HOMA index: 2.82), and her BMI had increased to 33.9 kg/m^2. She was referred to a dietitian, who recommended a hypocaloric diet and increased physical activity. In November 2023, clinical and laboratory tests confirmed pharmacological compensation of panhypopituitarism. MRI showed no signs of CP recurrence. However, the patient experienced nocturnal awakenings to eat, leading to a diagnosis of eating disorder (ED) with pansyndromal overeating. Psychoanaleptics were added to the regimen, but weight gain continued (BMI: 35.9kg/m^2).
Results
This case underscores the complexities in managing HO, where despite the optimization of hormone replacement therapy, caloric restriction, increased physical activity, and pharmacological control of the ED, the patient was unable to achieve a normal body weight.
Conclusions
The identification of etiological factors contributing to HO, along with the development of novel or combined therapeutic strategies, could provide a

multifaceted approach to managing hyperphagia, insulin resistance, hypopituitarism and psychosocial rehabilitation. Such interventions may lead to more effective and sustainable weight loss outcomes and help minimize the risk of long-term complications.

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EP993

JOINT2213

Determinants of advanced non-alcoholic fatty liver disease steatosis in the obese women: results of a tunisian study

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Background
Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease, closely linked to obesity and diabetes. Due to its silent nature, it remains underdiagnosed. The aim of our study was to screen for NAFLD in a population of obese women and identify the factors associated with its severity.
Methods
This is a cross-sectional study conducted on 40 obese female patients. Physical activity level was evaluated using the Ricci and Gagnon questionnaire. NAFLD screening was performed using Fibroscan. Advanced steatosis was defined as a stage of S2 or higher, and advanced fibrosis was defined as a stage of F2 or higher.
Results
Mean age was 43.56 $\pm$ 12.75 years. The majority of patients were inactive (65%). The mean duration of obesity was 19.95$\pm$12.93 years. The mean BMI was 40.36$\pm$7.17 kg/m^2, with morbid obesity observed in 45% of the patients. Abdominal obesity was present in all patients, with a mean waist circumference of 119.80 $\pm$ 14.61 cm. Steatosis was found in 75% of the patients: 17.9% at stage S1, 17.9% at stage S2, and 38.5% at stage S3. As for fibrosis, it was present in 90% of the patients: F1 in 52.5%, F2 in 15%, F3 in 5%, and F4 in 17.5%. Patients with advanced steatosis were mostly inactive (83% vs 41%; P = 0.009). A stage S2 or higher was associated with the duration of obesity (24.05$\pm$13.87 years vs 14.31$\pm$9.19 years; P = 0.02) as well as the presence of metabolic syndrome (61% vs 24%; P = 0.019). Anthropometric data revealed that severe steatosis was associated with higher BMI (43.31$\pm$7.43 kg/m^2 vs 37.00$\pm$5.00 kg/m^2; P = 0.004), increased waist circumference (125.09$\pm$14.70 cm vs 112.65$\pm$11.34 cm; P = 0.006) and waist-to-height ratio (0.79$\pm$0.11 vs 0.69$\pm$0.08; P = 0.006), higher fat mass (54.63$\pm$12.30 kg vs 43.48$\pm$8.66 kg; P = 0.003) and a higher visceral fat percentage (30% vs 0%; P = 0.03). Furthermore, advanced steatosis was associated with higher ALT levels (26.26 $\pm$ 8.64 IU/lvs 18.00 $\pm$ 4.58 IU/L; P = 0.001), a higher GGT levels (35% vs 6%; P = 0.038) and a lower platelet count (283.62 $\pm$ 74.45 x1000/mm^3 vs 342.56 $\pm$ 75.84 x1000/mm^3; P = 0.024).
Conclusion
Our study emphasizes the need for targeted screening and interventions to manage NAFLD focusing on risk factor monitoring and an active lifestyle.

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EP994

JOINT4001

Impact of SGLT-2 inhibitors on metabolic and cardiovascular health: a comparative analysis of patients with and without diabetes

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Background
Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, particularly dapagliflozin, have shown promise in improving glycemic control, weight reduction, and cardiovascular function in patients with diabetes mellitus (DM). However, the differential effects of dapagliflozin in diabetic vs non-diabetic individuals, as well as potential gender-based variations in treatment response, remain under investigation. This study compares the effects of dapagliflozin on key metabolic and cardiovascular parameters—fasting glucose, postprandial glucose, HbA1c, body mass index (BMI), weight loss, and ejection fraction (EF)—in both diabetic and non-diabetic patients, with a particular focus on gender differences.
Methods
A cohort of 17 diabetic patients and 18 non-diabetic individuals were treated with dapagliflozin over three months. Baseline and post-treatment measurements were collected for fasting glucose, postprandial glucose, HbA1c, BMI, weight loss, and EF. Statistical analyses compared the outcomes between diabetic and non-diabetic groups and evaluated gender-specific differences in response to treatment.
Results
Patients with Diabetes: Dapagliflozin significantly reduced fasting glucose (8.9–12.7 mmol/lto 5.8–7.8 mmol/l)and postprandial glucose (8.9–14.8 mmol/lto 6.7–9.9 mmol/L). HbA1c levels improved by 0.5%–1.2%. Weight loss ranged from 1.5–3.2 kg, with men experiencing greater reductions. EF increased by 2%–6%, indicating improvements in cardiac function. Patients without Diabetes: Minimal changes were observed in fasting and postprandial glucose levels. HbA1c remained stable (4.3%–5.5%). Weight loss was less pronounced (0.2–2.1 kg), while EF improved by up to 8%, likely reflecting better baseline cardiac function. Gender Differences: Men exhibited more significant reductions in fasting glucose and BMI. Women showed greater improvements in postprandial glucose, with stable cardiovascular benefits.
Conclusions
Dapagliflozin offers significant improvements in glycemic control, weight loss, and cardiac function in diabetic patients, while non-diabetic individuals experience notable cardiovascular benefits and modest weight loss. Gender differences in response suggest that men benefit more from reductions in fasting glucose and BMI, while women show more significant improvements in postprandial glucose levels. These findings support the broader use of dapagliflozin for managing cardiometabolic health beyond diabetes.

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EP995

JOINT3400

Evaluation of patients undergoing bariatric surgery: our experience

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Introduction
According to the World Health Organization (WHO), obesity is considered the pandemic of the 21st century. Currently, 1 in 7 people worldwide suffer from obesity, and according to the 2023 World Obesity Atlas, it is projected to affect 1 in 4 people by 2035.
Objectives
To describe the characteristics of patients with obesity who underwent bariatric surgery and attended Nutrition consultations at the Hospital Universitario de Canarias during June, July, and August 2024.
Materials and Methods
A descriptive observational study was conducted on a sample of 138 patients with obesity who underwent bariatric surgery and were evaluated by the Endocrinology and Nutrition Department at the Hospital Universitario de Canarias between June and August 2024. The variables analyzed included sex, weight one year after surgery, maximum body mass index (BMI), comorbidities such as hypertension (HTN), type 2 diabetes mellitus (T2DM), obstructive sleep apnea syndrome (OSAS), percentage of total weight loss, type of surgery performed, and remission of comorbidities.
Results
A total of 138 patients were studied, of whom 111 (80.4%) were women and 27 (19.6%) were men. The median maximum weight was 133 kg, with a mean maximum BMI of 49.89 kg/m^2. Among the comorbidities, 51.4% had hypertension, 66.7% had T2DM, and 17.4% had OSAS. The most commonly performed surgery was gastric bypass (71%), followed by sleeve gastrectomy (18.8%) and Scopinaro procedure (5.1%), while newer techniques such as SADI-S (2.9%) were less frequently used. A total weight loss of 36.88% was observed one year after surgery. Regarding T2DM remission, 26.1% of patients achieved

full remission, 65.2% showed improvement, and 8% had no changes, with an 18% reduction in HbA1c levels compared to baseline values.
Conclusions
Bariatric surgery remains a therapeutic option for patients with severe obesity who are unable to achieve weight reduction through lifestyle modifications and/or pharmacological treatment. The significant weight loss observed is directly associated with improvement in comorbidities and plays a crucial role in preventing future diseases.

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EP996

JOINT2801

Impact of respiratory function (FEV_1) on disease progression and mortality in patients with als: association with bioelectrical and biochemical parameters

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Introduction
Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects functional, nutritional, and respiratory status. The assessment of respiratory parameters such as forced expiratory volume in one second (FEV_1), bioelectrical, and biochemical markers allows for determining their impact on disease progression and mortality.
Objectives
In a cohort of patients with autoimmune lateral sclerosis: To analyze the relationship between respiratory function parameters (FEV_1) and bioelectrical, biochemical, and clinical indicators. To assess the association between respiratory function and mortality.
Materials and Methods
A prospective cohort study was conducted in patients attending the multidisciplinary ALS clinic at Hospital Puerta del Mar (Cádiz). Baseline respiratory function tests and morphofunctional assessments were performed. Mortality was evaluated after a mean follow-up of 18 months.
Results
The cohort included 22 patients, 52.6% women, with a median age of 65 years and a mean weight of 64.7 kg (BMI 23.7). At disease onset, 68.1% presented spinal symptoms, and 72.7% had bulbar involvement at baseline assessment. The predominant disease stages were: stage II (45%) and stage III (27.2%). The median ALSFRS-R score was 35, indicating moderate progression. Dysphagia was present in 59% of patients, and 54% had nutritional risk or malnutrition (VSG B or C). After 18 months of follow-up, 31.8% of patients had died. Twelve patients (54.5%) had $FEV_1 < 80\%$, which was associated with more advanced disease stages III-IV (OR: 24.8 [1.17–52.6]; $P = 0.006$), moderate-to-severe ALSFRS-R scores (OR: 8.17 [1.03–64.9]; $P = 0.037$), and higher mortality (OR: 9 [0.84–94.9]; $P = 0.045$). FEV_1 showed a positive correlation with bioelectrical impedance vector analysis (BIVA) parameters, including phase angle (PhA) ($r = 0.56$; $P = 0.008$) and body cell mass (BCM) ($r = 0.47$; $P = 0.033$), and a negative correlation with C-reactive protein (CRP) levels ($R = -0.754$; $P = 0.002$).
Conclusion
FEV_1 correlates with biochemical and bioelectrical parameters, and values below 80% are associated with advanced ALS stages, greater disease severity, and increased mortality. Baseline FEV_1 assessment, combined with morphofunctional evaluation, may help identify patients at higher risk of poor disease progression, guiding the intensification of multidisciplinary treatment and closer monitoring.

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EP997

JOINT2896

Understanding 'controlled obesity': perspectives of people with obesity on a new classification

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The Brazilian Association for the Study of Obesity (ABESO) and the Brazilian Society of Endocrinology and Metabolism (SBEM) have recently proposed a new classification of obesity based on the maximum weight attained in an individual's lifetime, as an additional tool to enhance understanding of the disease and facilitate discussions about treatment. In this classification, people with obesity (PwO) who lose a certain percentage of their weight are categorized as having "reduced" or "controlled" obesity. While the classification aims to improve patient care, there is limited data on PwO perceptions. To explore this, a cross-sectional online survey was conducted with 500 PwO, including an explanation and clinical case illustrating the new classification. The survey revealed that 94% of participants were certain or almost certain of their maximum weight, however 64% of them had never been asked about it by a healthcare professional (HCP). 65% of PwO believe that reaching a normal body mass index is necessary for improving their health and quality of life, despite evidence indicating that modest weight loss can enhance health outcomes. After reading about the new classification, 82% found it useful for changing perceptions about obesity treatment; 66% felt it would encourage them to seek treatment; 63% believed it would help with treatment maintenance; and 74% indicated they would feel better achieving "controlled obesity," even if the weight loss fell short of their goals. The majority agreed that the classification could help establish realistic goals (77%), reduce biases from HCPs towards PwO (68%) and make HCPs less strict with patients about weight loss (64%). For 74% of PwO, HCPs should adopt the new classification in treating obesity. Overall, PwO perceived the classification as beneficial for encouraging treatment and reducing stigma.

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EP998

JOINT2545

Relationship of iodine concentration with inflammatory and anthropometric characteristics and body composition in young adults

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Iodine is a mineral categorized as a trace element. The majority of iodine in the body is located in the thyroid gland. Its primary function in the human body is the synthesis of hormones and the preservation of healthy thyroid activity. Iodine is crucial for the control of the immune system. It functions as an antioxidant, prooxidant, and possesses anti-inflammatory properties by modulating the release of cytokines and other inflammatory mediators. Iodine is mostly absorbed by the body via dietary sources, particularly iodized salt. The research aimed to investigate the dietary iodine intake in young adults, assess urinary iodine concentration in this demographic, explore the correlation between iodine concentration and inflammatory characteristics, analyze the relationship between iodine concentration and body composition, and evaluate the association between iodine concentration and anthropometric characteristics. The investigation involved 70 young adults aged 19 to 24, comprising 35 men and 35 women. Iodine metabolism disorders and confirmed thyroid diseases were exclusion criteria. Inflammatory and anthropometric parameters, body composition, urinary iodine concentration, and dietary iodine intake were examined. The median iodine concentration in the subjects' urine is 120.77 μg/l,while the median dietary iodine intake is 624.66 μg. The median body mass index is 23.72 kg/m^2. The

median body composition consists of 32.6% muscular tissue and 27.4% fat tissue. The median waist diameter is 75.5 cm, and the upper arm circumference is 27.8 cm. The median neutrophil-to-lymphocyte ratio is 1.5. No significant association between iodine levels in urine and any observed data was detected. The participants in this study exhibit an excessive dietary iodine intake and a urinary iodine concentration indicative of a population with adequate intake. No substantial correlation was seen between urinary iodine content and inflammatory, anthropometric, or body composition variables.

Key Words
iodine, inflammation, anthropometry, body composition.
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EP999

JOINT2875

GLP-1 receptor agonists and management of diabetes mellitus 2 and obesity in multiple sclerosis

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Multiple sclerosis is a demyelinating disorder of the central nervous system of autoimmune etiology and pathophysiology. The disorder is managed by the administration of immunomodulating agents. It may be accompanied by disability. As multiple sclerosis impairs mobility, obesity may accompany the disease. Additionally, diabetes mellitus type 2 may emerge. The aim was to describe a cohort of patients with multiple sclerosis, obesity and diabetes mellitus type 2 who were managed by the administration of GLP-1 receptor agonists. A cohort of 5 patients (4 female and 1 male), aged 35-55 years, is described who were followed up for multiple sclerosis. Patients were obese, BMI 31-39. Additionally, the presence of diabetes mellitus type 2 was diagnosed in 3 of the patients. GLP-1 receptor agonists were administered to this group of patients once weekly. Weight loss was noted after 6 months in this group of patients, weight loss ranging from 1.2 to 6.7 kg. GLP-1 receptor agonist administration was continued. No adverse effects were noted, apart from nausea in one of the patients. Multiple sclerosis is an autoimmune disorder characterized by demyelination. The disease causes mobility limitation and may be accompanied by obesity. Appropriate and effective obesity treatment is crucial in this group of patients as it may facilitate mobility and may prevent disability deterioration. The administration of GLP-1 receptor agonists is a proper treatment modality for this patient group as it seems not to be accompanied by severe adverse effects. In addition, it induces weight loss and acts therapeutically as an antidiabetic agent.

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EP1000

JOINT1136

The relationship between insulin resistance, BMI, free testosterone and estradiol levels in male adults and adolescents

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Introduction
This abstract explores the complex relationship between IR, BMI, free testosterone and estradiol levels in male adults and adolescents, highlighting the bidirectional influences that exacerbate metabolic and hormonal dis-regulation. Insulin resistance is linked to low free testosterone levels due to increased inflammation, weight gain (especially visceral fat) and impaired function of the hypothalamic-pituitary-gonadal axis. Visceral fat leads to more aromatase activity, converting testosterone into estradiol, which lowers testosterone levels further. Chronic hyperinsulinemia suppresses luteinizing hormone (LH), reducing the production of testosterone in the testes.

Objectives
The aim of this study was to analyze the association between Insulin resistance, BMI, Free testosterone and estradiol levels in male adults and adolescents.
Material and Methods
Cross-sectional study of 26 male patients from 13 to 44 years Including criteria were. Insulin resistance >2.27 and BMI >25 kg/m^2 Patients were divided into two age groups: A). 13-18 years (12 patients) and B). 19-44 years (14 patients) Free Testosterone deficiency was defined as levels $<$ 15 pg/ml in adults and $<$ 12.3 pg/ml in adolescents or excess estradiol levels more then 43 pg/ml in adults and >23 pg/ml in adolescents. In group A the studied population had a mean age of 15, mean HOMA -IR of 5.07, mean BMI - 33.2 In group B the studied population had a mean age of 30.5 and mean HOMA -IR of 6.4,. mean BMI- 35.
Results
Free Testosterone deficiency prevalence was 35.7 % in adults and 16.7 % in adolescents, while high estradiol prevalence were respectively 50 %(adults) and 25 %(adolescents) in groups, BMI values were 33. $\pm$10.5 (A) and 35 $\pm$10.5(B).
Conclusions
Our small study suggests a interplay between insulin resistance, low testosterone and high estradiol levels. The findings indicate that hormonal imbalances may contribute to worsening metabolic dysfunction, highlighting the importance of addressing both insulin sensitivity and hormone levels in treatment strategies. Further large-scale studies are needed to confirm these results and develop effective therapeutic approaches for mitigating associated health risks.

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EP1001

JOINT2566

Home parenteral nutrition: experience in a tertiary hospital

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Introduction
Home parenteral nutrition (HPN) is the nutrition access of choice in patients with documented intestinal failure and inability to receive enteral nutrition exclusively.
Material and Objective
Retrospective descriptive study of patients who received HPN during 2023. Demographic variables related to HPN administration and nutritional status were analysed. The objective was to analyse the experience in the use of HPN and possible complications arising from the infusion in the Hospital Reina Sofia of Cordoba.
Results
11 patients. 9/11 women. Median age 61 years (30-87). Median follow-up time with HPN was 34 months (SDS 26.7). 8 patients with indication for HPN due to short bowel syndrome (SBS), 2 due to intestinal fistula, 1 due to extensive intestinal mucosal disease. The cause of SBS was mesenteric ischaemia (1), Crohn's disease (2), surgical complications (3), intestinal volvulopathy (1), adhesive syndrome (1). 72.7% (8) had an ostomy. Initially, 9/11 patients had PICC and 2/11 had Hickman as a central access route. At the end of follow-up, 100% of patients had PICC. According to the severity classification of chronic intestinal failure in adults: 3 FE1, 1 FE2, 3 PN1, 4 PN2. Mean kcal provided by HPN 1264 $\pm$ 155Kcal. 1 patient receiving Teduglutide treatment for 13 months. 4/11 patients had infectious catheter-related complications. 4/11 patients had catheter-related mechanical complications, mostly associated with catheter obstruction. 2/11 patients had their HPN withdrawn after 43 months (mean) of treatment, due to cure or improvement of their disease and nutritional parameters. 1 patient died due to catheter-associated complications. Weight prior to initiation of HPN 49.8 $\pm$ 11.4 kg, weight at last HPN follow-up 58.24 $\pm$ 13.6 kg [t -2.187, $P = 0.071$]. BMI prior to initiation of HPN 19.8 $\pm$ 4.76 kg/m^2. BMI at last HPN visit 24.6 $\pm$ 7.8 kg/m^2 [t -2.01, $P = 0.071$]. There is a trend towards improvement in albumin, pre-albumin, transferrin, total cholesterol, triglycerides, lymphocytes and haemoglobin after HPN, although the differences are not statistically significant.
Conclusions
The age and indication for HPN in our series is similar to the literature. There was an improvement in the weight and BMI of the patients after HPN and we did not find statistically significant differences in the improvement of nutritional parameters, although there was a trend towards improvement.

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EP1002

JOINT2582

Clinical and biological aspects of malnutrition in adults

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Introduction
Malnutrition is a common and insidious problem that often goes underdiagnosed. The aim of our study was to analyze the clinical and biological profiles of malnourished patients.
Materials and Methods
A cross-sectional study was conducted, including 35 patients followed for underweight in the outpatient department of the national institute of Nutrition. The following phenotypic criteria were collected: BMI, muscle strength (MS), and weight loss (WL).
Results
The mean age was 35.14 $\pm$ 15.95 years, with a predominance of females (82.9%). The mean BMI was 17.51 $\pm$ 4.3 kg/m^2. The average muscle strength (MS) and weight loss (WL) were 23.27 $\pm$ 10.1 kg and 15.83 $\pm$ 9.63%, respectively. The prevalence of malnutrition was 65.71%, according to the HAS recommendations, which include at least one phenotypic criterion and one etiological criterion. Severe malnutrition was observed in 56.52% of cases. The mean levels of albumin, hemoglobin, calcium, and magnesium were 41.73 $\pm$ 4.7 g/L; 11.98 $\pm$ 1.88 g/dl; 2.35 $\pm$ 0.11 mmol/l,and 0.8 $\pm$ 0.07 mmol/l,respectively. Hypoalbuminemia, anemia, hypocalcemia, and hypomagnesemia were noted in 9.1%, 45.71%, 5.7%, and 20% of cases, respectively. Malnutrition was associated with weight loss ($P = 0.001$). Anemia was linked to a reduction in muscle strength ($P = 0.03$). No correlations were found between magnesium levels and the different anthropometric parameters, nor between calcium levels and the parameters.
Conclusion
Malnutrition often presents subtly, underscoring the importance of early detection and heightened awareness among healthcare providers..

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EP1003

JOINT342

Cardiovascular risk profile and achievement of therapeutic targets in patients with diabetes mellitus

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Introduction
Type 2 Diabetes mellitus (T2DM) is a chronic condition associated with increased cardiovascular risk, which remains a significant cause of morbidity and mortality. Despite advances in diabetes management, many patients fail to meet therapeutic. The complexity of managing cardiovascular risk factors alongside glycemic control poses challenges in clinical practice.
Methods and Aims
A descriptive cross-sectional study was conducted on 80 patients with T2DM who had been attending outpatient consultations in the endocrinology department of a Tunisian medical center for at least six months. The objective was to evaluate major cardiovascular risk factors, stratify patients according to the 2023 ESC risk score, and assess treatment adherence along with the attainment of therapeutic goals.
Results
The average age of the patients was 57.9 years, with a female predominance (65%). Poor diabetes control was mainly attributed to inadequate therapeutic adherence in 33.8% of cases. Arterial hypertension was present in 46 patients. 26.3% of patients were not meeting therapeutic targets, Dyslipidemia was observed in 67.5% of patients. 27.5% of patients did not reach their LDL cholesterol targets. Obesity was present in 45% of cases, and 10% of patients had not quit smoking. The cardiovascular risk was moderate in 6.3% of patients, high in 61.3%, and very high in 32.5%.
Conclusion
This study underscores the importance of better strategies to achieve cardiovascular risk targets in diabetic patients to prevent complications and improve long-term health outcomes.

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EP1004

JOINT128

Rapid ultrasound measurement of preperitoneral abdominal fat at detection of (NASH) in obese children's evolution of this new strategy after 2 years follow up

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Introduction
NASH is an increasingly relevant finding in the pediatric population affected by obesity. In adults, the evolution of this steatosis towards fibrosis and correlation with metabolic syndrome is increasingly significant. The existence of a rapid and validated in-office screening tool would be very useful.
Main objective
To evaluate whether the measurement of intraperitoneal fat measured through nutritional ultrasound allows for the diagnosis of non-fatty hepatic steatosis or metabolic risk in overweight/obese patients. Establish if there is any type of correlation between abdominal fat measurements obtained by nutritional ultrasound and those obtained in routine clinical practice of these patients using liver ULTRASOUND if this is performed within routine clinical practice.
Material and Methods
Patients who attend of Endocrinology due to overweight. BMI >2 SDS. MINDRAY Z50 ULTRASOUNDGRAPH. (**Hamagawa technique) through an** abdominal adipose ultrasound study (Superficial subepidermal fat – stored, deep and intraperitoneal energy-risk in adults for NASH). Comparison with ECO performed by expert radiologists.
Results
Study on 150 patients with deep ECHO by an expert pediatric radiologist and nutritional ECHO. NASH 90/150 (60%). Distribution mild 72/150 (48%), moderate 14/150 (9%) and severe 3/150 (1.7%). A Mann-Whitney U test was performed on 150 patients. The results showed that the cut-off point that presents confirm a positive correlation between NASH YES/NO would be an average of 0.82 cm CI[0.70-0.94] 95% using Mann-Whitney U. Children who lost weight (fat mass by impedanciometer TANITA) after unless 12 mouths has measures of pre-peritoneal fat less than children who not.
Conclusion
There is a significant number of pediatric cases with NASH in the obese population. The use of rapid nutritional ECO (preperitoneal fat) is related by a linear and positive correlation with the presence of NASH studied by traditional ECO in expert hands.

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EP1005

JOINT576

Overweight and obesity among healthcare professionals in tunisia: prevalence and associated factors

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Introduction
Obesity has become a major public health problem because of its potential impact on health and its alarming increase worldwide. The objectives were to estimate the prevalence of overweight and obesity among healthcare professionals (HCPs) and to examine their associated factors.
Methods
We conducted a cross-sectional study during the period August2022-November 2022 among HCPs in the two-university hospital Habib Bourguiba and Hedi Chaker of Sfax governorate, Southern Tunisia. To screen for EDs, we opted for the validated French version of the Eating Attitude Test (EAT-26).
Results
The median age was 30 years (Interquartile range (IQR) = [26-40]). In this study, 253 HCPs were aged 35 years or more (68.4%). Females represented 74.6% of

participants ($n = 276$). The mean Body Mass Index (BMI) was 24.79 ± 3.74 kg/m^2. The prevalence of overweight was 40.8%. Among the participants, 24.6% were at high risk of developing eating disorders. In multivariate analysis, factors independently associated with the prevalence of overweight in HCP were a number of working years $\geq$ 10 years (adjusted odds ratio (AOR) $= 5.7$; $P < 0.001$), large weight variation $\geq$25Kg during adulthood (AO $r = 3.5$; $P = 0.038$), distortion in body image perception (AO $r = 2.2$; $P = 0.01$), dissatisfaction with the current weight (AO $r = 5.3$; $P < 0.0001$) and high risk of developing eating disorders (ED) according to the EAT-26 score (AO$r = 1.8$; $P = 0.041$).

Conclusions

The alarming figures for overweight have been illustrated, justifying the introduction of preventive measures in the workplace in order to avoid the deleterious consequences.

Key words

obesity; overweight; healthcare professionals; epidemiology; risk factors.

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EP1006

JOINT3874

Elevated liver enzymes in a patient with obesity and sleep-related eating disorder during semaglutide therapy

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Background

Semaglutide, a GLP-1 receptor agonist, is widely used for weight management and has been associated with improvements in liver enzymes and hepatic steatosis. Reports of hepatotoxicity are rare.[1].

Case Presentation

A 42-year-old female with a history of obstructive sleep apnea and sleep-related eating disorder presented for weight management. She had been on semaglutide for two years, achieving a 40-pound weight loss. In December 2023, she contracted COVID-19, followed by multiple infections treated with consecutive courses of antibiotics. In April 2024, she reported fatigue and malaise; laboratory tests revealed elevated liver enzymes (AST 222 U/l,ALT 333 U/L). Semaglutide and amoxicillin were discontinued, but liver enzymes further increased (AST 600 U/l,ALT 342 U/l)before gradually declining. Subsequent use of Bactrim led to a transient rise in liver enzymes.

Discussion

The temporal association between semaglutide discontinuation and the rise in liver enzymes suggests a potential link. However, the concurrent use of multiple antibiotics and recent infections complicate the attribution of hepatotoxicity solely to semaglutide. Notably, semaglutide has been associated with liver enzyme reductions in patients with obesity and type 2 diabetes, and recent studies have indicated its potential benefits in improving liver fibrosis in patients with metabolic dysfunction-associated steatohepatitis.[2].

Conclusion

This case underscores the importance of monitoring liver function in patients receiving semaglutide, especially those with complex medical histories and concurrent medication use. Further research is warranted to elucidate the hepatic effects of semaglutide and its safety profile in patients with predisposing factors for liver dysfunction.

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Keywords

Semaglutide, Liver enzyme elevation, Obesity, Sleep-related eating disorder, Drug-induced liver injury, GLP-1 receptor agonist, Weight management, Antibiotic-associated hepatotoxicity.

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EP1007

JOINT1247

Linkage between obesity and bone metabolism

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Introduction

Obesity affects bone metabolism through various mechanisms. Adipocytes and osteoblasts originate from a common progenitor, mesenchymal stem cells. Obesity itself by promoting adipocytes differentiation can lead to osteoporosis. Whereas chronic inflammation also shown associated with obesity and can also increase osteoclast activity, resulting in bone resorption. We tried to identify more common factors for development of obesity and osteoporosis.

Material and Methods

We gathered available data from internet Published data from the past two decades from sources such as MEDLINE, PubMed, Scopus, and Web of Science were systematically analyzed to evaluate to common factors development of obesity and osteoporosis.

Results

Literature search showed range of factors. Major factor is hormonal Influences. Adipose tissue is an active endocrine organ that secretes various hormones and cytokines, increasing fat mass leads to their higher production and can significantly affects bone metabolism. The interplay between energy metabolism and bone health is complex, with bone cells actively participating in metabolic regulation. Osteocalcin: This bone-derived hormone influences glucose metabolism and fat mass. Dysregulation of osteocalcin in obesity can affect both metabolic health and bone quality. Bone Marrow Adiposity: Increased adiposity within the bone marrow can interfere with bone remodeling by altering the balance between osteoblast and adipocyte differentiation. Dietary factors, high fat intake can interfere with calcium absorption, affecting bone health. Weight loss interventions, including bariatric surgery, have been shown to have mixed effects on bone health, sometimes leading to decreased BMD and increased fracture risk. Mechanical factor Increased body weight in obese individuals leads to greater mechanical loading on the skeleton, which stimulates bone formation through mechanotransduction. This process involves the conversion of mechanical stimuli into biochemical signals that promote osteoblast activity and bone mineralization. However, the distribution of this loading and its effects on different bone sites can vary, potentially leading to uneven bone strength. TNF-α and IL-6: These cytokines increase osteoclast activity, leading to enhanced bone resorption. The chronic inflammatory state associated with obesity can thus predispose individuals to bone loss and increased fracture risk despite higher bone mineral density.

Conclusion

The relationship between bone and adipocytes is multifaceted, involving shared origins, hormonal influences, mechanical loading, cell signaling, and metabolic factors. Understanding these connections is crucial for developing strategies to improve bone health and manage obesity-related bone issues.

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EP1008

JOINT2271

A case report of Familial hypercholesterolemia

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Introduction

Familial hypercholesterolemia (FH) is a prevalent autosomal co-dominant disorder within the group of primary dyslipidemias, characterized by elevated plasma cholesterol levels, particularly low-density lipoprotein cholesterol (LDL-C), which is significantly increased. FH results in early-onset and progressive cardiovascular disease (CVD), often becoming clinically evident during childhood and adolescence. As a result, it is crucial to tightly regulate cholesterol metabolism. Early diagnosis and prompt, intensive treatment are essential for managing the condition.

Patients et Methods

This case report outlines the situation of a patient diagnosed with familial hypercholesterolemia, who is currently under follow-up in the Endocrinology, Diabetology and Metabolic diseases department of the Mohamed VI university hospital center in Marrakech.

Results

A 17-year-old patient with no significant medical history presented for screening for familial hypercholesterolemia (FH). Her father and sister were already being treated for FH in our department. Born to non-consanguineous parents, her

developmental milestones were reported as normal. There is no history of chest pain, shortness of breath, hypertension, diabetes, hypothyroidism, or other chronic conditions, and she is not taking any medications. On clinical examination, aside from moderate obesity, particularly in the abdominal area, she exhibited a buffalo hump and acanthosis nigricans. Her lipid profile showed a total cholesterol level of 282 mg/dl, LDL at 202 mg/dl, while triglycerides and HDL cholesterol were within normal ranges. Further investigations into the underlying cause and potential cardiovascular complications were normal. The patient was advised to follow a low-cholesterol diet, prescribed Rosuvastatin 10 mg, and scheduled for follow-up.
Conclusion
Diagnosing FH is crucial not only for the patient's prognosis but also for the family members who might inherit the condition. Early identification and prompt treatment can extend the lives of these patients and help prevent cardiovascular complications.
Keywords
Familial hypercholesterolemia, CVD, LDL cholesterol.
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EP1009

JOINT3689
Impact of PCSK9 inhibitors in the management of homozygous familial hypercholesterolemia: a case report
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Introduction
Familial hypercholesterolemia (FH) is a genetic disorder primarily caused by mutations in the gene encoding the LDL receptor (90%), apolipoprotein B (5%), or PCSK9 (1%), leading to elevated LDL cholesterol levels and a significantly increased risk of premature atherosclerotic cardiovascular disease. We report the case of a 24-year-old female with homozygous FH managed with PCSK9 inhibitors.
Case Report
The patient, a 24-year-old woman, had been followed since the age of 4 for homozygous FH. Her brother underwent coronary artery bypass grafting at the age of 27 for severe coronary artery disease. She presented with ischemic heart disease and severe aortic insufficiency. Surgical interventions, including coronary artery bypass and valve replacement, were deferred due to poorly controlled hypercholesterolemia despite treatment with rosuvastatin 20 mg/day and ezetimibe 10 mg/day. Physical examination revealed tendon xanthomas on the hands, elbows, and knees. Body mass index (BMI) was 31.17 kg/m^2, and blood pressure was 130/70 mmHg. Laboratory findings included total cholesterol (TC) at 9.28 g/l,LDL cholesterol (LDLc) at 8.03 g/l,and triglycerides (TG) at 1.1 g/L. Rosuvastatin was increased to 40 mg/day, and acetylsalicylic acid 100 mg/day was added. Cholestyramine was not tolerated. After 3 months of treatment, TC was 8.12 g/l,and LDLc remained at 8 g/L. Consequently, PCSK9 inhibitors were initiated at the dose of 420 mg subcutaneous injections monthly. This resulted in a 36% reduction in TC and a 41% reduction in LDLc.
Conclusion
This case highlights the complexity of managing homozygous familial hypercholesterolemia and the crucial role of PCSK9 inhibitors in improving lipid profiles. This treatment can reduce atherogenic risk and improve life expectancy in these high-risk young patients.
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EP1010

JOINT3692
Assessment of physical activity levels among paramedical staff: a cross-sectional study
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Introduction
The prevention of cardiovascular diseases remains a crucial challenge in healthcare, as they represent one of the leading causes of death worldwide. Physical inactivity exposes individuals to a significant risk of mortality due to cardiovascular diseases and all-cause mortality, representing a major concern for healthcare professionals.
Objective
To assess the level of physical activity among paramedical staff at the Intermediate Health Center of Sfax, Tunisia.
Patients and Methods
This was a descriptive cross-sectional study conducted among 41 paramedical staff members at the Intermediate Health Center of Sfax. We assessed their perception of physical activity in the workplace using a version of the BAECKE questionnaire adapted to the Tunisian dialect.
Results
The mean age of participants was 41 years (27–59 years) with a female predominance (75.7%). The majority (87.2%) had over 5 years of professional experience. The mean weight was 75.5 kg (59–110 kg), with a mean BMI of 29.6 kg/m^2. An android fat distribution was observed in 54.2% of participants. Twelve percent of respondents were obese. Among the participants, 78.6% spent most of their time seated vs 21.4% standing. Most respondents (85.7%) frequently felt fatigued at work, and 78.5% perceived their job as moderately or minimally physically demanding compared to others of the same age. The assessment of the Work Physical Activity Index (WPAI) identified three categories: high WPAI (25%), low WPAI (35%), and moderate WPAI (40%).
Conclusion
Promoting physical activity in the workplace improves cardiovascular health, and reducing desk hours may be associated with a decrease in adiposity, overweight, and obesity.
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EP1011

JOINT1920
Personalized diagnosis of obesity types using the typeobese bot
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Introduction
Obesity results from the interaction of genetic factors with numerous environmental factors. The comprehension of the molecular mechanisms of obesity progressed enormously in the last years thanks to the development of faster and more precise genetic screening tools applied in cohort studies or in examinations with focus on subjects and their families. In particular, whole-exome sequencing showed its power to identify new syndromes associated with obesity or new forms of obesity due to a single naturally occurring dysfunctional gene (i.e. monogenic obesity). In particular, obesity is a global medical and social issue, leading to complications such as cardiovascular diseases, type 2 diabetes mellitus, and oncological pathologies. One of the main challenges is the accurate diagnosis of obesity type, as different forms (endocrine, hypothalamic, alimentary, genetic, etc.) require specific treatment approaches. The implementation of innovative technologies, such as chatbots, can significantly improve the quality of diagnosis and treatment.
The aim of the study
To improve diagnosis of obesity types using a TypeObese Telegram bot to increase patient-centered treatment and improve the efficiency of medical care.
Materials and Methods
Based on literature analysis, international guidelines, and clinical observations, an algorithm for the differential diagnosis of obesity types was developed. This algorithm was implemented in the form of the TypeObese Telegram bot, which applies an individualized approach to each patient. The bot collects clinical data, analyzes examination results, and provides recommendations for additional diagnostics.
Results
The TypeObese Telegram bot supports physicians of various specialties working with obese patients. Its functionality includes iystematic collection of information on body mass, lifestyle, medical history, and comorbidities, differentiation of endocrine, hypothalamic, and other types of obesity, recommendations for further examinations, such as hormone, leptin, and insulin level analyses. Testing of TypeObese demonstrated its usability in both primary and secondary healthcare settings, high accuracy in identifying obesity types, reduction of cognitive load on physicians, and increased awareness of rare obesity forms, such as hypothalamic or genetic obesity.
Conclusions
TypeObese is an effective tool for optimizing the diagnosis of obesity types. Its implementation enhances treatment individualization, improves healthcare efficiency, and helps prevent complications. The integration of similar solutions into clinical practice is recommended to improve obesity diagnosis and management.
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EP1012

JOINT2348

Gut microbiota in obesity; mystic relation

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Obesity is a complex, multifactorial condition characterized by excessive adiposity, which results from an imbalance between energy intake and expenditure. Recent research has highlighted the critical role of gut microbiota in the pathogenesis of obesity. The human gut is home to trillions of microbes, including bacteria, fungi, and viruses, which influence host metabolism and immune function. Emerging evidence suggests that alterations in the gut microbiome composition are associated with obesity and metabolic disorders. The gut microbiota in obese individuals is often dysbiotic, with a reduction in microbial diversity and an increased ratio of Firmicutes to Bacteroidetes. This imbalance has been linked to increased energy harvest from the diet, as certain microbial species are capable of fermenting undigested carbohydrates into short-chain fatty acids (SCFAs), which can promote fat storage. Additionally, gut microbiota may influence adiposity through the modulation of hormones such as ghrelin, leptin, and insulin, which regulate appetite and metabolism. Furthermore, dysbiosis in obesity is associated with systemic low-grade inflammation, which plays a central role in the development of insulin resistance and metabolic syndrome. This inflammatory state is thought to be mediated by gut-derived endotoxins, such as lipopolysaccharides, which can translocate into the bloodstream, promoting inflammatory responses. Interventions targeting the gut microbiome, such as probiotic supplementation, prebiotic dietary fibres, and fecal microbiota transplantation, are under investigation as potential therapeutic strategies for obesity. While promising, these interventions require further validation in large-scale clinical trials. In conclusion, the gut microbiome plays a significant role in the pathophysiology of obesity, and understanding its intricate interactions with host metabolism may offer novel approaches to the prevention and treatment of this global health epidemic.

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EP1013

JOINT1432

Endothelial function and diabetes complications in patients with T2DM after coronary stent placement

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Introduction
Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality among patients with type 2 diabetes mellitus (Dm^2). Endothelial dysfunction, a hallmark of diabetes-related vascular complications, plays a central role in the pathophysiology of CVD. Last two decades due to cardiovascular intervention management improved CVD outcomes and early mortality cases were prevented among patients with Dm^2. We aimed to analyse data from literature how that improvement reflected in endothelial dysfunction especially in patients after stent placement.
Materials and Methods
Published data from the past two decades from sources such as MEDLINE, PubMed, Scopus, and Web of Science were systematically analyzed to evaluate the endothelial function in patients after stent placement.
Results
According to data from literature, as mechanisms of endothelial dysfunction in Dm^2 patients were considered inflammation, endothelial-mesenchymal transition, oxidative stress as well as cell death. In numerous studies reduced synthesis and accelerated breakdown of nitrogen monoxide was linked to endothelial dysfunction in diabetics with CVD. Furthermore, emerging evidence highlights the role of Asymmetric Dimethylarginine (ADMA), an endogenous inhibitor of endothelial nitric oxide synthase (eNOS), as a biomarker and risk factor for endothelial dysfunction. Elevated ADMA levels are associated with increased cardiovascular mortality in patients with coronary artery disease. Coronary stenting in diabetes individuals seen as an effective operation, exhibiting a high angiographic and clinical success rate comparable to that of non-diabetic patients. The significant developments in PCI devices (bare-metal stents and first- and second-generation drug-eluting stents), alongside technological innovations, clinical experiences, and supplementary pharmacotherapies, have substantially enhanced PCI results over time, especially in patients with diabetes mellitus complicated with coronary artery disease. However, in reviewed literature, T2DM patients had a higher prevalence of in-hospital myocardial infarction and an increased requirement for supplementary cardiac revascularization and need for thorough glycemic control after the operation. In terms of therapeutic targets in T2DM patients with CVD most of the research suggested metformin, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, miRNA, and stem cells, which possess potential for clinical application.
Conclusion
This study addresses a critical gap in understanding the endothelial function and diabetes complications in T2DM patients after undergoing coronary stent placement. Its findings will contribute to better clinical management and reduced burden of diabetes-related complications.

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EP1014

JOINT2849

Obesity as a chronic refractory to treatment disease which may be dealt with successfully

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Modern way of life is characterized by lack of physical activity and the abundance of food. This food abundance is due to the miracles of modern technology applied in farming which allows the production of enough food to sustain the increasing earth population. However, poverty still exists, leading to the necessity to consume food rich in carbohydrates and lipids. This modern way of life has led to the increasing incidence and prevalence of obesity. Obesity is characterized by increased morbidity and mortality which may be due to arterial hypertension, dyslipidemia and premature atherosclerosis and diabetes mellitus type 2. Numerous agents have recently emerged for the management of obesity with debatable results. The aim was to describe a cohort of patients with obesity followed up at a tertiary facility who were managed by multiple management plans and were led to successfully lose weight over a period of 5 years. A cohort of 30 patients with obesity is described. Patients presented with obesity and thyroid disorders and diabetes mellitus type 2 in 20 of the patients. They were managed by various treatment plans and various diets over a period of 5 years. In particular, triiodothyronine was administered to some patients if they had a coexisting thyroid disorder, metformin was administered to some patients if they had diabetes mellitus type 2 and GLP-1 receptor agonists were administered to some of the patients if they were refractory to treatment. A minority of the patients, 3 patients achieved weight loss with diet and a program of physical activity. A group of 23 patients were refractory to the administration of either triiodothyronine or metformin and a plan of diet and physical activity. This group of patients was administered GLP-1 receptor agonists and achieved weight loss 1.8-10.2 kg. Four patients were referred to surgeons for surgical treatment of obesity and returned for follow up with the administration of GLP-1 receptor agonists. One patient in the group who had surgical treatment developed a large abdominal abscess and had to have corrective surgery. Patients who had surgical treatment for obesity management achieved weight loss, however, they needed follow-up treatment with GLP-1 receptor agonists. Obesity is a chronic disease refractory to treatment. Recurrence is common. However, it appears that multimodal treatment with diet, a plan of physical activity and the use of multiple pharmaceutical agents including GLP-1 receptor agonists may lead to successful weight loss in the majority of patients.

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Multisystem Endocrine Disorders

EP1015

JOINT543

Optic disc drusen: an exceptional manifestation of pseudohypoparathyroidism

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Introduction
Optic disc drusen (ODD) are acellular calcified deposits located in the optic nerve head. Although they are generally asymptomatic and rare (prevalence of 0.3% to 2.4%), they can be associated with chronic hypocalcemia. We report a rare case of pseudohypoparathyroidism associated with bilateral ODD.
Case Report
A 16-year-old adolescent was hospitalized for severe hypocalcemia (1.17 mmol/l)revealed by a generalized tonic-clonic seizure, associated with hyperphosphatemia (2.49 mmol/L). The medical history revealed asthenia, anorexia, and chronic paresthesia evolving over 2 years, as well as an acute episode of muscle contractures with respiratory distress. The patient exhibited normal growth, psychomotor development, and pubertal progression. The diagnosis of pseudohypoparathyroidism was established based on the association of chronic hypocalcemia, hyperphosphatemia, and an elevated PTH level (446 pg/ml). Type IB was considered the most plausible form due to the absence of dysmorphic features or other endocrine abnormalities. Ophthalmological examination revealed bilateral pseudo-papilledema, confirmed as ODD by OCT, with no associated cataracts. Brain imaging showed calcifications of the basal ganglia consistent with Fahr syndrome, strengthening the link between hypocalcemia and calcified deposits. Management included parenteral and oral calcium supplementation combined with active vitamin D. Clinical and biochemical improvements were observed under treatment.
Discussion and conclusion
ODD in the context of pseudohypoparathyroidism represent an exceptional manifestation, likely facilitated by chronic hypocalcemia. The classical ocular manifestation of chronic hypocalcemia is peripheral cataracts. An association between cataracts and optic nerve drusen has been reported in a patient with Di George syndrome. The underlying pathophysiological mechanism remains unclear but is hypothesized to involve dysregulated calcium metabolism, as observed in other hypocalcemic syndromes. This case highlights the importance of systematic ophthalmological evaluation in patients with severe chronic hypocalcemia. Although no treatment exists for ODD, periodic monitoring is crucial to prevent long-term complications.

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EP1016

JOINT1660

The impact of 1-hour plasma glucose on the metabolic characteristics and pregnancy outcomes in polycystic ovary syndrome

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Purpose
To investigate the impact of 1-hour plasma glucose (1h-PG) on the metabolic characteristics and pregnancy outcomes in polycystic ovary syndrome (PCOS) patients.
Methods
A total of 1122 PCOS patients from Shanghai Tenth People's Hospital, Shanghai Renji Hospital, and Chenzhou First People's Hospital during 2019-2024 were recruited. Among them, 289 patients underwent assisted reproductive technology and 123 eventually delivered successfully. According to these patients' plasma glucoses, we classified the whole cohort into three groups: Group 1: fasting PG (FPG) $\leq$ 6.1 mmol/l,1h-PG $\leq$ 8.6 mmol/l,2-hour PG (2h-PG) $<$ 7.8 mmol/L; Group 2: FPG $\leq$ 6.1 mmol/l,8.6 mmol/L $<$ 1h-PG $<$ 11.6 mmol/l,2h-PG $<$ 7.8 mmol/L; Group 3: FPG $\leq$ 6.1 mmol/l,7.8 mmol/L $\leq$ 2h-PG $\leq$ 11.1 mmol/L. Geographical characteristics such as age, body mass index (BMI), blood pressure, waist-hip-ratio, PCOS classification; and clinical biomedical indicators, sex hormones and pregnancy outcomes were collected.
Results
For metabolic characteristics, when compared with Group 1, PCOS patients in Group 2 were more likely to have a higher incidence of hyperlipidemia, metabolic syndrome (MetS) and hyperuricemia, but were not significantly different from those of the Group 3. After adjustment for age, BMI and PCOS classification, the adjusted odds ratios (ORs) for incidence of hyperlipidemia, metabolic syndrome (MetS), and hyperuricemia in PCOS patients with Group 2 were 1.576 (1.121-2.216, $P = 0.009$), 1.804 (1.002-3.246, $P = 0.049$), 1.734 (1.224-2.457, $P = 0.002$), respectively. For pregnancy outcomes, PCOS patients in Group 2 were more likely to progress to gestational diabetes mellitus (GDM) than those of the Group 1, but were comparable to those of in Groups 3. After adjustment for age, BMI and PCOS classification, the adjusted OR for GDM in the Group 2 was 3.931 (1.122-13.777, $P = 0.032$).
Conclusions
Our study demonstrated that similar to 2h-PG, PCOS patients with elevated 1h-PG had a significantly higher risk of different metabolic disorders and GDM. Therefore, patients with PCOS should be emphasized the harmful effects of 1h-PG, which can be used for earlier screening and interventions in high-risk PCOS patients.

Keywords
polycystic ovary syndrome, 1-hour plasma glucose, metabolic disorders, gestational diabetes mellitus.
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EP1017

JOINT1297

Continuous glucose monitoring in patients with cushing's syndrome, before and after surgical therapy

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Background
Patients with endogenous Cushing's syndrome (CS) face an elevated cardiometabolic risk, which is linked to increased morbidity and mortality. This increased risk is partly driven by an impaired glucose metabolism, which is influenced by elevated cortisol levels and a disrupted circadian cortisol rhythm. The aim of this study was to improve the understanding of the glucose metabolism in patients with CS, utilizing continuous glucose monitoring (CGM) before and after surgical intervention.
Methods
This was a prospective, cross-sectional and longitudinal study. We included ten adult patients (9 female, 1 male) with CS (6 pituitary, 4 adrenal), and an HbA1c $<$ 7.0 %. The data collection with CGM was conducted before surgical intervention and 3 and 6 months postoperatively. At 3 months, all patients received a median hydrocortisone dose of 32.5 mg (IQR 15.0), which was reduced to 20.0 mg (IQR 10.0) at 6 months. At each time point continuously measured glucose concentrations, fasting glucose and insulin concentrations, HBA1c and BMI were compared.
Results
At baseline, patients had a median age of 36.7 years (26-50) and a median BMI of 33.2 kg/m^2 (23.8-51.7). Preliminary data indicate that the median (IQR) nocturnal glucose concentration was significantly higher at baseline (117.2mg/dl (26.55)) compared to three and six months post-surgery (99.53 mg/dl (23.63), $P = 0.022$; 100.77 mg/dl (10.78), $P = 0.022$). No significant differences were observed during the daytime. The median time (IQR) spent in the mild hyperglycemia range (140-180 mg/dl) per night (10pm to 6am) was significantly longer at baseline (13.70 % (20.65), 3 hours and 17 minutes), compared to three and six months post-surgery (4.71 % (9.76), 1 hour and 8 minutes, $P = 0.01$; 3.89 % (8.35), 56 minutes, $P = 0.044$). Fasting glucose and insulin concentrations, HbA1c or BMI did not change significantly.
Conclusion
These preliminary findings suggest that surgical therapy in patients with CS leads to significant improvements in nocturnal glucose control, with stabilization occurring within three to six months post-surgery. The results highlight the potential for CGM to offer valuable insights into glucose metabolism in CS, particularly during the night. Furthermore, CGM could contribute to the early detection of post-surgical relapse by identifying changes in glucose levels that may reflect a recurrence of the condition.

Keywords
Cushing's syndrome, continuous glucose monitoring, CGM, glucose, circadian.
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EP1018

JOINT621

Bridging the gap: a comprehensive analysis of adolescent PCOS treatments and outcomes across decades

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Background
Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder in adolescents, marked by menstrual irregularities, hyperandrogenism, and metabolic dysfunction. Early diagnosis and tailored treatments are essential to mitigate long-term risks such as infertility and diabetes. This review evaluates the effectiveness of lifestyle, pharmacological, and combination therapies in managing adolescent PCOS.
Objective
This study reviews treatment options and outcomes for adolescents with PCOS from 1990 to 2024, focusing on the efficacy of lifestyle interventions, pharmacological treatments, and combination therapies. Success rates, number of studies, and patient data were analysed for each treatment type.
Methods
Fifteen studies involving 1,062 adolescent patients were reviewed. Data were synthesized into three categories of therapy, with outcome success rates and patient improvements evaluated.
Results
• Lifestyle Modifications: Six studies, including 450 adolescents, demonstrated that diet and exercise significantly improved metabolic and reproductive outcomes, with 65%-80% success rates in reducing insulin resistance and improving ovulation. Weight reduction was particularly effective in obese patients, contributing to better glucose tolerance and reduced androgen levels. These foundational interventions are critical for long-term metabolic health.
• Pharmacological Treatments: Ten studies with 612 patients highlighted the efficacy of medications like metformin and oral contraceptives (OCs). Metformin showed success in normalizing glucose tolerance in 66.7% of cases and improving insulin sensitivity in 80%. OCs were effective in regulating menstrual cycles and reducing androgenic symptoms, with response rates between 60%-77.8%. Antiandrogens also showed promising results in managing hirsutism and acne, though specific response rates were not uniformly reported. Pharmacological therapies are essential for addressing hormonal imbalances and metabolic dysfunctions.
• Combination Therapies: Five studies comprising 230 patients reported the highest success rates (70%-80%) for combined approaches. Therapies such as lifestyle changes paired with metformin or OCs showed substantial improvements in ovulation, menstrual regularity, and insulin sensitivity. Myo-inositol combined with alpha-lipoic acid reduced insulin resistance by 65%. These findings underscore the synergistic benefits of integrating lifestyle and pharmacological interventions.
Conclusions
Combination therapies achieve the highest success rates in managing PCOS in adolescents, while lifestyle modifications remain foundational. Pharmacological treatments, particularly metformin and OCs, effectively address hormonal and metabolic dysfunction. This review emphasizes the importance of individualized, early interventions to optimize outcomes. Further research should focus on the long-term efficacy of these treatments and emerging therapeutic options.
Recommendations
• Tailored combination therapies with lifestyle modifications and pharmacological treatments improve outcomes in adolescents with PCOS.
• Long-term studies are needed to assess treatment durability and explore novel interventions.

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EP1019

JOINT2190

Does hormonal cross-talk exists between different endocrine glands: an indian prospective study of this unique phenomenon

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Background
Endocrine system (ES) is distinct amongst all organ systems (OS) in human body. ES is a conglomeration of different endocrine organs. So far, the only models of proof of physiological cohesiveness between anatomically separated endocrine glands within ES are APUD cell concept; HPA axis; HPG axis; biochemical pathways of hormones. We wanted to investigate a hypothesis, that there is hormonal inter-dependance between different endocrine organs. We took nontoxic goiter (thyroid) and primary hyperparathyroidism as prototypes.
Material and Methods
This prospective case-control study was conducted on 200 cases (175 thyroid and 25 parathyroid) and age matched 200 controls from healthy blood donors over a period of 12 months. Institutional ethical committee approval was obtained. All thyroid and parathyroid cases underwent uneventful curative thyroidectomy and parathyroidectomy respectively. Exclusion criteria were subjects with any febrile illness, candidates with stress, anxiety neurosis, allergies, chronic drug use, diabetes, systemic or chronic inflammatory disease or calcium/vitamin D supplements, any medication which interferes with the normal function of the hypothalamic-pituitary axis, menopausal age group. Serum samples were collected preoperatively, from all the subjects in both groups as per the standard collection times and procedures. Statistical analysis was performed by SPSS 20.0. P = value of < 0.05 was considered significant.
Results
Mean prolactin, Luteinising hormone (LH), follicular stimulating hormone (FSH), parathormone, cortisol and testesterone in thyroid cases and controls were 27.6 $\pm$ 8.1 ng/ml (12 – 87), 24.5 $\pm$ 1.7 IU/l(10– 57), 16.8 $\pm$ 3.3 IU/l(8.4 – 41), 24.5 $\pm$ 3.9 pg/ml (15 – 65), 7.1 $\pm$ 2.5 mg/dl (4- 16.5), 257 $\pm$ 56 ng/dl(167 – 478) and 14.6 $\pm$ 3.5 ng/ml (8 – 18), 11.4 $\pm$ 2.5 IU/l(2.5 – 12.5), 6.1 $\pm$ 2.9 IU/l(3.5 – 21), 21.2 $\pm$5.3 pg/ml (9 – 46), 11.3 $\pm$ 3.6 mg/dl (5.5- 19), 214 $\pm$ 45 ng/dl (115 – 368) respectively. There was statistically significant difference of prolactin, LH, FSH and cortisol values between thyroid cases and controls. But statistical difference was significant only for prolactin, FSH and LH between parathyroid cases and controls.
Conclusions
This study highlights an unique model of endocrine homeostasis and hormonal cross talk within the ES. The results provides a distinct proof to screen for subclinical endocrine diseases. But, the exact pathophysiological mechanism and significance of hormonal cross talk between varied endocrine organs needs active research.

Key words
Thyroid; Parathyroid; Prolactin; Goiter; Cortisol; Insulin.
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EP1020

JOINT2955

Synchronous pheochromocytoma and papillary thyroid carcinoma - is CACNA1H the culprit?

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Background
Thyroid carcinoma in patients with pheochromocytoma is 14 times more likely to occur than in general population, however papillary thyroid carcinoma(PTC) has been rarely reported in association with pheochromocytoma. We present the case of a patient diagnosed with synchronous pheochromocytoma and PTC with negative genetic testing for common mutations.
Case report
A 48 years old woman with significant familial history in the oncological field presented to our clinic for a right adrenal nodular lesion accidentally discovered after an abdominal-pelvic CT scan performed for back pain. The endocrine tests revealed increased values of plasma and urinary metanephrines and nonmetanephrines and a right thyroid nodule (TIRADS-4). Fine-needle aspiration biopsy showed atypia of undetermined significance (Bethesda 3). The patient has been subject of right adrenalectomy and subsequent total thyroidectomy. Immunohistochemistry of adrenal tumor showed pheochromocytoma, PASS score = 8, suggestive of aggressive tumor behavior, chromogranin A diffuse positivity in the tumor and Ki-67 = 7%. Thyroid histopathological report revealed unifocal right PTC, pT1bN0, low risk group. The patient was screened for germline mutations by next-generation sequencing (TruSight One Sequencing panel, Illumina) for a panel of 4813 genes including: *RET*, *SDHx, VHL, TMEM, MAX* and many other

susceptibility genes cited in current literature as being involved in genetic etiology of pheocromocytoma. The analysis could not find any pathogenic or likely pathogenic variants related to the phenotype. Instead, we found a monoallelic missense variant of uncertain significance in a gene for calcium voltage-gated channel subunit 1G, *CACNA1G* (NM_018896.5): c.1382G>A (p.Arg461Gln). The alpha 1 subunit of the family of T-type low voltage-operated calcium channels (VOCCs) includes three isoforms encoded by the genes *CACNA1G* (CaV3.1), *CACNA1H* (CaV3.2), and *CACNA1I* (CaV3.3). *CACNA1H* variants have recently been associated with pheochromocytoma (1). The particularity of the case is the association between adrenal paraganglioma and PTC, together with the oncological family history. Although pheochromocytomas secrete mainly catecholamines and their metabolites, they can also secrete many other peptides such as insulin-like growth factor II, that might cause the development and growth of papillary thyroid carcinoma. However these do not explain the family history of various cancers.

Conclusions

The association of PTC and pheochromocytoma in this patient may be coincidental, but it seems more likely to result from genetic variants in genes still awaiting identification.

Reference

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EP1021

JOINT2603

Co-existence of type 1 diabetes mellitus, thyroid dysfunction, and myasthenia gravis: a case report

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Introduction

Autoimmune diseases share a common predisposition and can coexist in the same patient. Type 1 diabetes, hyperthyroidism, and myasthenia gravis have similar immunopathological bases. The coexistence of these three conditions is rarely reported in the literature but has significant diagnostic, therapeutic, and prognostic implications. We report a case of this association.

Case Report

A 23-year-old male was diagnosed with type 1 diabetes in December 2022 at the age of 21 and he was managed with a basal-bolus insulin regimen. During follow-up, he reported progressive fatigue worsening throughout the day and dysphagia. Clinical examination revealed left eyelid ptosis, leading to a diagnosis of myasthenia gravis in February 2023. He was hospitalized in the neurology department and treated with pyridostigmine 480 mg/day and corticosteroids, with good clinical improvement. During a subsequent hospitalization in June 2023, the patient presented with weight loss, polyphagia, palpitations, and diarrhea. Examination revealed a small, homogeneous goiter, inactive bilateral exophthalmos, and distal tremors. Laboratory tests showed TSH < 0.014 µUI/ml, FT4: 88.4 pmol/l,positive anti-TPO antibodies at 90.8 UI/ml, negative anti-TG antibodies. Based on these findings, Graves' disease was suspected, and the patient was started on thiamazole 30 mg/day and propranolol 120 mg/day.

Conclusion

These conditions highlight the complex interplay between autoimmunity, genetics, and immune dysfunction. A gene associated with early-stage type 1 diabetes and myasthenia gravis (sialitis and peri-insulitis) has been mapped to chromosome 1 near the Bcl-2 locus. Additionally, the CTSL2 gene, encoding cathepsin V, a cysteine protease involved in antigen presentation in human cortical thymic epithelial cells, may play a role in the autoimmunity of these three diseases. A personalized approach is essential for diagnosis, treatment, and long-term follow-up of these patients.

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EP1022

JOINT1585

A clinical case of a patient with alstrom's disease in the practice of an endocrinologist

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Objective

Alstrom syndrome is a hereditary disorder caused by a double dose of a mutated gene. This leads to clinical manifestations including retinal degeneration (resulting in blindness), obesity, TD2M, neurosensory hearing loss, and early-onset dilated cardiomyopathy. Currently, only one gene has been identified as causing this syndrome: ALMS1. We present a clinical case of a patient with Alstrom syndrome as encountered by an endocrinologist.

Materials and Methods

Patient A.A., an 18-year-old male, presented to the endocrinologist complaining of a 3-4 kg weight gain over the past 6 months, decreased visual acuity since childhood, photophobia, hearing loss, and short stature. At age 1 year, an ophthalmological examination revealed nystagmus, photophobia, low visual acuity and hereditary retinal dystrophy and mixed astigmatis. Usher syndrome was suspected but excluded through genetic testing. He has been overweight since childhood. At age 14, an audiological examination revealed grade 2 progressive neurosensory hearing loss. At age 17, he consulted an endocrinologist due to short stature (158 cm). His father is 180 cm tall, his mother 164 cm, his older brother 189 cm. Hand X-rays showed a bone age consistent with 17-18 years. Pituitary MRI revealed no adenoma. At age 18, Alstrom syndrome was genetically confirmed. In 2024, at Endocrinology Research Center the examination revealed a weight of 85.4 kg, height of 158 cm, and BMI of 34.1 kg/m^2. He had brown striae on his upper extremities, minimal body and facial hair, and firm breasts on palpation. Hormonal testing excluded endocrine causes of obesity (endogenius hypercortisolism, hyperprolactinemia, and hypothyroidism). Normogonadotropic hypogonadism was diagnosed (LH 5.6 IU/l,FSH 11.6 IU/l,total testosterone 4.85 nmol/L). An urological consultation diagnosed secretory infertility, and hormone replacement therapy was recommended. Growth hormone deficiency was ruled out (GH 0.18 ng/ml, IGF-1 260.8 ng/ml). There was no evidence of impaired glucose metabolism. Orlistat was recommended to manage his weight and prevent progression of dysmetabolic complications. An ophthalmological consultation confirmed Alstrom-Hallgren syndrome, with findings of tapetretinal abiotrophy, partial optic nerve atrophy, horizontal nystagmus, convergent strabismus, and early posterior capsular cataract. Significantly, ECG did not reveal dilated cardiomyopathy.

Conclusion

The ALMS1 gene mutation underlies the patient's reduced vision, hearing, obesity, diabetes, and short stature, significantly impacting his quality of life and lifespan. This presents a significant social problem. This clinical case highlights the importance of early diagnosis of genetic disorders by primary care physicians and the need for a multidisciplinary approach in managing patients with rare diseases.

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EP1023

JOINT1948

Hormonal impacts of energy drinks on adolescents: a comprehensive review

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Background

Energy drink consumption among adolescents has increased significantly in recent years, raising concerns about its potential effects on hormonal balance and overall health. These beverages, typically high in caffeine and sugar, can disrupt crucial hormonal processes during adolescence—a critical period for growth, reproductive development, and maturation. This review examines the effects of energy drinks on cortisol, melatonin, insulin, growth hormone (GH), testosterone, and reproductive function.

Objectives

The aim is to evaluate the hormonal disruptions caused by energy drinks in adolescents and to discuss the implications of these disruptions on adolescent growth, reproductive health, and stress regulation.

Methods

A comprehensive review of peer-reviewed studies published between 2000 and 2024 was conducted. Articles were selected based on their focus on energy drink consumption and its impact on hormonal regulation in adolescents. Studies were reviewed for their methodology, participant demographics, and reported outcomes.

Results

Adolescents consuming energy drinks are at risk of significant hormonal imbalances that may impair growth, stress regulation, and reproductive health. Excessive caffeine intake elevates cortisol levels, leading to increased stress and

potential suppression of reproductive hormones. Caffeine delays melatonin production, disrupting sleep-wake cycles and reducing sleep quality. High sugar content impairs insulin sensitivity, increasing the risk of metabolic disorders like diabetes. Poor sleep quality suppresses GH secretion, critical for linear growth and puberty-related growth spurts. Elevated cortisol and disrupted sleep patterns may suppress testosterone production, delaying puberty in boys. Energy drinks' high caffeine and sugar content may reduce sperm motility and count by increasing oxidative stress..
Conclusion
Energy drinks can disrupt hormonal balance in adolescents, affecting cortisol, melatonin, testosterone, and reproductive function. Limiting intake and educating adolescents and parents about these risks is critical to supporting healthy growth and development.

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EP1024

JOINT1752

Hereditary xerocytosis and secondary haemochromatosis - a rare cause of progressive endocrine dysfunction

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Hereditary xerocytosis (HX), or dehydrated hereditary stomatocytosis, is a rare haemolytic anaemia caused by gain-of-function mutations in the *PIEZO1* gene, located on chromosome 16q23-24. The *PIEZO1* gene encodes the PIEZO1 protein, a mechanosensitive cation channel that regulates cell volume and is highly expressed in the red blood cell (RBC) plasma membrane. In HX, mutations disrupt ion transport, causing excessive calcium influx. Elevated intracellular calcium activates the Gardos channels, leading to significant potassium efflux and water loss. These changes cause RBC dehydration, reduced deformability, shortened lifespan, and eventual apoptosis. We report the case of a 22-year-old male with a complex medical history. At 16 years old, he was referred to the endocrinology department for delayed puberty. Laboratory investigations revealed low levels of luteinizing hormone, follicle-stimulating hormone, and testosterone, alongside a negative response to the gonadotropin-releasing hormone agonist stimulation test. He was diagnosed with hypogonadotropic hypogonadism and prescribed testosterone therapy. His medical history also included haemolytic anaemia, initially diagnosed as hereditary spherocytosis at the age of 6, which required intermittent red blood cell transfusions. He underwent splenectomy at the age of 9, followed by cholecystectomy at 13 due to cholelithiasis and mechanical jaundice. Despite the splenectomy, haemolysis persisted, and sporadic transfusion requirement continued. At 22 years old, the patient developed non-autoimmune diabetes mellitus and growth hormone deficiency, prompting an evaluation for iron overload. Laboratory investigations revealed ferritin levels exceeding 700 ng/ml and a transferrin saturation of 81%. Given the atypical progression of haemolysis and the new endocrine complications, genetic testing was subsequently performed, identifying a heterozygous mutation in *PIEZO1* c.7483_7488dup, p.(Leu2495_Glu2496dup), affecting the C-terminal region of the *PIEZO1* gene. This confirmed a diagnosis of HX, providing a unifying explanation for the patient's hematologic and endocrine findings. Assessement by T2* magnetic resonance imaging (MRI) showed significant iron overload in the heart, liver and pancreas. Iron chelation therapy and annual MRI evaluation are advised. The phenotypic variability of rare haemolytic anaemias may lead to misdiagnosis and suboptimal treatment. Accurate diagnosis is critical, as it directly impacts patient management. HX, as demonstrated in this case, can be misdiagnosed as hereditary spherocytosis due to overlapping clinical features. However, unlike hereditary spherocytosis, in which splenectomy is a cornerstone of treatment, splenectomy is contraindicated in HX because of the increased risk of thromboembolic complications. This highlights the importance of molecular diagnostics in guiding personalized management, helping to prevent therapeutic missteps, and improving long-term outcomes.

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EP1025

JOINT3364

Pseudohypoparathyroidism due to GNAS inactivation: a case report

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Background
Pseudohypoparathyroidism (PHP) is a rare genetic disorder characterized by target organ resistance to parathyroid hormone (PTH) caused by mutations in the *GNAS* gene or other upstream targets. This condition often presents with hypocalcemia, hyperphosphatemia, and characteristic skeletal abnormalities. Due to its diverse clinical manifestations, PHP is frequently misdiagnosed, resulting in delayed treatment and increased risk of complications. We present a case of PHP initially misdiagnosed as epilepsy, highlighting the importance of recognizing hypocalcemia as a differential diagnosis in seizure disorders.
Presentation
A 9-year-old girl with a history of congenital hip dislocation and no significant family history was admitted for evaluation of recurrent seizures. No previous records of hypocalcemia were noted. Her first seizure occurred at the age of three and was diagnosed as epilepsy, leading to treatment with sodium valproate. Despite this, she continued to experience 1–2 seizures annually, which escalated to daily seizures three weeks before hospitalization. Upon neurological examination, severe hypocalcemia was identified, and the child was referred to an endocrinologist for further investigation. Physical examination identified features of Albright hereditary osteodystrophy (AHO), including a round face, short stature (-2.0 SD), central obesity (+2.6 SD), brachydactyly, scoliosis, and developmental delay. Initial laboratory results revealed severe hypocalcemia (ionized calcium: 0.65 mmol/L), hyperphosphatemia (2.97 mmol/L), normal magnesium (0.72 mmol/L), vitamin D sufficiency (78.3 ng/ml), and significantly elevated PTH levels (766 pg/ml). Additional biochemical findings included elevated TSH (20.3 mUI/l)with normal FT4 (14 pmol/L), indicating multi-hormonal resistance. The radiographic evaluation confirmed shortened metacarpal bones, left hip dislocation, hip dysplasia, bilateral femoral flattening, and tibial shortening. Genetic testing via next-generation sequencing identified a heterozygous *GNAS* variant (c.2T>C; p.Met1?), a previously unreported mutation in *GNAS*-related disorders. *ClinVar* and *In silico* analysis classified this variant as *likely pathogenic* according to ACMG/AMP guidelines. The child was treated with calcitriol (20 ng/kg/day), oral calcium, and levothyroxine. Following treatment, seizures ceased completely, PTH and TSH levels normalized, and the patient showed a significant height increase of 6.5 cm over nine months (-2.0 SD to -1.5 SD).
Conclusion
This case highlights the diagnostic challenges of PHP, particularly in patients presenting with neurological symptoms such as seizures. We emphasize the importance of serum calcium, phosphate, and PTH evaluation in children with unexplained seizures or AHO-like features. Genetic analysis can provide diagnostic confirmation in ambiguous cases, guiding appropriate management and improving patient outcomes.
Keywords
Pseudohypoparathyroidism, *GNAS* mutation, hypocalcemia, Albright hereditary osteodystrophy.

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EP1026

JOINT468

Unraveling biological determinants of advanced fibrosis risk in type 2 diabetes patients with MASLD

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Introduction
Metabolic-Associated Steatotic Liver Disease (MASLD) is increasingly prevalent among patients with Type 2 Diabetes Mellitus (T2DM), often leading to advanced fibrosis. Identifying biological factors that influence fibrosis risk in this population is crucial for improving patient outcomes. This study aims to explore the key biological determinants associated with advanced fibrosis in T2DM patients with MASLD.
Methods
We realized a comparative and analytical study including T2DM patients with confirmed MASLD, followed at the Endocrinology-Diabetology Department of Hedi Chaker University Hospital in Sfax, Tunisia. We used the fibrosis-4 index (FIB-4) and the NAFLD fibrosis score (NFS) to evaluate the risk of advanced fibrosis among patients. High risk of advanced fibrosis was indicated by a FIB-4 score exceeding 2.67 and an NFS score exceeding 0.675. The patients were categorized into two groups: a high-risk group for advanced fibrosis and an intermediate and low-risk group.

Results
101 T2DM patients with MASLD were included. Liver enzymes and platelet count were excluded from the analysis as they are integral components of the NFS and FIB-4 scores. When groups were formed based on the NFS score, the prothrombin level was significantly lower in the high-risk advanced fibrosis group compared to the other group (78.0 [50.0-98.0] vs. 99.0 [94.0-100.0], respectively; $P = 0.008$). Comparison of groups based on the FIB-4 score did not confirm this significant difference in prothrombin level but revealed other significant associations: elevated alkaline phosphatase levels were linked to a higher risk of advanced fibrosis ($P = 0.033$), and albumin levels were lower in the high-risk group ($P = 0.041$). Other biological parameters, including total bilirubin, conjugated bilirubin, gamma-glutamyl transferase, thyroid-stimulating hormone, and uric acid, were not associated with advanced fibrosis risk regardless of the scoring method used.
Conclusion
Biological parameters such are crucial for assessing fibrosis risk in T2DM patients with MASLD, highlighting the need for comprehensive biomarker evaluation in this population.

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EP1027

JOINT2522

Autoimmune polyendocrine syndrome type 1 or acquired immunodeficiency syndrome? a complex case of type 1 diabetes, hypoparathyroidism, and hiv infection

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Introduction
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome is a rare autosomal recessive disorder caused by mutations in the *AIRE* gene. It is characterized by the triad of chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency. We report the case of a 33-year-old male suspected to have this rare syndrome and who was diagnosed with an underlying human immunodeficiency virus (HIV) infection.
Case presentation
We present a case report of a 33-year-old male admitted to our department for the management of poorly controlled type 1 diabetes mellitus (T1DM), with a hemoglobin A1c level of 10%, progressing over five years. Initially, the patient was placed on a basal-bolus insulin regimen; however, he self-discontinued rapid-acting insulin and reduced the dosage of long-acting insulin due to recurrent hypoglycemic episodes accompanied by recent weight loss. His medical history included a gastric ulcer and esophageal candidiasis. Laboratory investigations upon admission revealed hypocalcemia at 1.64 mmol/l(reference range:2.20-2.65mmol/l) and hyperphosphatemia at1.8 mmol/l(reference range:08-1.40 mmol/l), with normal magnesium levels. Further analysis demonstrated a low parathyroid hormone (PTH) level of 11 pg/ml (reference range: 15–65 pg/ml) and a slightly low vitamin D level of 26.8 ng/ml, consistent with a diagnosis of primary hypoparathyroidism. The coexistence of primary hypoparathyroidism and esophageal candidiasis raised suspicion for APECED syndrome, particularly given the patient's autoimmune T1DM background. Diagnostic evaluations ruled out adrenal insufficiency via a Synacthen test, and autoimmune screening for celiac disease yielded negative results. During hospitalization, the patient developed inflammatory arthralgias in the wrists and ankles. A detailed clinical history revealed unprotected sexual encounters, prompting comprehensive immunological and infectious evaluations. While immunological tests were unremarkable, serological testing identified an underlying HIV infection. The presence of esophageal candidiasis led to the diagnosis of acquired immunodeficiency syndrome (AIDS).
Conclusion
This case illustrates the diagnostic complexity of differentiating APECED syndrome from immunodeficiency disorders such as AIDS, particularly in patients with overlapping clinical features such as hypoparathyroidism and recurrent infections like esophageal candidiasis. The unexpected diagnosis of HIV infection in this patient underscores the necessity of considering infectious etiologies in the differential diagnosis of polyendocrine disorders, even in the presence of autoimmune conditions like T1DM.

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EP1028

JOINT2533

Hypercortisolemia and its impact on type 2 diabetes

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Introduction
Cushing's syndrome (CS) is a rare endocrinopathy characterized by prolonged hypercortisolism, which can arise from several etiologies. Due to its heterogeneous clinical presentation and overlap with other conditions, the diagnosis of CS is often delayed, sometimes for years after the initial onset of symptoms.
Case report
A 56-year-old woman with a medical history of type 2 diabetes (T2D), hypertension (HTN), dyslipidemia, and osteopenia presents for follow-up in our outpatient clinic, referred by her primary care physician. Her treatment plan included metformin and dapagliflozin for T2D, irbesartan and amlodipine for HTN, atorvastatin for dyslipidemia, and vitamin D for osteopenia. Her primary complaints included generalized weakness and difficulty losing weight despite following a low-carbohydrate diet. Additionally, she reported gradual weight gain over the past four years, particularly in the abdominal region. Her BMI had increased from 29.1 kg/m^2 to 34.2 kg/m^2, and her waist circumference measured 109 cm. At the time of assessment, her blood pressure was 145/95 mmHg, and her glycated hemoglobin (HbA1c) was 8.6%. Consequently, hydrochlorothiazide and semaglutide were added to her regimen to address her blood pressure and glycemic control. After three months, the patient's HbA1c increased slightly to 8.8%, and her blood pressure was 141/88 mmHg. A complete blood count and metabolic panel were ordered, along with fasting and postprandial blood glucose tests. While the patient's fasting blood glucose ranged from 115 to 132 mg/dl, her postprandial glucose levels were notably elevated, reaching up to 280 mg/dl, particularly after lunch and dinner. Considering these findings, the patient underwent morning cortisol and ACTH testing, which revealed low ACTH and elevated cortisol levels. A low-dose dexamethasone suppression test showed no significant decrease in cortisol levels (4.78 µg/dl). An abdominal computed tomography (CT) scan was then conducted, identifying a 2.4 cm left adrenal nodule, consistent with an adrenal adenoma, while the right adrenal gland appeared normal. The patient was referred to an endocrine surgeon, and a minimally invasive adrenalectomy was scheduled three months later. Throughout this period, her blood glucose and blood pressure were carefully managed. Postoperative histopathology confirmed the presence of an adrenal adenoma, with no evidence of malignancy.
Conclusion
This case underscores the importance of considering hypercortisolism as a differential diagnosis in patients with T2D who struggle with achieving optimal blood glucose control. Clinicians should remain vigilant in identifying such conditions, as they can complicate the management of diabetes and other comorbidities, undermining treatment effectiveness and patient outcomes.

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EP1029

JOINT406

A rare coexistence of auto-immune diabetes mellitus with collagenous colitis and scleroderma: a case report

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Introduction and Background
The coexistence of multiple autoimmune diseases either systemic or organ-specific has been described in the literature. Here, we report a case of Latent Autoimmune Diabetes in Adults (LADA) associated with cutaneous systemic scleroderma (SSc), a rare and scarcely documented entity.
Case Report
A 41-year-old man, diagnosed with LADA two years prior, was treated with a basal-bolus insulin regimen. Concurrently, the patient developed symptoms of malabsorption, including chronic non-bloody watery diarrhea, abdominal pain, weight loss, iron deficiency anemia, hypoalbuminemia, and significant glycemic instability. Auto immune Adrenal insufficiency, thyroidis, and celiac disease were excluded. Colonoscopy with biopsy confirmed the diagnosis of microscopic colitis, collagenous subtype. Two years later, the patient presented with progressive diffuse thickening and hardening of the skin, accompanied by limited

joint mobility, particularly in the lower limbs.A cutaneous biopsy revealed sclerodermiform features, with significant fibrosis and no evidence of malignancy, consistent with systemic sclerosis.
Discussion
Collagenous colitis, one of the primary subtypes of microscopic colitis (MC), is a chronic inflammatory condition of the colon characterized by watery diarrhea. Although the exact etiology remains unclear, autoimmune dysfunction has been strongly involved, as evidenced by its association with various autoimmune comorbidities. Auto-immune diabetes caracterized by the destruction of pancreatic β-cells, has also been linked to MC. A nationwide matched case–control study in Sweden reported an 80% increased prevalence of Type 1 Diabetes in MC patients compared to the general population, with a stronger association observed for collagenous colitis than lymphocytic colitis. Systemic sclerosis (SSc) is an autoimmune connective tissue disorder marked by fibrosis and commonly presenting with skin involvement. Cases of coexistence between autoimmune diabetes and SSc are rare, and the underlying mechanisms remain poorly understood. Interferons are believed to play a significant role as immunomodulators and inhibitors of collagen production. In this case, the histopathology was characteristic of systemic sclerosis. However, distinguishing between diffuse skin hardening caused by systemic sclerosis and other conditions, such as scleroderma-like syndrome or diabetic scleroderma, can be challenging. Diabetic scleroderma is attributed to the non-enzymatic glycation of collagen. Chronic hyperglycemia may stimulate fibroblast proliferation and extracellular matrix production, contributing to skin hardening.
Conclusion
This case highlights the need to recognize rare autoimmune associations and integrate routine screening for comorbidities in patients with autoimmune backgrounds. Further research is needed to elucidate underlying mechanisms and improve therapeutic approaches.

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EP1030

JOINT1761

Unexplained recurrent paronychia: a closer look at an overlooked diagnosis

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Background
Pseudohypoparathyroidism (PHP) and related disorders are a group of rare diseases associated with the phenotype known as Albright's hereditary osteodystrophy (AHO), which includes round face, short stature, brachydactyly, ectopic ossifications, and intellectual disability. These conditions are caused by heterozygous inactivating mutations in the GNAS gene, leading to resistance to hormones acting via G protein-coupled receptors. The diagnosis is often delayed as the phenotypic features and hormonal resistance become apparent over time, with subtle manifestations in early childhood.
Case Presentation
We describe the case of a 9-year-old girl who was followed at the Endocrinology Department for stunted growth. Born at 32 weeks with intrauterine growth restriction, at the age of 2 years she was diagnosed with celiac disease and hypothyroidism with negative thyroid autoimmunity and normal gland position. The chromosomal microarray (CMA) did not reveal any genomic imbalances and the genetic testing for SHOX gene mutations was negative. She underwent surgery for right thumb paronychia with associated onychodystrophy at the age of 4. At the age of 5, idiopathic central precocious puberty was diagnosed, and pubertal suppression was initiated. At 7 years, her height relative to bone age was at -3 Standard Deviation Score while a disproportionate growth pattern and an abnormal shortening of the fourth metacarpal became apparent. At 8.5 years, she had a recurrent episode of paronychia affecting the foot. Skeletal X-rays showed dysmorphic features of metacarpals, metatarsals, and phalanges, along with ossifications in the soft tissues around the right big toe and the retrocalcaneal area on the left. These findings were consistent with skeletal dysplasia. Next-generation sequencing revealed a pathogenic *de novo* variant in the GNAS gene (c.1102_1125del, p.Asp368_Val375del) located in exon 13. Genetic analysis and radiological investigations ultimately revealed that the recurrent episodes of paronychia were, indeed, heterotopic ossifications, a hallmark feature of Albright hereditary osteodystrophy.
Conclusions
This case underscores the diagnostic challenges of PHP-related disorders in children, in which phenotypic features may be subtle or misinterpreted. Hypothyroidism, with a normally positioned thyroid gland, is one of the earliest signs, along with ectopic ossifications, which should be actively investigated, particularly in periarticular areas, hands, and plantar region. Additionally, even in syndromic short stature cases, precocious puberty can occur and mask the underlying condition. Awareness of AHO and its hallmark features, along with early genetic testing, are crucial for prompt diagnosis and timely management.

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EP1031

JOINT673

The role of MRI and ferriscan in diagnosing and managing endocrine and growth complications in thalassemia major

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Background
Patients with thalassemia major are at high risk of endocrine dysfunction and growth impairments due to iron overload in multiple organs. Accurate assessment of iron deposition is crucial for optimizing chelation therapy and mitigating complications. MRI T2* and Ferriscan have emerged as reliable, non-invasive tools for quantifying liver iron concentration (LIC) and detecting iron deposition in endocrine organs.
Objective
This review highlights the benefits of MRI and Ferriscan in diagnosing and managing endocrine and growth abnormalities in thalassemia major by analyzing findings from the past two decades.
Material and Methods
Twenty studies from 2006 to 2023 were reviewed, including a total of over 1,500 patients with thalassemia major. Data were synthesized on MRI T2* and Ferriscan applications for assessing iron burden in endocrine-related organs (pituitary, liver, pancreas, and heart), as well as their correlation with clinical outcomes.
Results
1. Liver Iron Concentration (LIC): Ferriscan consistently demonstrated high accuracy in LIC quantification, outperforming serum ferritin in patients with moderate-to-severe iron overload (Padeniya *et al*., 2020; Kildemoes *et al*., 2023). LIC monitoring significantly improved chelation therapy adherence and reduced overall iron burden (Calvaruso *et al*., 2014; Nichols-Vinueza *et al*., 2014).
2. Pituitary Iron and Endocrine Dysfunction: MRI T2* reliably detected pituitary iron deposition, correlating with hypogonadotropic hypogonadism and growth hormone deficiency (Wang *et al*., 2006; Morad *et al*., 2021).
3. Pancreatic Iron and Diabetes Risk: Pancreatic T2* showed early iron overload, enabling timely intervention to reduce diabetes risk (Au *et al*., 2007).
4. Cardiac and Multiorgan Correlations: MRI T2* effectively predicted cardiac iron, reducing cardiac events through tailored chelation (Farhangi *et al*., 2017; Nichols-Vinueza *et al*., 2013).
5. Correlation with Endocrinopathies: Higher LIC and cardiac iron levels strongly correlated with endocrine complications, emphasizing the importance of comprehensive iron monitoring (Kanbour *et al*., 2018; Chirico *et al*., 2015).
Discussion
MRI T2* and Ferriscan are indispensable in assessing iron deposition and guiding treatment strategies in thalassemia major. By accurately quantifying organ-specific iron levels, they enable early detection and management of endocrine dysfunction, improving growth outcomes and reducing complications.
Conclusion
MRI and Ferriscan significantly enhance diagnostic accuracy and management of endocrine and growth abnormalities in thalassemia major. Their routine use is essential for optimizing patient outcomes by tailoring chelation therapy to mitigate iron overload and prevent long-term complications.

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EP1032

JOINT727

The Unique features of growth and endocrine changes in patients with sickle ß-thalassemia

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Background
Sickle cell/β-thalassemia (HbS/β-thal) is a rare hemoglobinopathy caused by compound heterozygosity for mutations in the β-globin gene. It encompasses two

significant types: HbS/β?-thalassemia (complete absence of β-globin production) and HbS/β?-thalassemia (partial β-globin synthesis). The condition exhibits significant clinical heterogeneity, with an estimated global prevalence of 1.5% in regions with high rates of hemoglobinopathies.
Objective
This review aims to synthesize findings on the unique growth and endocrine alterations observed in patients with HbS/β-thal, emphasizing their relationship with disease severity and pathophysiological mechanisms.
Methods
A comprehensive table of findings from multiple studies focusing exclusively on HbS/β-thalassemia patients was reviewed, highlighting clinical and laboratory observations related to growth and endocrine dysfunction.
Results
1. Growth Impairment:.
• Patients with HbS/β?-thal showed significantly lower body mass index (BMI) and higher malnutrition rates than HbS/β?-thal patients, with a strong correlation between BMI and hemoglobin levels.
• Bone mineral density (BMD) was notably reduced in HbS/β? patients, reflecting heightened susceptibility to osteoporosis and osteopenia due to chronic hemolysis, inflammation, and endocrine disruption.
2. Endocrine Dysfunction:.
• HbS/β? patients exhibited more profound hypogonadism, characterized by reduced levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), alongside poor gonadal response.
• Delayed puberty and reduced insulin-like growth factor-1 (IGF-1) levels were observed in both HbS/β? and HbS/β? patients, linked to iron overload and pituitary damage.
• HbS/β^+ patients were more prone to acute chest syndrome, possibly due to elevated BMI and hemoglobin levels, which may exacerbate blood viscosity and complications.
Conclusion
The growth and endocrine alterations in HbS/β-thal patients are multifactorial, stemming from anemia, chronic inflammation, iron overload, and mutation severity. HbS/β?-thal patients typically experience more severe outcomes, with marked growth retardation, lower BMI, and extensive endocrine dysfunction. Early interventions, including chelation therapy and endocrine management, are critical to improving the quality of life and mitigating complications in these patients. Future research should explore individualized therapeutic approaches for these unique phenotypes. Table 1: Summary of HbS/β-Thalassemia Studies.

Table: Key Growth and Endocrine Features of HbS/β-Thalassemia Phenotypes.

Phenotype	Growth Findings	Endocrine Findings
HbS/B0Thal	Lower BMI, severe growth impairment, reduced BMD, delayed puberty	Hypogonadism, reduced IGF-1, pituitary dysfunction, severe anemia impact
HbS/B+Thal	Higher BMI, less severe growth retardation	Milder endocrine dysfunction, prone to acute chest syndrome due to higher Hb levels

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EP1033

JOINT180
Unravelling the connection: papillary thyroid carcinoma in MEN1 syndrome
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Background
Recent studies have highlighted a notable incidence of papillary thyroid carcinoma (PTC) in patients with multiple endocrine neoplasia type 1 (MEN1).
Case Presentation
We present the case of a 34-year-old Chinese male diagnosed with MEN1 R527X nonsense mutation through genetic screening. Although the patient was asymptomatic, laboratory investigations revealed primary hyperparathyroidism. He underwent total parathyroidectomy with deltoid implantation. Intraoperative frozen section analysis identified follicular cells in the lymph nodes of the tracheoesophageal groove. Subsequent total thyroidectomy confirmed the presence of multifocal papillary thyroid microcarcinoma. Importantly, no lymphovascular invasion, perineural invasion or extrathyroidal extension was observed.
Discussion
MEN1 is a hereditary tumor syndrome predominantly linked to endocrine tumors, including primary hyperparathyroidism, pancreatic neuroendocrine tumors, and pituitary adenomas. Nonsense mutations, such as R527X, lead to premature termination of protein synthesis, producing a truncated menin protein that loses its tumor-suppressive function, thereby increasing susceptibility to tumors. A recent study identified a 4.52% incidence of PTC in MEN1 patients, surpassing the rate in the general population . While menin is expressed in thyroid tissues, evidence of retained heterozygosity at the *MEN1* locus in PTC suggests that *MEN1* gene deletion is not directly involved in the PTC oncogenesis . PTC in MEN1 patients is often diagnosed incidentally during comprehensive surveillance for various endocrine tumors or during surgical interventions for other MEN1-related tumors. Additionally, it is possible that genetic or epigenetic factors independent of *MEN1* gene mutations contribute to the increased incidence of PTC in MEN1 patients.
Conclusion
Although the incidence of PTC is elevated in MEN1 patients, current evidence suggests that *MEN1* gene mutations do not directly cause the development of PTC. Further research is needed to explore the potential genetic or epigenetic mechanisms involved.

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EP1034

JOINT2905
Growth and puberty of children living HIV/AIDS in a reference service in northeastern brazil
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Human immunodeficiency virus (HIV) infection is a highly relevant pediatric pathology worldwide. Due to metabolic alterations inherent to the disease and factors related to treatment, children living with HIV/AIDS may present growth alterations and delayed pubertal development. Early introduction of antiretroviral therapy (ART) has increased the survival rate of this population and improved the anthropometric prognosis of infected children and adolescents. The study is justified by the scarcity of current data on the subject of the global pediatric population and aims to evaluate the growth and pubertal development of children and adolescents living with HIV/AIDS followed in a specialized service in Maranhão (Northeast Brazil). This is a cross-sectional observational study that has included, to date, 76 patients, followed at the service between October 2022 and July 2024 and evaluated by a single observer. Descriptive analysis was carried out using the SPSS version 20.0 program. It was observed that the average age was 8 years, the majority were brown, with an age at diagnosis of less than one year and an average use of ART of 5.3 years. Appropriate z-score weight for age was observed in 64.5% of the population, appropriate z-score height for age in 82.9% and appropriate z-score BMI z-score in 76.3% of cases. Of the individuals evaluated, 52 (68.4%) were in the pre-pubertal phase, while 24 were in the puberty phase. Of the 24 patients already in puberty, 21 (87.5%) had normal puberty, two had precocious puberty and one had delayed puberty. For females, the average age at the onset of thelarche was 8.10 years $\pm$ 1.7, pubarche was 10 years $\pm$ 0.8, and menarche was 11.6 years $\pm$ 0.4. For males, the average age of the gonadarche was 11. 6 years $\pm$ 1.4 and that of the pubarche was 12 years $\pm$ 1.2. This study identified that the majority of children and adolescents living with HIV presented adequate growth and pubertal development.

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EP1035

JOINT2583
Primary adrenal insufficiency in a patient with type 1 diabetes
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Introduction
Autoimmune diseases, such as autoimmune thyroiditis or celiac disease are frequently associated with type 1 diabetes. Adrenal insufficiency has been rarely observed but it deserves a timely diagnosis. A latent insufficiency always manifests in situations of stress, such as infection, surgery or trauma and then represents a potentially life-threatening condition.
Case presentation
In October 2024, a 36-year-old patient suffering from type 1 diabetes since the age of 12, was transferred to the Department of Endocrinology from the Department

of Surgery for further examination of suspected adrenal insufficiency. The patient's medical history revealed that he was being treated with insulin glargine U300 and prandial aspart only before lunch with good glycometabolic control according to HbA1c level (HbA1c 6.8%) but he had frequent hypoglycemic episodes in the morning, 2-3 times a week. Two weeks earlier, he had had a surgery and cholecystectomy was done due to Mirrizi's syndrome. Post-operatively, on the second day, he had ketoacidosis, which was treated in Intensive Care Unit. Due to severe pain and clinical presentation of an acute abdomen, CT scan was performed and five days after the first operation, another surgery, appendectomy, was performed. Postoperatively he presented with general weakness, hypotension, low glycaemia and hyponatremia and hypo-chloremia. Considering the discoloration of the skin, biochemistry findings and clinical presentation, adrenal insufficiency is suspected so further investigation continues at the Department of Endocrinology. The thyroid and sex hormone status was normal. Adrenal axis evaluation showed normal basal cortisol, unexpected for the postoperative period and very high ACTH levels. Cortisol levels in Synacthen test showed no increase, while adrenal insufficiency was confirmed. Antiadrenal antibodies were positive and serum levels of 21-hydroxylase antibodies were above 10 U/ml. Oral hydrocortisone at 15 mg/day divided in 2 daily doses was started. Due to normal PRA there was no need to start mineralocorticoid therapy. Continuous glycemia monitoring was performed and he was discharged from hospital. Three months later, he reported subjectively better quality of life, TIR above 70% and no nocturnal hypoglycemic arousals. Since there is a possibility of Schmidt syndrome, frequent monitoring of thyroid hormones is necessary.

Conclusions

Type 1 diabetes needs prompt recognition or periodical screening of potentially associated autoimmune conditions. Adrenal insufficiency even though rarely encountered among young patients, may be initially symptomless and characterized by slow progression until it turns into acute adrenal crisis, which represents a potentially life-threatening condition.

Keywords

adrenal insufficiency, type 1 diabetes, Schmidt syndrome.

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EP1036

JOINT2548

Management of hyperandrogenism in hemodialysis patient with PCOS: challenges and therapeutic strategies

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting women of childbearing age. The mechanisms of this syndrome are due to hormonal imbalance, resulting in excessive production of androgens, particularly testosterone. this case report illustrates a case of renal failure at the hemodialysis stage with sopk.

Observation

31-year-old patient who has as antecedent: ESRD due to renal amyloidosis at hemodyal stage, cerebral venous thrombosis and IVC thrombosis on antic-oagulant of the antivitamin K family presented with moderate hirsutism evolving over the past 4 years, associated with rapidly worsening androgenic alopecia and cycle disorders. clinical examination reveals negative Homans sign, Absence of ancanthosis nigricans, a BMI of 21 kg/m^2 and a feriman score of 22. External genitalia examination: clitoral hypertrophy prader 1 Creatinine levels were 53 mg/hormonal investigation found Testosterone level =1 .45 ng/ml FSH =4.67 mu/ml LH=27 mu/ml 17 OH PROGESTERONE =1.5 ng/ml D4ANDROS-TENDIONE = 5.3 ng/ml SDHEA= 410 ng/ml negative ovarian tumour markers metabolic panel showed dylipidemia with normal glycated hemoglobin Surrenal MRI was normal, and pelvic MRI of enlarged ovaries with multiple follicular formations (greater than 12 follicles/ovary).

Discussion

The management of sopk in the context of end-stage renal failure and thrombosis antcd represents a challenge to the practitioner. Given the multiple contra-indications encountered with the usual treatments (oestroprogestogenic contra-ception, anti-androgenic progestins), therapeutic options will be directed towards 2nd-line treatments, notably spirinolactione, finasteride and flutamide. The data in the literature have demonstrated the possibility of using these treatments in this context, provided that the minimum effective doses are respected and regular monitoring of kalemia, INR and liver function is carried out. In safety studies concerning the use of mineralocorticoid receptor antagonists in hemodialysis patients, spirinolactone caused only a negligible change in baseline kalemia levels. In our patient, the choice of treatment was spironolactone at a dose of 50 mg/day, in in concession with the nephrologists.

Conclusion

The management of sopk in the context of ESRD and thrombosis antecedent remains a challenge for the practitioner, requiring a multidisciplinary approach involving specialists in endocrinology, nephrology and haematology.

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EP1037

JOINT2948

Multiple endocrine and non-endocrine tumors in a patient with type 1 multiple endocrine neoplasia

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a rare hereditary endocrinopathy with a prevalence of 1–9 cases per 100,000. It is characterized by the development of multiple endocrine and non-endocrine tumors, with the classical triad involving the parathyroid glands, pituitary gland, and duodenopancreatic neuroendocrine tumors (NETs).

Clinical Case Description

Since the age of 27, Patient M. experienced episodes of tremor and visual disturbances associated with fasting. At 37 years old, following recurrent renal colic episodes, kidney ultrasound revealed a left adrenal tumor. Further evaluation showed elevated prolactin levels (4,200 IU/ml; reference range: 63.6–349.8), and brain MRI confirmed the presence of a pituitary adenoma. One year later, the patient was started on cabergoline 0.5 mg twice weekly. Concurrently, laboratory tests showed increased parathyroid hormone (PTH) levels (26.2 pmol/l; reference range: 1.16–7.06), hypercalcemia (ionized calcium: 1.51 mmol/l; reference range: 1.10–1.30), and vitamin D deficiency (13.85 ng/ml) . Thyroid and parathyroid ultrasound revealed a thyroid nodule in the right lobe and a smaller hypoechoic lesion. Chest CT identified multiple rounded foci in both lungs. At age 39, prolactin levels remained elevated despite increasing the cabergoline dose to 1.5 mg weekly. MRI confirmed persistent pituitary adenoma, and the patient was diagnosed with primary hyperparathyroidism. Additionally, thyroid ultrasound revealed a 36×24×20 mm nodule in the right lobe, classified as EU-TIRADS 4. Fine-needle aspiration biopsy indicated a Bethesda IV lesion, while calcitonin levels were 6.6 pg/ml. Further investigations revealed multiple pancreatic NETs on abdominal CT and nodular adrenal hyperplasia in both glands. A 72-hour fasting test confirmed fasting hypoglycemia with elevated proinsulin levels. Chest CT showed multiple pulmonary foci (3–11 mm). Physical examination revealed numerous papillary skin formations on the torso, forearms, legs and feet, histologically established to be fibromas. The patient underwent thyroidectomy and parathyroidectomy, with histological analysis confirming follicular thyroid carcinoma in the right lobe and parathyroid hyperplasia. After completing radioactive iodine therapy, whole-genome sequencing identified a de novo MEN1 mutation. Three months later, the patient underwent partial resection of the right lower lung lobe. Immunohistochemical analysis confirmed a Grade 2 atypical pulmonary carcinoid. Consequently, combination therapy with capeci-tabine and temozolomide was initiated.

Conclusion

This case underscores the importance of comprehensive diagnostic evaluation in patients with MEN1. While the classical triad of tumors is well recognized, MEN1 patients may present with a broader spectrum of neoplasms, necessitating individualized and multidisciplinary treatment approaches.

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EP1038

JOINT5

Neurofibromatosis type 1 with polycystic liver disease and hypertension in the young as a co-occurrence with heterozygotic PKHD1 variant: a case report and review of the literature

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Background
Neurofibromatosis type 1 (NF1) is a common genetic condition (estimated prevalence at 1:3000 live births) and 0.1-5.7% of patients with NF1 will develop pheochromocytomas and paragangliomas in their lifetime. However, other causes of hypertension (HT) in the young among these patients could be presented and polycystic liver disease is not a part of NF1 syndrome. While autosomal recessive polycystic kidney disease (ARPKD) caused by biallelic pathogenic variants in the polycystic kidney and hepatic disease 1 (*PKHD1*) gene are rare (estimated prevalence at 1:20,000 live births), the frequency of heterozygous carrier state of *PKHD1* gene is relatively common at 1 in 70 among general population. Polycystic liver disease had been described among patients with heterozygotic *PKHD1* variant. We herein report a rare case of an NF1 patient who presented with HT in the young and incidental finding of polycystic liver disease.
Case Report
A 37-year-old Thai patient with history of NF-1 (clinically diagnosed at the age of 20 from presence of café au lait spots and neurofibromas) consulted with HT in the young for 2 years without other symptoms. No family history of hypertension or other genetic disorders had been reported. Abdominal computed tomography revealed polycystic liver disease and a simple renal cyst with normal both adrenal glands. Laboratory studies showed normal results. Whole exome sequencing (WES) confirmed molecular diagnosis of NF1 with heterozygous pathogenic variants c.5268+1G>A of *NF1* and heterozygous pathogenic variants c.7594_7597del of *PKHD1* gene. Given the results of genetic testing and no identified other causes of HT, co-occurrence of NF1 and HT-associated heterozygotic *PKHD1* variant were diagnosed in this patient.
Conclusions
Our case highlights the diagnostic challenges of atypical phenotypes among individuals with NF1 might depend on the background of other genes. With increasing affordability of WES, its utility in uncovering the possibility of being affected by two inherited genetic conditions should be considered when findings are incompatible with the primary disease. The co-occurrence of *NF1* and *PKHD1* variants by chance or causative relationship should be further investigated in the future.

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EP1039

JOINT1836

Association of diabetes mellitus, primary hypothyroidism, and addison's disease in a patient followed for glycogen storage disease type iii

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Introduction
Glycogen Storage Disease Type III (GSD III) is a rare metabolic disorder characterized by hepatic and muscular glycogen storage defects, leading to liver dysfunction, cardiomyopathy, and metabolic complications. We report the case of a patient followed for GSD III who presented with diabetes mellitus, peripheral adrenal insufficiency, and primary hypothyroidism.
Case Presentation
A 41-year-old female patient was admitted to the hospital for an adrenal insufficiency crisis. She gives a complex medical history of GSD III, diagnosed at the age of 7, complicated by liver cirrhosis and hypertrophic cardiomyopathy with heart failure and epilepsy since infancy. At the age of 38, she was diagnosed with diabetes mellitus and peripheral hypothyroidism. She was under SGLT2 inhibitors, DPP-4 inhibitors, and L thyroxine. The diagnosis of primary adrenal insufficiency was retained. The patient was put on hydrocortisone and basal insulin. DPP4 inhibitors were stopped. Therapeutic education on the risk of hypoglycemia was done since the patient presented several factors precipitating hypoglycemia namely GSD III at the cirrhosis stage and adrenal insufficiency.
Conclusion
The overlapping metabolic and endocrine abnormalities in this patient highlight the necessity for a multidisciplinary management approach. This case underscores the importance of routine metabolic and endocrine evaluations in GSD III, particularly given the emerging associations with hypothyroidism and adrenal insufficiency. This case represents the first documented instance of both hypothyroidism and adrenal insufficiency in GSD III, highlighting the need for further research into endocrine dysfunction in the disease.

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EP1040

JOINT3561

Primary hyperparathyroidism and autoimmune diseases: a case report

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Introduction
Primary hyperparathyroidism (PHP) is the most common cause of hypercalcemia. Patients with autoimmune diseases can develop hypercalcemia but it is exceptionally due to PHP. The association of PHP withautoimmunedisordersis-describedveryrarely in the literatureso far. There are only few cases of immunemediatedhyperparathyroidism, associatedwith anti-calcium- sensingreceptorautoantibodies. The exact etiology of PHP in autoimuune diseasesis not known. The underlying pathophysiology was supposed to be either a common genetic predisposition or the extension of the autoimmune process to the parathyroid glands, which is still under debate. Our objective is to report a rare case associating a background of autoimmunity and primary hyperparathyroidism.
Observation
A 44-year-old woman with medical history of lupus, vitiligo, antiphospholipid antibody syndrome, GogerotSjogren's syndrome, arterial hypertension and dyslipidaemiawas referred to our department with primary hypercalcaemia in the face of bone pain with inflammatory arthralgia and functional impotence. Her biology showed a parathyroid hormone level of 121pg/l,a calcemia of 2.92 mmol/land a vitamin D level of 18 ng/ml. A cervical ultrasound and parathyroid MIBI scintigraphywere performed, showing a left inferior parathyroid nodule measuring 21*15*13mm. A left inferior parathyroidectomywas performed with anatomophatological findings of a parathyroid adenoma and a postoperative parathyroid hormone level of 19pg/land serum calcium of 2.3mmol/l.
Conclusion
Primary hyperparathyroidism and autoimmune diseases are two serious conditions. Their association is exceptional, but it can make their management more complicated. It is important for clinicians to remember that PHP is still the most common cause of hypercalcaemia. Therefore, when hypercalcaemia occurs in autoimmune diseases, it is prudent to carry out a full investigation to determine the most appropriate treatment to avoid potential complications.
Disclosure of interest
none declared.

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EP1041

JOINT2035

Late diagnosis and course of the treatment of patient with pseudohypoparathyroidism type 1 A and growth hormone deficiency with excellent height outcome

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Background
Pseudohypoparathyroidism type 1A is a rare endocrine disorder in children due to mutations in GNAS gene. Typical presentations include hypocalcemia, hypothyroidism. Phenotypic characteristics (obesity, skeletal findings, short stature, developmental delay). Short stature with poor final adult height is a common presentation. Resistance to GHRH is described, there are cases of GH deficiency. GH has been used in the treatment of patients with PHP type 1A. There are no reports of combined use of GH and letrozole in patients with pseudohypoparathyroidism type 1A.
Objectives
To describe a rare case when a child was diagnosed with pseudohypoparathyroidism type 1 A later due to milder presentation, who was also later diagnosed with GH deficiency and had a great response to treatment with GH in conjunction with letrozole use.
Methods
A 4 years old male presented with obesity. Work up revealed mild hypothyroidism TSH=11.8 UIU/ml (reference 0.3-4.5), fT4=0.94 ng/ml (reference 0.89-1.7), negative thyroid antibodies. Newborn screen borderline for congenital hypothyroidism, patient was presumed to have mild form of congenital hypothyroidism, started on levothyroxine. At age 5 developed low calcium 8.3 mg/dl (reference 8.7- 10.4) with low 25 vitamin D, started vitamin D with improvement in calcium. At age 12 years calcium 6.7mg/dl, PTH =447 pg/ml (reference 18-88). Physical exam short 4th

metacarpals. Genetic testing confirmed GNAS gene mutation, patient was diagnosed with pseudohypoparathyroidism type 1A. Started calcitriol, calcium carbonate. Physical exam at age 12: Tanner III, advanced bone age. GH stim test peak of GH = 15 ng/ml. patient was not a candidate for GH therapy, started on letrozole. Growth velocity decreased, patient had another GH stim test with peak of GH = 4.1 ng/ml. Started GH therapy with increase in growth velocity from 3.6 cm/year to 8.8 cm/year.
Results
This is a case report of a child with PHP type 1A, whose diagnosis was delayed due to late presentation of hypocalcemia. Patient developed GH deficiency, treated with GH and aromatase inhibitor with great height outcome.
Conclusion
PHP type 1A is a rare disorder with multiple endocrine disorders related to hormonal resistance. Diagnosis can be delayed as hormonal problems may develop later in life. Earlier and fast progressing puberty happens in male patients with PHP type 1A, can worsen short stature. Testing for GH deficiency is important to reveal patients that can benefit from GH use. Combination of GH and aromatase inhibitor helps to improve final adult height in patients with PHP type 1A.

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EP1042

JOINT2236

Primary hypoparathyroidism and hashimoto's thyroiditis- a rare autoimmune disease combination

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Background
Primary Hypoparathyroidism is a rare disorder characterized by hypocalcemia and hyperphosphatemia resulting from inadequate PTH synthesis and secretion. Even though neck surgery is the most common etiology, the non-surgical forms have been linked to autoimmune dysregulation and activation of humoral or cell-mediated immunity against parathyroid cells. Hashimoto's thyroiditis, a common autoimmune cause of hypothyroidism. Both conditions can occur as an isolated endocrinopathy or as part of autoimmune polyglandular syndrome (APS), which is characterized by the functional impairment of multiple endocrine glands. Their coexistence is exceedingly rare but may suggest shared genetic and autoimmune mechanisms.
Case presentation
A 35-year-old Caucasian female was referred to the clinic with typical symptoms and complaints of hypocalcemia. For the past several years, patient had multiple hospitalizations due to episodes of hypocalcemia with tetany and seizures, requiring calcium infusions. Her medical history was remarkable for infertility with diminished ovarian reserve. The patient denied any history of neck surgery or irradiation. Regarding her family history, there was no evidence of cancer or genetic disorders among first-degree relatives. However, her father had type 2 diabetes. On Physical examination Trousseau's and Chvosteck's signs were positive. Laboratory studies revealed Primary Hypoparathyroidism with severe hypocalcemia—0.4mmol/l,low PTH levels – 2.64 pg/ml, high phosphorus—1.8 mmol/l,hypomagnesemia—0.63mmol/land low levels of Vitamin D-1,25—13ng/l. An electrocardiogram showed a prolonged QT interval. Brain MRI revealed no abnormalities. Infertility workup showed decreased ovarian reserve: AMH-0.527ng/ml FSH -14mIU/ml. transvaginal ultrasonography revealed low AFC. Combined calcium and calcitriol supplementation was commenced, with laboratory and clinical improvement. Assisted reproductive technology (ART) was used to aid in achieving pregnancy without success. The patient discontinued yearly checkups, and two years later, she was referred to an endocrinologist after a spontaneous pregnancy miscarriage. Laboratory tests revealed Hashimoto's subclinical hypothyroidism (TSH – 4.94mIU/ml; FT4-14.53pmol/l; ANTI-TPO – 221U/ml; ANTI-TG—1068 U/ml) and mild hypocalcemia due to irregular calcium supplement intake (Calcium – 1.02 mmol/L). Thyroid ultrasound showed an enlarged, heterogeneous thyroid (30cc) with hypoechoic nodules. Treatment with levothyroxine, calcium and calcitriol with lifestyle modifications resulted in symptom resolution. After several months of achieving laboratory and clinical improvement, infertility treatment is scheduled.
Conclusion
The coexistence of Primary hypoparathyroidism, Hashimoto's thyroiditis, and diminished ovarian function is exceedingly rare, but suggests a potential shared autoimmune pathogenesis. Further research is needed to explore possible genetic and immunological links. Since disease is lifelong, essential follow-up is needed to avoid complications and recurrence.

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EP1043

JOINT402

Beyond the triad: surgical management of endocrine and skeletal complications in mccune-albright syndrome

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Introduction
McCune-Albright Syndrome (MAS) is a rare, multisystem disorder arising from a post-zygotic activating mutation in the *GNAS* gene. This mutation leads to constitutive activation of the G protein α-subunit. The classic triad of MAS includes fibrous dysplasia, *café-au-lait* spots, and precocious puberty. This case report describes a 65-year-old woman with MAS, highlighting the complexity of managing this condition. It shows the critical role of a multidisciplinary approach, with a focus on surgical interventions and the use of translaryngeal ultrasound (TLUS).
Case Report
A 65-year-old woman presented with a history of MAS diagnosed in early adulthood. At the age of 61, she was diagnosed with hyperthyroidism. This necessitated a total thyroidectomy, which was performed as a staged procedure due to recurrent laryngeal nerve injury (RLN) during the initial right lobectomy. The left lobectomy was delayed until RLN recovered after close monitoring with TLUS. Mild hypercalcemia and neck ultrasonography led to the diagnosis of hyperparathyroidism, which was confirmed by fine-needle aspiration with positive PTH "washout", despite a negative MIBI scan. Surgical intervention included removal of a left lower parathyroid adenoma. Furthermore, the patient developed acromegaly, with elevated IGF-1 levels and characteristic clinical features. This prompted treatment with somatostatin analogues and ultimately two transsphenoidal pituitary surgeries. The procedures were technically challenging due to the presence of extensive fibrous dysplasia of the skull base. The cause of acromegaly was somatotroph hyperplasia involving the entire pituitary gland, with the presence of mammosomatotropic adenoma. The patient also experienced significant skeletal complications due to fibrous dysplasia, requiring multiple orthopedic surgeries.
Discussion
This case underlines the complexity of MAS. The patient showed a range of abnormalities that underscore the need for comprehensive evaluation and personalized treatment. It also presents the surgical challenges, emphasizing the need for careful planning and experienced surgeons. The staged thyroidectomy demonstrates the importance of careful consideration of potential complications, like RLN injury, and the use of tools like TLUS to guide surgical decision-making. Finally, this case reinforces the importance of a coordinated multidisciplinary approach involving different specialists to effectively manage the diverse manifestations of MAS.
Conclusion
This case report illustrates the complex and multifaceted nature of MAS. Surgical intervention plays a crucial role in managing this disorder. The integration of advanced imaging techniques, such as TLUS, can enhance surgical safety and efficacy. A multidisciplinary approach is essential for optimizing patient outcomes and improving the quality of life in individuals with MAS.

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EP1044

JOINT725

Effects of intensive iron chelation therapy on glucose abnormalities in beta-thalassemia major patients

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Background
Beta-thalassemia major is a transfusion-dependent condition characterized by chronic iron overload, leading to glucose abnormalities, endocrine dysfunctions, and impaired growth. This study evaluates the impact of intensive iron chelation therapy on these complications using real-world evidence from published literature.
Methods
A systematic review of 23 studies published between 2007 and 2023 involved 2,385 patients with beta-thalassemia major or intermedia. The studies assessed the effectiveness of iron chelation therapy using metrics such as serum ferritin, MRI-derived liver and pancreatic iron burden, glucose tolerance tests (OGTT), and endocrine outcomes.

Table 1. Real Impact Table from Big Table Data.

Outcome	Observed Change	Patients Impacted (% Real)	Comments
Glucose Abnormalities	Improvement in glucose tolerance	44%	Pancreatic T2* MRI outperformed serum ferritin in predicting improvements.
Insulin Sensitivity	Increased in patients with reduced liver/-pancreatic iron	68%	Strongly linked to early chelation therapy.
Hypogonadism	Reduction in prevalence	50%	Residual dysfunction remained in severe cases.
Growth Hormone Deficiency	Limited improvement in growth velocity	25%	Late diagnoses resulted in irreversible axis damage.
Linear Growth	Slight height catch-up	33%	Most effective in children receiving early therapy.
Delayed Puberty	Onset normalized	38%	Early chelation showed greater efficacy in mitigating pubertal delays.

Results
- Iron Chelation Therapy Impact:.
  - Glucose Abnormalities: Improvements were observed in 44% of patients with glucose tolerance abnormalities following intensive chelation therapy. Pancreatic T2* MRI proved superior to serum ferritin in predicting glucose abnormalities.
  - Insulin Sensitivity: Increased insulin sensitivity was reported in patients achieving reduced liver and pancreatic iron burden, with an estimated improvement in 68% of cases.
  - Endocrine Dysfunction:.
  - Hypogonadism: Prevalence was reduced in 50% of patients after chelation adjustments guided by pituitary MRI findings.
    - Growth Hormone Deficiency: Limited improvement in growth-velocity, with only 25% of patients showing significant catch-up growth due to irreversible damage in late-diagnosed cases.
    - Delayed Puberty: Onset normalized in 38% of patients, particularly in those who received early and aggressive therapy.
- MRI Utility: MRI assessments were consistently better at correlating iron burden with glucose and endocrine outcomes compared to serum ferritin. Pituitary and pancreatic iron deposition strongly predicted dysfunctions.
- Emerging Therapies: The data remains preliminary.

Conclusions
Intensive iron chelation therapy significantly improves glucose tolerance, insulin sensitivity, and some endocrine dysfunctions in beta-thalassemia major patients. However, limitations remain in reversing severe growth impairments. MRI is indispensable for accurate organ-specific iron monitoring and guiding treatment adjustments. The integration of advanced therapies, including gene therapy, may further enhance long-term outcomes.

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EP1045

JOINT1357

Hereditary primary hyperparathyroidism is still challenging - beyond genetic screening

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Objective
Hereditary forms of primary hyperparathyroidism (PHPT) are much less common and often challenging the clinicians especially when active screening and genetic testing are lacking.
Methods
We report 4 members of a MEN 1 family identified from a Romanian cohort of 271 PHPT patients from a tertiary endocrinology center (4,5% had familial forms). Familial syndrome confirmation came after active screening despite long-standing history of PHPT and other associated endocrine tumors that were managed by different doctors never rising suspicion, along with low patient compliance. **Case 1:** 44 years old man (proband), with history of recurrent nephrolithiasis since age 26, PHPT first diagnosed at age 38 with total thyroidectomy and 2 glands parathyroidectomy (PTX), acromegaly (GH+PRL pituitary macroadenoma) at age 43, bilateral adrenal tumors with left adrenalectomy for Cushing syndrome at age 44 (8/5,8 cm); persistent mild HPTH, pancreatic tumors (gastrinemia 5900 pg/ml), right stable adrenal tumor (3/2 cm) at age 48; he denied surgeries, was frequently lost to follow-up and eventually died from right metastatic adrenocortical carcinoma (ACC). **Case 2**: 41 years old brother, diagnosed with PHPT multiglandular disease (hypercalcemia since age 37; range 11,2-12,4 mg/dl, no nephrolithiasis), biochemically cured by 3 glands and ½ PTX. Other tumoral findings: non-functional pituitary macroadenoma with hypogonadotropic hypogonadism, gastrinoma with Zollinger-Ellison syndrome (gastrinemia 56.050 pg/ml, medically controlled), multiple non-functional pancreatic tumors, bilateral non-functional adrenal tumors. **Case 3:** 72 years old father diagnosed with PHPT multiglandular disease (history of nephrolithiasis since age 30, PHPT with right inferior PTX at age 43, persistence of hypercalcemia since age 51 (range 10-12,5 mg/dl), bisphosphonates treated osteoporosis since age 70, persistent PHPT confirmation at age 72. PTX (2 and ½ glands) with auto transplant was performed. Other tumoral findings: pituitary incidentaloma, pancreatic non-functional uncinate tumor (2,3 cm), bilateral non-functional adrenal tumors, subcutanuous lipomas. **Case 4:** 20 years old daughter of case 2, was identified by screening with prolactinoma at age 9 and PHPT at age 19.
Discussion
HPTH persistence was the rule in this family with late MEN 1 diagnosis (decades). Clinical and hormonal screening was rewarding as the proband's brother and his daughter were diagnosed and treated adequately. Bilateral adrenal tumours were seen in 3 cases; Cushing syndrome and ACC are rare events in MEN 1.
Conclusions
Clinical and hormonal screening is fast and accessible allowing early diagnosis and adequate management of the patients and the other family members, even when genetics is not available.

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EP1046

JOINT3568

Surgical management, diagnostic challenges, and long-term outcomes in a patient with MEN1: a unique case report

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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant disorder characterized by tumors of the parathyroid glands (PTG), pancreas, and anterior pituitary. Surgical management is often required, but long-term complications can be severe. Here, we present a unique case of a young patient with MEN1 and recurrent primary hyperparathyroidism (PHPT), who underwent total pancreatectomy, leading to diabetes mellitus (DM).
Clinical Case
A 27-year-old woman was diagnosed with MEN1 syndrome (heterozygous *c.203delC p.T70fsX118* mutation) following the incidental discovery of a pancreatic mass during an abdominal ultrasound. In 2012, she underwent resection of the right adrenal gland and cholecystectomy, along with total duodenopancreatectomy for multiple pancreatic tumors, which were histologically confirmed as somatostatinomas. As a result, she developed fulminant diabetes, necessitating intensive insulin therapy. In 2013, at the Endocrinology Research Centre, she underwent paraadenomectomy of four hyperplastic PTGs with autotransplantation of parathyroid fragments into the right forearm due to symptomatic PHPT. However, despite surgery, PTH levels remained persistently high. A modified Casanova confirmed high PTH production recurrence at the site of autotransplantat but with "hypoparathyroid" dependance on 2 mg of alfacalcidiol and 1000 mg of calcium consistent with immunoactive but inactive PTH circulation. After three years of calcium and alfacalcidol therapy, PTH levels was 84 pg/ml (non autotransplanted arm), with corrected calcium at 2.58 mmol/l(2.15–2.55) and normocalciuria. Given the continued elevation of PTH and calcium, further diagnostic workup was undertaken. Ultrasound revealed hyperplasia of the autotransplanted PTG fragments in the right forearm muscle. A repeat Casanova test confirmed recurrent PHPT, prompting autograft removal, which resulted in PTH decrease (8.3 pg/ml) and reintroduction of "hypoparathyroid" state. Additionally, brain MRI identified a 2.3 × 4.4 mm pituitary adenoma. Two years later, the patient was diagnosed with hyperprolactinemia, with stable adenoma size, and was prescribed cabergoline. In 2020, due to worsening glycemic control (HbA1c 7.5%), she was transitioned to insulin pump therapy, leading to stabilization within individual target ranges. Screening for diabetic complications revealed diabetic distal polyneuropathy. Currently, the

patient exhibits positive clinical outcomes, including PHPT remission and optimized glycemic control.
Results
This case highlights the complexities of identifying the primary source of PTH secretion in patients with autotransplanted PTG fragments, the risks associated with repeated surgeries, and the challenges of achieving glycemic stability in absolute insulin deficiency.

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EP1047

JOINT3621

Multiple endocrine neoplasia type 1 phenotype with negative genetics

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Introduction
Multiple endocrine neoplasia are rare, with a prevalence of 1 in 200,000 in the general population. The diagnosis is confirmed by identifying a genetic mutation. However, in sporadic cases, this mutation remains undetected.
Case Report
We report the case of a 74-year-old female patient with a family history of papillary thyroid carcinoma in her daughter. She has been followed in our department for 10 years due to recurrent primary hyperparathyroidism. She underwent three surgical interventions for primary hyperparathyroidism over a 10-year period, each time revealing a parathyroid adenoma. This condition was complicated by osteoporosis. Suspicion of multiple endocrine neoplasia (MEN) prompted further investigations: Bilateral adrenal nodular thickening was observed. Hormonal evaluation of these nodules revealed ACTH-independent Cushing's syndrome. Pituitary imaging identified a 7 mm left-sided, non-secreting pituitary microadenoma. Genetic analysis for MEN1, AIP, CDKNIB, CaR, CDC73, and GNA11 was negative. The patient was started on calcimimetics for her primary hyperparathyroidism. Medical treatment is planned for her ACTH-independent Cushing's syndrome.
Discussion
The association of primary hyperparathyroidism, bilateral adrenal adenomas with ACTH-independent Cushing's syndrome, and a pituitary microadenoma supports the diagnosis of multiple endocrine neoplasia type 1 (MEN1). However, genetic testing for MEN1 mutations was negative. Indeed, in 5-10% of MEN1 cases, no mutation is detected. In such instances, the simultaneous occurrence of endocrine tumors typically associated with MEN1 mutations may result in a phenocopy. Other genetic mutations could be responsible for a MEN1-like phenotype, such as CDKN1B mutations, which cause multiple endocrine neoplasia type 4. Additionally, mutations in CaSR, AIP, and CDC73 have been implicated in MEN1-like syndromes. However, genetic testing for all these genes in our patient was negative. This case could represent a MEN1-like phenotype due to an unidentified etiology or the coincidental occurrence of multiple endocrine tumors.

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EP1048

JOINT2278

Clinical case report: rare association of MEN2B syndrome and type 1 diabetes

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Multiple Endocrine Neoplasia type 2B (MEN2B) is a rare autosomal dominant disease caused by mutations in the RET proto-oncogene. It is associated with medullary thyroid cancer (MTC) and pheochromocytoma, along with systemic manifestations, including marfanoid habitus, mucosal neuromas, and gastrointestinal ganglioneuromatosis. We present a case of a 33-year-old man with uncontrolled hypertension, sinus tachycardia, hyperhidrosis, and marfanoid habitus. He was diagnosed with bilateral pheochromocytoma and subsequently MTC. Genetic testing confirmed a heterozygous RET mutation (pMet918Thr, exon 16), consistent with MEN2B. He underwent bilateral adrenalectomy, with pathology confirming benign pheochromocytomas. Later that year, he had surgery for MTC with lymph node metastases (total thyroidectomy with bilateral central and lateral neck lymph node dissection). Despite treatment, he remains with persistent disease, with a calcitonin doubling time of 36 months. He is now under replacement therapy with hydrocortisone (20 + 10 mg/day), fludrocortisone (0.1 mg/day), and levothyroxine (125 mg/day). The patient exhibits marfanoid features, including tall stature, pectus excavatum, arachnodactyly, and scoliosis. Additionally, he presents mucosal neuromas of the tongue and lips. Ocular complications have arisen due to absent tear production, leading to severe corneal ulceration. His gastrointestinal history includes intestinal ganglioneuromatosis, with surgeries at the age of 9 and 30 for bowel obstruction and perforated diverticulitis with peritonitis, respectively. He also has valvular heart disease, manifesting as mitral and tricuspid valve prolapse. Of particular interest is the onset of type 1 diabetes at the age of 34, one year after the MEN2B diagnosis. He is managed with multiple daily insulin injections (degludec and aspart), but his glycemic control remains suboptimal (HbA1c 10%). While secondary diabetes is common in patients with pheochromocytoma due to excessive catecholamine secretion, the coexistence of type 1 diabetes in MEN2B is extremely rare, with very few cases documented in the literature. This case illustrates the complexity of MEN2B, with its combination of neuroendocrine tumors and extensive multisystemic involvement. The unique coexistence of type 1 diabetes adds complexity to the patient's care, highlighting the need for ongoing research to explore any potential connections between MEN2B and autoimmune dysregulation. Multidisciplinary care is essential for managing the diverse complications of this rare syndrome.

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EP1049

JOINT480

The "4 A" syndrome: a rare etiology of adrenal insufficiency in pediatric endocrinology: about a case report

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Introduction and Background
Allgrove syndrome, also known as "4A syndrome," is a rare autosomal recessive condition characterized by Alacrimia, Achalasia, Adrenal insufficiency, and Autonomic disturbances, among other features.
Case Report
We present the case of a 19-year-old female, born to consanguineous parents, who first exhibited symptoms at age 3 with alacrimia, initially mistaken for an allergic reaction. At 12, she presented with acute gastrointestinal symptoms, generalized hyperpigmentation, hypotension, and growth delays. Hormonal testing confirmed primary adrenal insufficiency (cortisol: 4.5 µg/dl, ACTH: 344 ng/L), and she was treated with hydrocortisone. Etiological investigations revealed a positive Schirmer's test, confirming alacrimia, and she was started on artificial tears. Achalasia was diagnosed via esophagram, showing impaired cardia motility, and treated with Heller's myotomy at age 14, leading to good progress. By 16, the patient developed polyradiculoneuropathy, confirmed by EMG findings of sensory and motor demyelination with axonal damage. Treatment with pregabalin, alpha-lipoic acid, acetyl-L-carnitine, and coenzyme Q10 yielded satisfactory results. However, she continues to experience severe learning difficulties. The clinical presentation strongly suggests Allgrove syndrome despite the absence of genetic confirmation.
Discussion
Allgrove syndrome is marked by adrenal insufficiency, alacrimia, and achalasia, often accompanied by progressive neurological impairments. Mutations in the **AAAS gene** on chromosome 12q13 are implicated. Alacrimia, the earliest and most constant sign, results from cholinergic innervation degeneration. Achalasia occurs in 75% of cases due to absent ganglion cells in the lower esophagus. Adrenal insufficiency, predominantly glucocorticoid defect due to ACTH resistance typically emerges early in life, with mineralocorticoid involvement in 15% of cases. Neurological manifestations include motor neuropathy, amyotrophy, and, rarely, amyotrophic lateral sclerosis or epilepsy.
Conclusion
Early diagnosis and a multidisciplinary approach are critical for managing Allgrove syndrome. Regular monitoring, steroid dose adjustments, and patient education are essential for improving outcomes.

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EP1050

JOINT2004

Prader-willi syndrome: a 17-year retrospective study on clinical features and genetic findings

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Introduction
Prader-Willi syndrome (PWS) is a genetic disorder that exemplifies parental imprinting. It is a complex multisystemic condition with age-dependent phenotypic variability.
Methods
We conducted a descriptive, retrospective study of patients diagnosed with PWS and followed in the Department of Pediatrics A at Hedi Chaker University Hospital over a 17-year period (2008–2024).
Results
Eight patients, ranging in age from birth to 11 years, were included. Seven out of eight presented with dysmorphic features. Neonatal hypotonia was observed in five cases. Delayed motor development was noted in seven patients, and behavioral characteristics typical of PWS were reported in two children. A documented transition between nutritional phases was observed in one patient, while obesity was present in five cases. Endocrine disorders were identified in five patients, with hypogonadism in all of them, including cryptorchidism (5 cases), scrotal hypoplasia (2 cases), and micropenis (3 cases). Adrenal insufficiency was reported in one case, and diabetes in another. Additionally, one patient had epilepsy, and skeletal abnormalities, such as bilateral hip dysplasia, were observed in another. FISH analysis confirmed a deletion at the SNRPN locus in one patient. Methylation studies established the diagnosis in six patients, and whole-exome sequencing identified the condition in one case. Maternal uniparental disomy was detected in one patient, who also had homogeneous Klinefelter syndrome. All patients received multidisciplinary care. Growth hormone therapy was initiated in one patient, with ongoing monitoring. Unfortunately, one patient died due to respiratory failure.
Conclusion
Prader-Willi syndrome is a rare genetic disorder with potentially severe multisystemic complications. This study underscores the critical importance of early diagnosis and a tailored, multidisciplinary management approach.

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EP1051

JOINT1487

Congenital hyperinsulinism due to a heterozygous glud1 variant without hyperammonemia: a case report

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Introduction
GLUD1 hyperinsulinism, also known as hyperinsulinism-hyperammonemia (HI/HA) syndrome, is a form of congenital hyperinsulinism caused by activating mutations in the GLUD1 gene, which encodes the enzyme glutamate dehydrogenase (GDH). This condition is characterized by recurrent episodes of hypoglycemia and mild, persistent hyperammonemia. Patients may also experience developmental delays and seizures, potentially due to increased GDH activity in the brain. The condition is typically inherited in an autosomal dominant manner, although de novo mutations can occur. Diagnosis is often confirmed through genetic testing, revealing heterozygous mutations in the GLUD1 gene. Cases of *GLUD1*-related congenital hyperinsulinism without hyperammonemia have been reported, despite it being a key feature of the syndrome.
Case Presentation
A male infant, born to healthy non-consanguineous parents via elective cesarean at 38.4 weeks, APGAR score 9/9, birth weight 2800g (p10-25), length 50 cm (p75-90). Only initial stabilization steps were required. At 30 hours of life, the patient presented with cyanosis, diaphoresis, and hypoglycemia (36 mg/dl). Despite glucose supplementation, he developed a partial seizure, prompting further evaluation. Laboratory tests showed elevated ammonia (110) and insulin 24 uU/ml, leading to a diagnosis of congenital hyperinsulinism after ruling out fatty acid oxidation disorders. On physical examination, the patient had no dysmorphic features. Consultations with the genetics and endocrinology departments were requested, and the diagnostic approach was initiated for hypoketotic hypoglycemia. Congenital hyperinsulinism was considered the primary diagnosis, with fatty acid oxidation disorder as a differential diagnosis. An expanded metabolic screening was performed, which was reported as normal, leading to the final diagnosis of congenital hyperinsulinism. He was treated with octreotide and glucose without significant clinical improvement until diazoxide was initiated. Diazoxide was then gradually tapered and discontinued by the age of one year. Genetic testing (WES with CNV analysis) identified a GLUD1 heterozygous variant of uncertain significance (VUS) as rs750420022, potentially linked to hyperinsulinism-hyperammonemia syndrome, which follows an autosomal dominant inheritance pattern. However, the variant was also found in the asymptomatic mother, reducing its clinical significance. The final diagnosis was Transient Congenital Hyperinsulinism.
Final Comments: Although hyperammonemia is a common feature of the HI/HA syndrome, it is not universal in all cases of GLUD1 mutations. Phenotypic variability may be due to the specific nature of the GLUD1 gene mutation, highlighting the importance of genetic analysis for the differential diagnosis of patients with hyperinsulinism, even in the absence of hyperammonemia. Early diagnosis and treatment are crucial to preventing long-term neurological complications.

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EP1052

JOINT248

Endocrinology and immunology: exploring their intersection in autoimmune disorders

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Background and Aims
The relationship between the endocrine and immune systems is increasingly recognized as a complex and significant intersection. Many endocrine glands are susceptible to autoimmune diseases, which often present at a young age and have a high prevalence in the population. This presentation aims to explore the origins of autoimmune processes in endocrine disorders, investigate the mechanisms behind immune system dysfunction, and identify potential therapeutic targets for intervention.
Methods
A comprehensive literature review was conducted based on recommendations and guidelines related to "Endocrinology and Immunology." Published studies were retrieved from PubMed, Elsevier, Wiley Online Library, Google Scholar, and Web of Science. The review included clinical trials and articles available in English.
Results
Recent studies highlight the critical role of endocrine hormones in regulating all biological processes throughout life. The secretion of these hormones must remain continuous and balanced; any disruption can lead to the formation of mutant proteins and auto-antigens. The immune system employs a surveillance mechanism where autoreactive T cells target and remove these abnormal proteins and tissue fragments to maintain homeostasis. The detection of autoantibodies serves as a surrogate marker for autoimmune endocrine disorders, and screening for these autoantibodies can help identify individuals at risk at an early stage. Disruption of immune homeostasis and immune surveillance mechanisms predisposes individuals to autoimmune endocrine disorders.
Conclusions
Autoimmune endocrine disorders are increasingly recognized as a consequence of the fragility of the immune surveillance system. Understanding these autoimmune mechanisms is crucial for the development of new targeted therapies that go beyond hormone replacement treatments. Early identification of individuals at risk is essential for restoring immune homeostasis before the onset of autoimmune disease.
Keywords
Endocrine disease, Autoimmunity, Targeted therapies, Immune surveillance, Autoantibodies.

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EP1053

JOINT3546

A case history of prader-willi syndrome: 20 years observation period

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Backgroud
Prader–Willi syndrome (PWS) is a rare disorder due to the absent expression of paternally active genes in chromosome 15. The mutation results in altered hypothalamus development and function, which impairs satiety, numerous hormonal deficits, changes in slee microstructure and other comorbidities.
Aims
We report a case of Prader-Willi syndrome over a period of 22 years between 2002 and 2024.
Case history
The first visit to the endocrinologist was on the second year of patienìs life. Both testes were undescended. Gonadotropin treatment was suggested but with no result, so orchiopexy of undescended testes was performed at the age of 3. Since early childhood patient had excessive weight that gradually increased, insatiable appetite, facial features of Prader–Willi syndrome that were confirmed by genetic analysis at the age of 8 (microdeletion 15q11-q13). He was treated by lifestyle intervention, his family was very motivated. And at the age of 14 he began to receive testosterone replacement for hypogonadism and small genitalia. At 24 years patienìs weight was 118 kg, height 170 cm, BMI 40 kg/m^2. At that time diabetes mellitus was diagnosed HbA1c 12.2%, C peptide 2,34 (0,367-1,47). During short period of basis-bolus insulin therapy his appetite remarkably increased and he gained 15 kg. Abdominal ultrasound imaging revieled nonspecific hepatomegaly. The therapy was changed to glyclasidi, metformin, basal insulin and glucagon-like peptide-1 (GLP-1). And a successful rapid weight reduction and decline of HbA1c 7.42% was received. The patient had normal thyroid status TSH 1.41 but decreased IGF–1 level 115,2 (130-295). Brain magnetic resonance imaging was unremarkable. Growth hormone therapy (GHT) is known to improve body composition, height and body mass index, improve cognitive function and long-term health-related quality of life. On the other hand literature represents the cases of patients with Prader-Willi syndrome worsening snoring during growth hormone therapy. And respiratory failure is the leading cause of mortality in individuals with PWS, making early diagnosis and the treatment of respiratory problems crucial for their survival. Our patient had demonstrated obstructive sleep apnea and excessive daytime sleepiness. Possible adverse effects of GHT on the respiratory system limited our ability of GHT implementation in patient.
Conclusion
Using consensus diagnostic criteria for PWS 1993, our patient fulfilled clinical diagnosis. Glucagon-like peptide-1 was effective in treating hyperphagia, weight reduction and as glucose lowering agent. Further investigations on GHT effect on the respiratory system is needed.

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EP1054

JOINT2303

Hyperthyroidism and thrombosis of a varicocele: an unexpected linka case report

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Introduction
Venous thromboembolic disease (VTE) is a multifactorial condition primarily associated with hypercoagulable states. Hyperthyroidism is one such condition, promoting a procoagulant state. We report a case of varicocele thrombosis associated with hyperthyroidism, with no other identified risk factors.
Case Report
A 48-year-old man with no significant medical history was followed in the endocrinology department for hyperthyroidism due to a Grave disease with multinodular goiter. Clinically, he presented with thyrotoxicosis syndrome without an obvious goiter or exophthalmos. Laboratory tests revealed a TSH level of 0.01 mIU/land FT4 at 29.5 pmol/l,with positive TSH receptor antibodies. He was started on antithyroid therapy, followed by definitive treatment with radioactive iodine. Inflammatory markers and hemostasis tests were within normal ranges. Additionally, the patient experienced testicular pain with a sensation of heaviness. A scrotal ultrasound revealed left varicocele thrombosis. He was treated with analgesics and oral anticoagulants, leading to a favorable clinical and biological outcome.
Discussion
Hyperthyroidism induces a hypercoagulable state, promoting a prothrombotic condition and increasing the risk of VTE disease. Varicocele thrombosis is a rare cause of testicular pain. Other reported etiologies include trauma, obstruction of venous drainage by malignant tumors, genital and/or inguinal infections, and coagulation disorders.
Conclusion
Hyperthyroidism can be considered a risk factor for thrombosis, implying that it should be discussed as a probable etiology, especially in the presence of other clinical elements.
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EP1055

JOINT2520

Neuromyelitis optica and endocrine comorbidities: a case report

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Introduction
Neuromyelitis optica (NMO) is a rare, inflammatory, autoimmune demyelinating disease of the central nervous system (CNS), primarily affecting the optic nerves and spinal cord. The presence of anti-aquaporin-4 (AQP4) antibodies plays a key role in its pathogenesis. Given the high expression of AQP4 in the hypothalamus and other endocrine-related regions, NMO is frequently associated with endocrine dysfunctions, particularly autoimmune thyroid disorders. This case highlights the intersection between NMO and endocrine comorbidities.
Observation
We report the case of a 50-year-old woman with a one-year history of NMO, initially presenting with ophthalmoplegia and progressive bilateral visual impairment. She was treated with plasmapheresis, high-dose corticosteroids, and azathioprine. Eleven months later, she was referred for the evaluation of an incidental thyroid nodule and signs suggestive of thyroid dysfunction. Laboratory investigations revealed positive anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TG) antibodies, confirming Hashimoto's thyroiditis. Clinical examination showed a palpable, heterogeneous thyroid gland, euthyroidism, and persistent asthenia. Further endocrine evaluation ruled out adrenal insufficiency and diabetes insipidus.
Discussion and Conclusion
Autoimmune thyroid disease, including Hashimoto's thyroiditis and Graves' disease, is the most frequently reported endocrine comorbidity in NMO. The detection of AQP4 in thyroid follicular cells suggests a potential pathogenic link. Studies indicate that up to 40% of NMO patients may have concurrent autoimmune disorders. Moreover, recent research suggests that the presence of anti-TPO antibodies may correlate with increased severity of myelitis in NMO. Patients with elevated anti-TPO levels tend to have higher disability scores on the Expanded Disability Status Scale (EDSS), a greater number of spinal cord lesions, and more frequent longitudinally extensive transverse myelitis (LETM). This association could be explained by a more aggressive immune response or by the role of thyroid hormones in myelin repair. In addition, hypothalamic involvement in NMO, although rare (reported in 2.5%–3% of cases), can be highly specific and pathognomonic due to the strong expression of AQP4 in this region. Hypothalamic lesions may manifest as isolated clinical features, including dysautonomia, hypersomnia, metabolic disturbances, and endocrine dysfunctions such as central adrenal insufficiency and the syndrome of inappropriate antidiuretic hormone secretion (SIADH). SIADH results from impaired osmoregulation due to astrocytic damage in the hypothalamus, leading to hyponatremia and altered fluid balance. Given these associations, a systematic endocrine assessment is recommended in NMO patients to optimize management and improve long-term outcomes.

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EP1056

JOINT533

Assessment of bone health, psychological wellbeing and clinical spectrum in turner syndrome: experience from a tertiary healthcare centre from north india

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Background
Turner's syndrome (TS) presents with diverse clinical manifestations. The patients with TS are predisposed to develop osteopenia, osteoporosis and fractures owing to low bone mineral density (BMD). Prevention strategies and screening for poor bone health and psychological health should be initiated early in the course of disease to prevent further complications.
Objectives
To assess the clinical spectrum in patients with TS including the assessment of bone health and psychological wellbeing for which there is a paucity of data in the literature.
Methods
A cross-sectional observational study from a tertiary healthcare centre from north India. Karyotype proven TS (n: 67) attending the endocrinology outpatient department were included. All the subjects were evaluated for anthropometry, detailed records of clinical features and detailed physical examination. Areal BMD (L1-L4) estimation and the Z-score using HOLOGIC-DXA machine were performed in all patients. Psychological assessment was done using GAD7 (Anxiety) and PHQ9 (Depression) questionnaire for participant age $\geq$11 years.
Results
The most common karyotype found was 45X (54%) followed by 45Xi; Xq (13%). The median age of diagnosis was 15 years (4-27 years). Short stature (91%) and delayed puberty with primary amenorrhea (82%) were the predominant presenting complaints. The patients with menarche or HRT $>$2 years had significantly higher mean BMAD [0.243 (0.03) vs. 0.21 (0.02) gm/cm^3; $P<0.05$] compared to prepubertal or patients with HRT for less than 2 years. The rate of mild to severe anxiety and depression in TS patients were significantly higher than that of healthy control (P value: <0.05) but not that of type 1 diabetic controls (p: >0.05).
Conclusions
Short stature & primary amenorrhea were the most common clinical presentation often leading to late diagnosis of Turner's syndrome. Bone mineral density was significantly lower in patients with delayed puberty or inappropriate HRT, which suggest that timely and appropriate estrogen therapy is necessary to maintain appropriate bone health. While assessing the BMD in participants with TS, adjustment for height and/or smaller bones due to short stature is necessary to avoid false interpretation. Anxiety and depression were often unnoticed but were present in a significant number of patients. We must include routine and regular assessment of psychological wellbeing in management protocol of TS for early detection and management of psychological disorder in subjects with TS.

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EP1057

JOINT254

Association of primary hyperparathyroidism and papillary thyroid carcinoma in a patient with brown tumor and parkinsonism

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Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by increased parathyroid hormone secretion, leading to hypercalcemia and renal, gastrointestinal, neuromuscular, psychological and skeletal manifestations. We would like to introduce the non-common clinical manifestations of PHPT like Brown tumor and Parkinsonism.
Case report
A 64-year-old female was admitted to the Mikaelyan Institute of Surgery complaining of general weakness, pain in the right lumbar region and fever. The patient was diagnosed with Ureterolithiasis, right-ureteral stone obstruction, right-sided ureter hydronephrosis, and pyelonephritis and was preparing for surgery. A right-sided nephrectomy and right-sided ureterolithotomy were performed. In medical history: Schizophrenia for about 25 years, hemimaxillectomy for a giant cell tumor in the upper jaw 10 years ago. The patient has been on Haloperidol 10mg for more than 25 years and Trihexyphenidyl 2mg for the past 7 years. The patient exhibited reduced interaction during the initial examination and appeared very indifferent. Objective neurological examination revealed the following findings: combined rest and action tremor Tremor observed in the chin, accompanied by noticeable oral dyskinesias. Gait is characterized by wide-based steps with shuffling. The patient was diagnosed Drug-induced Parkinsonism. Blood tests: Hb-76g/l(N 115-152), Creatinine-128umol/l(44-100), Ca ionized-2.20mmol/l(1.13-1.32), PTH-409.6pg/ml (15-65), Vitamin D-10.6ng/ml (30-100), TSH-3.85 uIU/ml (0.3-4.5). Neck ultrasound: tissue formation in the left parathyroid gland and multiple thyroid nodules (TI-RADS 4). The patient refused to do FNA. Dual-energy X-ray absorption: T-score at L1-L4 -5.1, hip T-score -5.4. Full-Body CT Scan: multiple lytic lesions involving bones, probable Brown tumor. Esophagogastroduodenoscopy: atrophic gastritis. The patient started treatment with Vitamin D_3, rehydration and correction of anemia. After 1 month, she underwent left parathyroidectomy and total thyroidectomy. The histology showed parathyroid adenoma and papillary microcarcinoma of the left thyroid. PTH level decreased immediately after surgery (from 551.2 to 69.98). The patient's neurological condition also improved. After surgery the patient was given Vitamin D_3, Calcium gluconate and Levothyroxine. The patient is currently under the follow-up.
Conclusion
Approximately 90% of cases of hypercalcemia are caused by hyperparathyroidism or malignancy. Our patient had both. Except common manifestations of hypercalcemia and PHPT, the patient had also rare manifestations, such as brown tumor. It is a non-neoplastic, reactive bone lesion resulting from excessive PTH secretion. Hypercalcemia is known to cause neuropsychiatric dysfunction too. Evidence of hyperparathyroidism associated with parkinsonism is rare. In our patient parathyroidectomy provided a significant remission of parkinsonism. Therefore, in this case, Parkinsonism may not only be drug-induced, but also hypercalcemia-induced.

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EP1058

JOINT769

Factors influencing linear growth in children with beta-thalassemia major: a comprehensive review of studies (2000–2025)

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Background
Growth disorders are highly prevalent among children with beta-thalassemia major, affecting both height and weight. Chronic anemia, iron overload, and endocrine dysfunctions contribute to growth retardation, significantly impacting quality of life. Despite advancements in transfusion and chelation therapies, growth impairment remains a major complication in this population.
Objectives
To evaluate the key factors influencing linear growth in children with beta-thalassemia major, focusing on age, sex, serum ferritin levels, GH-IGF1 axis, liver iron concentration, and transfusion status, and to assess real predictors of growth outcomes.
Methods
This review includes 30 studies published between 2000 and 2025, encompassing 2,500 children and adolescents with beta-thalassemia major. Data on height, weight, serum ferritin, GH-IGF1 axis, liver iron burden, and transfusion status were analyzed for their impact on growth outcomes.
Results
- **Age and Sex:** Growth retardation was observed across all age groups, with increased severity during adolescence due to delayed puberty. No significant differences were noted between sexes in growth outcomes.
- **Serum Ferritin Levels:** Elevated ferritin ($>$2500 ng/ml) was inversely correlated with height and weight. High ferritin levels were associated with endocrine dysfunctions, including growth hormone (GH) deficiency and hypogonadism.
- **GH-IGF1 Axis:** GH deficiency and low IGF-1 levels were prevalent among patients with growth failure. Studies highlighted the significant role of the GH-IGF1 axis in predicting growth outcomes.
- **Liver Iron Concentration:** High liver iron burden ($>$7 mg/g dry weight) was negatively associated with linear growth due to its impact on endocrine glands and hepatic function.
- **Transfusion Status:** Regular transfusions maintaining pre-transfusion hemoglobin $>$9 g/dl improved growth outcomes, while inadequate transfusion schedules exacerbated growth delays.

• **Real Growth Prediction:** A combined analysis of these factors across studies demonstrates that real growth prediction is when accounting for regular transfusions, early chelation therapy, controlled ferritin levels, and optimization of the GH-IGF1 axis. Patients with these managed parameters showed a significantly higher likelihood of achieving normal growth trajectories compared to those with poorly managed conditions.

Discussion and Conclusions

This review highlights the multifactorial nature of growth impairment in children with beta-thalassemia major. Factors such as iron overload, GH-IGF1 axis dysfunction, and inadequate transfusion schedules are key contributors. Effective management strategies, including early chelation, regular transfusions, and endocrine evaluation, are critical for optimizing growth outcomes. Future research should focus on longitudinal studies to refine growth prediction models and explore novel therapeutic approaches. Clinicians should adopt a multidisciplinary approach to address the diverse challenges associated with growth disorders in this population.

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EP1059

JOINT946

The critical role of pituitary imaging in sickle cell disease: insights into growth and endocrine dysfunction

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Background

Pituitary imaging is vital for identifying structural and functional abnormalities contributing to endocrine dysfunction in sickle cell disease (SCD). Chronic hypoxia, iron overload, and microvascular damage often lead to growth hormone (GH) deficiencies, delayed puberty, and other complications. This review explores the role of imaging in diagnosing and managing these issues.

Objectives

1. To evaluate the diagnostic utility of imaging modalities, particularly MRI, in detecting pituitary abnormalities in SCD.
2. To investigate the relationship between structural pituitary changes and endocrine dysfunction.
3. To highlight the potential of advanced imaging biomarkers in risk stratification and monitoring.

Methods

A chronological review of studies from 1993 to 2024 was conducted, analyzing findings from MRI, CT, and advanced imaging techniques to assess their role in detecting pituitary abnormalities and associated endocrine dysfunctions in SCD patients.

Results

- Early studies identified empty sella and vascular insults linked to growth impairments (Broadbent *et al*., 1993; Soliman *et al*., 1995, 1997).
- MRI established itself as the gold standard for detecting pituitary siderosis, reduced gland size, and structural atrophy strongly associated with GH deficiency (Smiley *et al*., 2008; Vadivelan *et al*., 2024).
- Functional MRI revealed links between metabolic stress, reduced connectivity, and cognitive deficits (Fields *et al*., 2020). Blood-brain barrier disruptions further highlighted vascular-neuroendocrine interplay (Lin *et al*., 2021).
- Quantitative imaging biomarkers enhanced the understanding of hemodynamic and structural disruptions, aiding in early detection and monitoring of dysfunctions (Stotesbury *et al*., 2021).
- Animal models demonstrated white matter injury and astrocyte activation contributing to cognitive and motor dysfunctions, mirroring human findings (Hazra *et al*., 2023).
- Pituitary imaging findings such as iron deposition and structural abnormalities were directly associated with panhypopituitarism, delayed puberty, and hypothyroidism (Shekhar *et al*., 2021).

Conclusion

Pituitary imaging, especially MRI, is essential for diagnosing structural abnormalities and functional disruptions in SCD. Advances in biomarkers and quantitative techniques promise improved detection, monitoring, and personalized interventions to mitigate endocrine dysfunctions in SCD.

Keywords

Sickle Cell Disease, Pituitary Imaging, Endocrine Dysfunction, MRI, Growth Hormone Deficiency, Iron Overload, Biomarkers.

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EP1060

JOINT729

Impact of iron deficiency anemia on growth and endocrine functions: reversibility with treatment

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Background

Iron deficiency anemia (IDA) is the most prevalent micronutrient deficiency globally, affecting over 40% of children under five years old, particularly in low- and middle-income countries. Beyond its hematological impact, IDA can disrupt endocrine functions, including growth, thyroid, pituitary, and adrenal systems. These disruptions contribute to growth retardation, hormonal imbalances, and altered metabolic homeostasis. This review synthesizes evidence from clinical and experimental studies to evaluate the effects of IDA on growth and endocrine functions and highlights the reversibility of these effects following iron therapy.

Objectives

To assess the impact of IDA on growth and endocrine functions (thyroid, pituitary, and adrenal) and to evaluate the effectiveness of treatment in reversing these impairments.

Methods

A systematic review of 12 studies published between 1990 and 2023 was conducted, including 567 patients with IDA and several experimental animal models. The studies were analyzed for the impact of IDA on growth velocity, IGF-I secretion, thyroid hormones, and adrenal reserve (ACTH and cortisol), and the reversibility of these effects with treatment.

Results

1. **Growth:** IDA significantly reduces growth velocity and IGF-I secretion. Among 567 patients across the studies, most exhibited impaired height-for-age z-scores and reduced BMI. Post-treatment, iron therapy restored growth velocity and improved IGF-I levels in all studies.
2. **Thyroid Function:** Mild hypothyroidism, characterized by reduced thyroid hormone secretion, was documented in 5 studies, accounting for 220 patients. Iron supplementation normalized thyroid hormone levels in all treated patients.
3. **Pituitary Function:** Suppressed GH and IGF-I secretion were reported in 6 studies, including 345 patients. Post-treatment normalization of GH and IGF-I secretion significantly improved growth and metabolic markers.
4. **Adrenal Function:** Reduced adrenal reserve (low ACTH and cortisol levels) was observed in severe IDA cases in 4 studies, involving 145 patients. Iron supplementation restored adrenal function, demonstrating reversibility with therapy.

Discussion

The review highlights the systemic impact of IDA on growth and multiple endocrine axes. The reversibility of these effects with iron therapy underscores the critical importance of early diagnosis and treatment. Thyroid and adrenal functions were particularly sensitive to IDA but improved significantly post-treatment. Growth markers such as IGF-I and BMI responded robustly, showcasing the critical link between iron availability and endocrine health.

Conclusions

IDA profoundly affects growth and endocrine functions, including thyroid, pituitary, and adrenal systems. Iron therapy effectively reverses these impairments, emphasizing the importance of timely intervention. Future research should explore long-term outcomes and optimize treatment strategies for IDA-related endocrine dysfunctions.

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EP1061

JOINT2762

Graves disease of pubertal age associated with DIDMOAD (wolfram) syndrome

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Introduction

Graves disease is an autoimmune disease characterized by hyperthyroidism due to circulating thyroid-stimulating autoantibodies that bind to and activate thyrotropin receptors, causing the hyperplasia and hyperfunction of thyroid gland. The symptoms are wide ranging as thyroid hormone affects many body systems. The disease is common in people with age below than 40 and mainly in women. Graves disease is caused by a combination of genetic and environmental factors while genetics being the main cause. Genetic predisposition to Graves ‘

disease is caused by multiple genes. Wolfram Syndrome is a rare autosomal recessive progressive neurodegenerative disorder with estimated prevalence of 1 in 500,000 r, also known as DIDMOAD syndrome for its four most common features (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness). Patients present with nonautoimmune and non-HLA linked diabetes mellitus associated with optic atrophy in the first decade, diabetes insipidus and sensorineural deafness in the second decade, renal tract abnormalities early in the third decade and multiple neurological abnormalities early in the fourth decade. In the literature available, we did not find a description of the combination of Graves' disease and DIDMOAD syndrome.
Case report
An 8 years old boy was diagnosed with type 1 diabetes with ketosis on presentation and treated with insulin. However, upon diabetes compensation polydipsia and polyuria continued and the following week diabetes insipidus was diagnosed. MRI of the brain was only significant for posterior arachnoid cyst 1.5x2.5x1.7 cm between the cerebellar hemispheres. Genetic analysis for Wolfram syndrome was not available at that time, therefore patient underwent annual optic nerve funduscopy, audiometry and ultrasound of the urinary tract. After 5 years, he developed hearing loss and early signs of macular atrophy, as well as ureteral dilation. Finally, genetic analysis was done abroad and WFS1 gene mutation was identified.
Conclusion
Apparently, this is one of the first descriptions of the combination of Graves disease and DIDMOAD syndrome in the world literature and definitely the first in Armenia. Taking into account that in some countries genetic analysis for Wolfran Syndrome may not be readily available, annual survey for all the components of the syndrome is recommended. This is especially important in atypical and fast progressing cases of Wolfram syndrome.

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EP1062

JOINT3520

Therapeutic difficulties in the treatment of a girl with primary hypoparathyroidism

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Introduction
Primary hypoparathyroidism is a rare cause of persistent hypocalcaemia and hyperphosphataemia in children. It may occur either as a component of a genetic syndrome e.g. 22q Deletion (DiGeorge Syndrome) or autoimmune processes in the parathyroid glands. CASE PRESENTATION: We report a seventeen-year-old girl diagnosed with primary hypoparathyroidism at the age of ten, who initially presented severe hypocalcaemia with repeated seizures. The autoimmune hypoparathyroidism had been confirmed in the Department of Paediatrics, Endocrinology, Diabetology with Cardiology Divisions, Medical University of Białystok with low PTH concentration (<3pg/ml), typical biochemistry (total serum calcium concentration 0.8 mmol/l,plasma phosphate 4.1 mmol/l)and positive INF-omega antibodies. Other hormonal analyses showed no thyroid or adrenal disorders. Ultrasonography showed no parathyroid pathology. Long QTc (over 0.5 seconds) was present in the ECG. Hypocalcaemia was initially treated with intravenous and oral calcium, vitamin D_3 and vitamin D analogue - alfacalcidol. Sevelamer, a phosphate-binding drug was used for the management of hyperphosphataemia. Moreover the girl was given dietary recommendations to reduce phosphate in the diet. The patient was also treated with beta-blocker for LQTc syndrome. Although the calcium serum concentration increased initially, it remained below the normal reference range, and phosphate level remained over the norm despite the treatment. Other accompanying symptoms (intermittent fever, elevated CRP and radiological features of pneumonia and pericarditis) allowed the diagnosis of systemic lupus erythematosus (SLE) and the treatment with glucocorticoids was initiated, which improved parameters of calcium-phosphate balance. Further immunological examinations were negative for IL-22, IL-17A, IL-17F, IFN-lambda, IFN-alpha2A, and CaSR antibodies. Genetic diagnosis excluded AIRE and CaSR mutations. During first five years of therapy calcium concentrations persisted in the lower limit and phosphate concentration slightly above the norm with no clinical symptoms of electrolyte disorders. Attempts to increase oral calcium dosage resulted in a complication as nephrocalcinosis. After another two years of therapy the girl presented with hypocalcemia and hyperphosphatemia, that required the modification of the oral therapy. Her current daily calcium supplementation is 4 x 1000mg and phosphate-binding drug dosage is 4 x 800mg.
Conclusions
Although primary hypoparathyroidism is a rare endocrinopathy in children, it often causes therapeutic difficulties, as there is no standard hormone replacement therapy.

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EP1063

JOINT3535

Atypical marfan syndrome (MFS) in a pediatric endocrinology practice

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Introduction
Marfan syndrome (MFS) is a connective tissue disorder caused by mutations in the **FBN1** gene, typically affecting the cardiovascular, skeletal, and ocular systems. While diagnosis is usually made clinically, genetic testing is often required in atypical cases to confirm the diagnosis. This report presents a 12-year-old girl diagnosed with Marfan syndrome through genetic testing despite lacking classic cardiovascular and ocular symptoms typically associated with the condition.
Case report
The patient was referred for evaluation due to accelerated growth to the endocrinologist. She also reported fatigue, shortness of breath on exertion, and frequent urination. The patient was born from a first pregnancy. She had a sibling who passed away the day after birth, the father does not recall the cause of death. This family history raises the possibility of a hereditary condition. On examination, she had a tall, thin body, long fingers (**arachnodactyly**), and pectus carinatum, scoliosis, pectus carinatum, joint hypermobility, and stretch marks. However, she did not exhibit cardiovascular or ocular symptoms, such as aortic dilation or lens dislocation, which are classically associated with Marfan syndrome. Echocardiography: normal heart function with no evidence of aortic root dilation, though an incidental **mitral annular ring** was noted. Her ophthalmologic examination was normal. Genetic testing identified a **heterozygous pathogenic variant in the FBN1 gene (c.4930C > T, p.Arg1644Ter)**, confirming Marfan syndrome. This nonsense mutation results in a truncated **fibrillin-1** protein, which plays a crucial role in connective tissue integrity. The variant is classified as **pathogenic (ClinVar ID: VCV000200186)**, with a likely **de novo** inheritance, though parental testing is recommended.
Discussion
This case highlights the variability in Marfan syndrome presentation, particularly in patients without significant cardiovascular or ocular involvement. Despite the absence of aortic dilation or lens dislocation, skeletal features such as scoliosis and pectus carinatum were consistent with the diagnosis. **Genetic confirmation of the FBN1 mutation was essential**, as clinical criteria alone may not have been sufficient for diagnosis. Although the patient does not currently exhibit life-threatening cardiovascular complications, **regular monitoring** is crucial, as these issues may develop over time. Marfan syndrome is a progressive condition, and **aortic dilation, mitral valve prolapse, and lens dislocation can emerge later in life**.
Conclusion
Although the patient currently lacks cardiovascular and ocular abnormalities, **ongoing surveillance and multidisciplinary care** are essential to managing long-term risks. Regular cardiovascular, ophthalmologic, and orthopedic monitoring, along with **genetic counseling**, will be key in ensuring early detection and intervention for potential complications.

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EP1064

JOINT1833

POEMS sy-a rare etiology of endocrinopathy

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Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic premalignant plasma cell disorder that is characterized by the presence of serum M-protein less than 30 g/lor 3 g/dl, bone marrow (BM) clonal plasma cells less than 10%, absence of plasma cell myeloma (PCM) related end-organ damage (CRAB symptoms: hypercalcemia, renal insufficiency, anemia and, bone lesions) and absence of B-cell lymphoma or other disease known to produce an M-protein. MGUS is generally considered a preneoplastic disorder that does not always progress to overt malignancy. Diverse endocrinopathies occur in patients with plasma cell disorders. One possible scenario is the rather rare POEMS syndrome, which is a paraneoplastic syndrome with key manifestations of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. We present a case study which emphasizes the importance of multidisciplinary evaluation of MGUS.

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EP1065

JOINT568

The impact of endocrine diseases on mental health

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Introduction
Endocrine diseases are linked not only to physical health issues but also to considerable psychological burdens that can negatively impact patients' overall well-being. This review seeks to examine different findings in this domain, investigating the connections between hormonal fluctuations and mental health outcomes, while also addressing novel approaches for diagnosis and treatment.
Methods
A systematic search of literature was conducted using the search terms endocrine diseases, mental health, well-being, and psychological interventions.
Results
The central nervous system has receptors for multiple hormones. Dysfunctions of the endocrine system can adversely impact the central nervous system either directly or through the consequences of the endocrine dysfunctions. The relationship between endocrine diseases and mental health has received heightened focus in recent years, as new studies revealed the significant impact that hormonal imbalances can have on psychological well-being. Endocrine diseases such as acromegaly, thyroid dysfunction (hyperthyroidism or hypothyroidism), parathyroid dysfunction (hyperparathyroidism or hypoparathyroidism), adrenal dysfunction (hypercortisolism or adrenal insufficiency), pheochromocytoma, diabetes, and hypogonadism, substantially affect the quality of life of a large number of patients. Most patients experience stress, low mood, and anxiety due to lack of serotonin. These emotions often drive individuals to opt for ultra-processed foods to quickly boost serotonin levels, leading to a vicious cycle and increasing the risk of conditions such as obesity and diabetes. These endocrine diseases disrupt the hormonal balance that regulates autonomic nervous system, cognitive function, stress response, and emotion, resulting in various mental health disorders like cognitive impairment, uncontrollable impulsive behavior, anxiety, depression, and psychosis. In addition to the appropriate treatment of the endocrine dysfunctions, psychological interventions such as cognitive-behavioral therapy and mindfulness-based stress reduction can enhance self-management skills, social functioning, and emotional well-being. The reported studies highlight the necessity of incorporating psychological care into the treatment of patients with endocrine diseases. Subsequent research should concentrate on empirical investigations to substantiate these insights and examine the practical application of the interventions in different clinical settings.
Conclusion
Endocrine diseases substantially affect the quality of life and lead to various mental health disorders such as cognitive impairment, anxiety, depression, and psychosis. The healthcare professionals should identify the underlying factors that may contribute to a patient's condition, fostering more accurate diagnoses and personalized treatment plans. By addressing the interplay between endocrine and mental health, providers can improve patient's outcome, enhance quality of life, and promote long-term well-being.

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EP1066

JOINT162

Endocrine and metabolic diseases associated with stress

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Introduction
Stress is a non-specific response to a stressor. Stress is universal, affecting plants, animals, and humans. It can be acute or chronic. The stressor in humans covers a variety of situations such as physical activity, extreme temperature, noise, workload, unemployment, financial difficulties, food insecurity, divorce, racism, harassment, fear, violence, injury, disease, war, and death of a loved one. Stress can have multiple effects on physiology and behavior, impact child development, and cause several medical disorders. This review presents an update on endocrine and metabolic diseases associated with stress.
Methods
A systematic search of literature was conducted using the search terms stress, stressors, hormones, endocrines diseases, and metabolic diseases.
Results
During stress, the release of several hormones is affected (increased or decreased release). The hormones that are increased include corticotropin-releasing hormone, arginine vasopressin, adrenocorticotropic hormone, prolactin, cortisol, catecholamines, and neuropeptide Y. The hormones that are decreased include gonadotropin-releasing hormone, thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, thyroxine, triiodothyronine, and insulin. Some of these hormonal changes may be necessary for a short-term protection but chronic stress can induce or potentiate several endocrine and metabolic diseases. Studies have reported that subjects with Cushing's disease (but not Cushing's syndrome), hyperprolactinemia (prolactin adenoma or idiopathic hyperprolactinemia), and Graves' disease (onset or relapse) have been exposed more to stressful life events than their matched controls. Stress in early life may be a risk factor for the development of type 1 diabetes. Gonadal function can also be impacted by stress resulting in oligospermia and impotence in men and menstrual irregularities, anovulation, and amenorrhea in women. Through multiple and complex biochemical changes, stress can induce abnormalities in food intake behavior and fat storage, causing weight gain (overweight, obesity) or weight loss (underweight). Decreasing the incidence of stressors and the reaction to them can prevent the occurrence of stress-related disorders. Several tools can be used. They include creation of a stress-free environment, relaxation techniques (soft music, yoga, and meditation), creative arts therapies (art, music, dance, and drama), herbal products (lemon balm and lavender), and medications (benzodiazepines).
Conclusion
Stress is a challenging experience with multiple effects on physiology and behavior and impact on child development. The abnormal release of several hormones during stress can cause endocrine and metabolic diseases. Stress is a significant global health issue imposing substantial societal costs. Establishing effective programs to reduce the incidence of stressors can help preventing the occurrence of stress-related endocrine and metabolic diseases.

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Pituitary, Neuroendocrinology and Puberty

EP1067

JOINT1212

Early detection of adrenal insufficiency after pituitary surgery: basal cortisol levels

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Introduction
Transsphenoidal surgery (TS) is the surgical treatment of choice for pituitary lesions. Postoperative involvement of the hypothalamic-pituitary-adrenal axis is associated with high morbimortality, and it is essential to identify those patients who require corticosteroid replacement therapy. Our objective is to evaluate whether basal cortisol levels in the early postoperative period are related to the presence of adrenal insufficiency (AI) at 4 weeks after surgery.
Case Report
Retrospective and observational study, with a duration of 6 months. Patients with Cushing's disease, previous AI and treatment with preoperative corticosteroids were excluded. In total, 27 patients were studied. The postoperative hormonal assessment included ACTH and cortisol on the 3rd day and, subsequently, at 4 weeks after surgery. The necessary data were collected from the Medical History of each patient. The perisurgical management protocol with glucocorticoids after pituitary surgery published by the Spanish Society of Endocrinology (SEEN) in 2021 was used, considering AI cortisol values lower than 4.1mg/dl (sensitivity 95.1%, specificity 100%). The mean age was 35 ± 19 years, and they were more frequent in women (56%). The majority were non-functioning pituitary adenomas (52%), functioning ones (25%) and 21% were other types of tumors, with craniopharyngiomas and hamartomas standing out (the latter as triggers of central organic precocious puberty). Macroadenomas were considered to be tumors $\geq$ 1cm and microadenomas $<$ 1cm. The mean size of the lesions was 26 ± 17mm. The mean concentration of ACTH and cortisol on the 3rd day was 24 ± 14pg/ml (7.20-63.30) and 21 ± 8mg/dl (6.0-18.4) respectively; while at one month they were 22 ± 8pg/ml and 13 ± 9mg/dl. No patient with cortisol concentrations higher than 4.1mg/dl on day 3 postoperatively developed AI at week 4. Five patients (18.5%) developed AI (3 craniopharyngiomas, 1 hamartoma, and 1 nonfunctioning adenoma, with sizes greater than 25mm). In patients with AI, mean cortisol on day 3 was 3.1 ± 0.9mg/dl and at week 4 was 2.8 ± 0.6mg/dl.
Discussion and conclusions
A cortisol level higher than 4.1mg/dl on the 3rd postoperative day seems to prevent the development of AI and could allow to identify patients who need

glucocorticoid replacement therapy while awaiting confirmation of secondary AI by ACTH testing. In our study, ACTH was always within the reference values and did not allow us to discriminate those patients with secondary AI. It should be noted that most large sillar and/or suprasellar lesions (craniopharyngioma type) developed central AI. The SEEN protocol is safe and effective in patients undergoing TS.

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EP1069

JOINT1979

Toxic pneumonitis in the context of cabergoline treatment

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Introduction
In prolactinoma patients, first-line therapy typically involves cabergoline (CAB) or bromocriptine. Adverse effects occur in 2.5-29% of CAB-treated patients. While CAB is generally safe regarding pleuropulmonary side effects, this case highlights its rare association with toxic pneumonitis, emphasizing the need for awareness of such adverse reactions despite limited available data.
Case
A 77-year-old man was diagnosed in 2019 with clear cell renal cell carcinoma and lung metastases (pT3aN0MxLVIR0 G3). Surgical treatment and first-line therapy with Sunitinib were administered. In 2022, the patient was diagnosed with nodular goiter, Hashimoto's thyroiditis, and hypothyroidism, treated with Levothyroxine to achieve euthyroidism. Galactorrhea was present, accompanied by hyperprolactinemia and a pituitary microadenoma. Bromocriptine was initiated but discontinued due to intolerance. The medication was replaced with CAB at 125 µg/week, gradually increasing the dose to 500 µg/week. Galactorrhea resolved, but the patient developed dyspnea, cough, and chest pain without fever. **Blood tests** CRP 4.2 (<5) mg/l,K 4.5 (3.5-5.1) mmol/l,Na 139 (136-146) mmol/l,creatinine 110 (59-104) µmol/l,leukocytes 8.6x10^9/l(3.9-8.8), neutrophils 6.4x10^9/l(1.8-7.4). Inflammatory markers within normal range. **Blood gas analysis** pH 7.38 (7.35-7.45), pCO2 39 (35-45) mmHg, pO2 92 (80-100) mmHg, HCO3- 24 (22-26), BE -1.6 (-2-+2) mEq/l,SaO2 98 (95-100)%. **ECG** Demonstrates normal findings. **Echocardiography** Ejection fraction 55%, impaired diastolic function. **Chest CT** Broad irregular areas with consolidation and bronchograms were predominantly observed in the right lung, with similar findings bilaterally, suggesting organizing toxic pneumonitis without tumor progression. Radiological and biochemical findings indicated cabergoline-induced toxic pneumonitis, leading to medication discontinuation. **Follow-up** Symptoms of toxic pneumonitis resolved within two weeks, with follow-up chest CT at one month showing resolution of pulmonary changes. In dynamic monitoring, prolactin levels increased without galactorrhea, and dopamine agonists were not resumed. After 1 year, pituitary MRI showed no significant adenoma size change, prompting continued active monitoring.
Conclusions
This case highlights the rare association between CAB and toxic pneumonitis, emphasizing the need for clinicians to stay vigilant for pulmonary side effects in patients on cabergoline, especially with respiratory symptoms. Early detection and discontinuation of the medication are key to mitigating these adverse effects.

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EP1070

JOINT3367

Analysis of miR 16-5p, miR 143-3p and miR 423-5p in patients with invasive non-functioning pituitary adenomas and prolactinomas

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Background
MicroRNAs (miRNAs) are small non-coding RNA molecules involved in the post-transcriptional regulation of gene expression. Pituitary adenomas (PA) are the second most common intracranial neoplasm, with invasive adenomas, defined as the tumor invading surrounding structures and the focal or extensive bones, acounting for 22%– 55% of PA cases. As circulating miRNAs are stable in human body fluids, the study aimed to analyze miR 16-5p, miR 143-3p and miR 423-5p expression in serum of patients with invasive non-functioning pituitary adenomas (NFPA) and prolactinomas, as candidates for non-invasive biomarkers.
Material and Methods
That was a prospective study with consecutive enrollment. The study included 62 Patients with NFPA and 19 Patients with macroprolactinoma qualified for transsphenoidal surgical resection. Clinical history, laboratory and imaging results, and endocrine tests were recorded. Peripheral blood was collected. MicroRNAs, without the high molecular RNA fraction, were isolated from serum samples using the double-column system for miRNA and RNA isolation, according to the manufacturer's protocol (A&A Biotechnology, Gdansk, Poland). The qPCR was performed using SolisFAST Probe qPCR Mix with UNG (Solis Biodyne, Tartu, Estonia). The expression levels of hsa-miR-191-5p, hsa-miR-16-5p, hsa-miR-143-3p, and hsa-miR-423-3p were determined using TaqMan MicroRNA Assays (Thermo Fisher Scientific, Waltham, MA, USA). hsa-miR-191-5p served as a reference miRNA. Relative expression level analysis was performed using the same software by comparing the expression level of the genes of interest with that of the reference gene. The control group (CG) consisted of 26 healthy volunteers. The statistical analysis was performed with MedCalc, with significance level set as $P < 0.05$.
Results
The analysis involved 62 patients with NFPA (47% males) and 19 patients with macroprolactinoma (74% males). The total concentration of microRNA was significantly lower in NFPA than in the CG ($P = 0.0419$). We did not observe that for prolactinoma. No correlation between selected miRNAs and tumor type was found, miR-143-3p ($P = 0.4610$), miR-16-5p ($P = 0.8767$), miR-423-5p ($P = 0.1459$). The expression of miRNA also did not correlate with invasiveness (cavernous or sphenoid sinus invasion, compression of the optic chiasm). We observed significantly lower levels of FSH, LH, estardiol, testosterone and fT4 in NFPA and prolactinomas than in control group ($P < 0.05$). IGF-1 and fT3 were significantly lower in NFPA than CG ($P = 0.024$, $P = 0.0067$, respectively).
Conclusions
Although the total expression of microRNA was significantly lower in NFPA, miR 16-5p, miR 143-3p and miR 423-5p are not useful as non-invasive biomarkers in patients with invasive non-functioning pituitary adenomas and prolactinomas.

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EP1071

JOINT3687

Early cardiovascular and metabolic benefits of rhGH therapy: positive changes in biomarkers and oxidative stress in adult-onset growth hormone deficiency

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Introduction
Adult-onset growth hormone deficiency (AO-GHD) increases mortality, mainly due to cardiovascular complications. Insulin-like growth factor 1 (IGF-1), a key mediator of growth hormone (GH) activity, is crucial for cellular growth, metabolism, and vascular homeostasis. IGF-1 deficiency in AO-GHD contributes to endothelial dysfunction, oxidative stress (OS), and elevated cardiovascular risk. Endothelin-1 (ET-1) regulates hypertension, atherosclerosis, and heart failure, while OS exacerbates vascular dysfunction via increased asymmetric dimethylarginine (ADMA), which reduces nitric oxide availability. This study evaluates recombinant human growth hormone (rhGH) therapy's impact on ET-1 and ADMA levels in AO-GHD, assessing its potential to reduce OS, improve endothelial function, and lower cardiovascular risk.
Methods
The study included 15 patients diagnosed with AO-GHD who underwent a 12-month course of rhGH therapy. IGF-1, ET-1, ADMA, total antioxidant capacity (TAC), and total oxidative capacity (TOC) were measured at baseline, 6 months, and 12 months. Body composition was assessed using dual-energy X-ray absorptiometry (DXA). Statistical analysis involved repeated-measures ANOVA and post hoc tests with Bonferroni correction.
Results
IGF-1 levels significantly increased at 6 and 12 months ($P = 0.0003$; $P = 0.0001$), while ET-1 decreased at 12 months ($P = 0.007$) and ADMA levels declined at both 6 and 12 months ($P = 0.01$). TOC decreased at 6 ($P = 0.02$) and 12 months ($P = 0.04$), whereas TAC increased at 12 months ($P = 0.02$). A

significant reduction in fat mass was observed at 6 months ($P = 0.006$), suggesting early improvements in body composition. IGF-1 correlated negatively with TOC ($P < 0.006$; $r = -0.73$) and positively with TAC ($P < 0.001$; $r = 0.83$). Post hoc tests confirmed significant differences between observation periods.

Conclusions

This study highlights the early therapeutic benefits of personalized rhGH treatment in AO-GHD, demonstrating significant cardiovascular and metabolic improvements within six months. The observed reductions in ET-1, ADMA, and TOC, alongside increases in TAC and IGF-1, suggest a potential reduction in cardiovascular risk and enhanced metabolic homeostasis. These findings support the monitoring of these biomarkers to optimize treatment strategies and improve patient outcomes.

Disclosure of Interest

None declared.

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EP1072

JOINT2474

Remission post endoscopic pituitary surgery for cushing's disease – experience of a regional tertiary centre in UK

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Background

This is service evaluation aimed to assess the remission rate against published literature of patients with confirmed diagnosis of Cushing's disease undergoing endoscopic endonasal pituitary surgery at a regional tertiary centre in the UK.

Methods

A cohort of 29 patients [19 females (65.5%) and 10 males (34.5%), aged 24–68 years] who underwent endoscopic surgical treatment for Cushing's disease at Southampton General Hospital (Southampton, UK) between 2016 and 2024 were included in this study. Demographics, clinical characteristics, preoperative diagnostic workup, and surgical outcomes were analysed. The confirmatory diagnostic tests employed included overnight (ODST) and low dexamethasone (LDDST) suppression tests (100%), pituitary MRI with contrast (100%), urinary free cortisol (100%), midnight salivary cortisol series (89%), inferior petrosal sinus sampling (31%, those with no visible adenoma on MRI or size <6mm), and methionine positron emission tomography (MET-PET) in cases of persistent or recurrent disease (20%).

Results

Preoperatively, 31% (9/29) of patients had type 2 diabetes mellitus, and 58% (17/29) were obese (BMI $\geq$ 30). MRI findings revealed macroadenomas in 31% (9/29) of patients and microadenomas in 69% (20/29). The overall remission rate was 82.8% (24/29), with early remission (postoperative morning cortisol < 55 nmol/lwithin one week) achieved in 51.7% (15/29) of patients. Delayed remission occurred in 31% (9/29); defined as subsequent normalising of urinary free cortisol and salivary cortisol level, or ongoing need for patients' glucocorticoids replacement. Persistent disease was observed in 17.2% (5/29) of patients. Remission rate was highest for microadenomas (90%, 18/20) compared to macroadenomas (55.5%, 5/9). Of those with macroadenomas, 33.3% (3/9) achieved early remission, 22.2% (2/9) had delayed remission, and 44.4% (4/9) with persistent disease. Cavernous sinus involvement was present in 31% (9/29) of patients and was associated with a lower remission rate [55.5% (5/9)]. Histology confirmed the diagnosis of corticotroph adenoma in 86.2% (25/29) of patients, with one case of ACTH staining gangliocytoma (3.4%, 1/29) and four cases of Crooke's hyaline changes (13.8%, 4/29). Of the Crooke's hyaline change cases, two had macroadenomas, one had delayed remission, and one had persistent disease, while all patients with microadenomas and Crooke's changes achieved early remission.

Conclusion

Endoscopic surgery for Cushing's disease at our centre yielded a favourable remission rate of 82.8%, with early remission occurring in over half of the patients. Adenoma size and cavernous sinus involvement were significant predictors of remission, with smaller microadenomas and the absence of cavernous sinus involvement associated with better outcomes.

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EP1073

JOINT77

Recovery of gonadal axis in patients with prolactinomas

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Introduction

Prolactinomas are the most common pituitary adenomas, leading to an increased secretion of prolactin. The symptoms vary and include symptomatic as well as asymptomatic courses. Symptoms are mainly caused by suppression of the hypothalamic–pituitary–gonadal axis (HPG axis). This causes galactorrhea, infertility, oligo-amenorrhea, impotence and osteoporosis as well as symptoms of mass effect (hypopituitarism, visual loss, optic chiasm compression, headaches). For most patients dopamine agonist therapy with Cabergoline represents the primary and most effective therapy. For individual therapy planning the knowledge of influencing factors and disease progression is essential. Our goal was to examine the time period until HPG axis is normalized, as well as the role of influencing factors.

Patients and methods

We retrospectively analyzed the data of patients who were treated in the specialist center of Amedes experts Hamburg between 2013 to 2023 from diagnosis until remission. From initially 410 patients 66 patients fulfilled all inclusion criteria. Diagnosis of suppressed HPG-axis was made by measuring diminished serum concentrations of LH, FSH, estradiol and testosterone. We measured the time period until those concentrations normalized under Cabergoline-therapy and assessed for a significant correlation between this time period and influencing factors using Spearmans rank correlation coefficient and non- parametric Mann-Whitney-U-Test.

Results

The mean duration until normalization of HPG axis under Cabergoline-therapy was 82 days. Statistical analysis showed significant correlation between this duration and initial prolactin levels as well as gender and age. Thus, patients with higher initial prolactin levels, older patients and males showed longer treatment durations. There was no correlation between the time period and adenoma size, Cabergoline dosage, comedication and accompanying diseases.

Conclusions

The acquired data allows for a more precise estimation of treatment duration and patient counseling. Furthermore, it can be useful in creating long term therapy concepts. Patients with prolonged suppression of HPG-axis could receive early hormonal replacement therapy if needed.

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EP1074

JOINT2100

Adiposity trajectories and predictors of obesity in patients with childhood-onset craniopharyngioma

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Objective

Hypothalamic obesity may affect long-term quality of life in patients with craniopharyngioma (CRP). We investigated factors influencing body mass index (BMI) z-scores and overweight or obesity(OWOB) over a 5-year postoperative follow-up in childhood-onset CRP patients.

Methods

We retrospectively reviewed 110 CRP patients (65 males), who underwent surgery (median age 8.0 years) between June 1998 and June 2019 with at least 5 years of follow-up without recurrence. Age at surgery, 2 kinds of hypothalamic involvement (HI) [Puget grade 0-1 vs. 2 ($n = 68$) and SNUH grade (29 anterior, 39 middle, 41 posterior)], surgical approach, timing of growth hormone (GH) initiation (within 3 year and 3+ years), and intensive lifestyle education (before or after year 2014) were included as factors affecting BMI z-scores over a 5-year period or OWOB at 5 years postoperatively.

Results
Significant changes were found in BMI z-scores and the rates of OWOB from the time of surgery (34.2%), to 1, 2, 3, and 5 postoperative years (48.2%, 43.7%, 39.1%, and 36.3%, respectively). In OWOB group at the time of surgery, BMI z-scores decreased significantly over a 5-year period ($P < 0.001$). In a linear mixed model, significant difference was found in BMI trajectory over a 5-year period between age groups at surgery (below or above 8.0 years of age) and between HI groups ($P < 0.001$ for all). BMI z-scores over a 5-year period are greater in higher HI compared to lower HI group [Puget grade (2 vs. 0-1, $P < 0.01$) and SNUH grade (posterior vs. anterior and middle, $P < 0.01$)]. No significant differences were observed based on surgical approach, timing of GH initiation, or lifestyle education interventions. When multivariate-adjusted model was constructed including age at diagnosis, initial BMI category and each HI grade, not only age at surgery and initial OWOB (both $P < 0.01$) but also Puget grade ($P = 0.001$) and SNUH grade ($P = 0.007$) were significant factors for OWOB at 5 years postoperatively.
Conclusions
While HI was common in childhood-onset CRP patients, with one third of patients classified as OWOB at diagnosis, the rates of OWOB increased until the first postoperative year and then showed a decreasing trend over a 5-year period. Age at diagnosis, initial BMI category, and high HI grade were independent predictors for postoperative 5 year OWOB. Children who are older ($\geq$ 8.0 years of age), severely damaged hypothalamus, and obese at diagnosis are at high risk of being obese 5 years after surgery.

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EP1075

JOINT2316

Cannulated prolactin test: a diagnostic approach to moderate hyperprolactinemia

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The aim was to determine the effectiveness of cannulated prolactin test in patients of reproductive age with moderate hyperprolactinemia (HP) and to analyze the frequency of specific and nonspecific complaints.
Materials and Methods
We examined 272 patients, 195w, 77m; age 30.2±9.9 yrs. After cannula insertion, prolactin was measured at 0(PRL0), 60(PRL1), and 120 minutes (PRL2). The results of the cannulated prolactin test (CPT) were considered positive- with HP remaining in all three samples (PRL0, PRL1, PRL2), negative -if HP was at PRL0 and/or PRL1 and without HP in all samples of the test. HP was diagnosed in accordance with the recommendations of the Endocrine Society: >20 ng/ml in men and >25 ng/ml in women. Mild HP is defined in men as a serum prolactin concentration between 19.5 and 100 ng/ml and in women 26.6 and 100 ng/ml.
Results
Median PRL0 was 30.1(21.2-41.2) ng/ml, median PRL1 24.8 (17.5-34.7) ng/ml and median PRL 2 ng/ml 19.5 (13.66-28.9). Approximately 1/3 (30.5%) of the patients reached a normal PRL0. Positive CPT was detected as pathological HP in 37.5% patients. Negative CPT was detected as stress-induced HP in 62.5 % patients. Determination of PRL0 with reference to pathological HP result in a high specificity and moderate sensitivity (sensitivity 54.1%, specificity 100.0%, positive predictive value (PPV) 100.0%, and negative predictive value (NPV) 51.8%, accuracy 69.3%). Determination of PRL1 with reference to pathological HP result in a high specificity and moderate sensitivity (sensitivity 67.1%, specificity 100.0%, positive predictive value (PPV) 100.0%, and negative predictive value (NPV) 71.76%, accuracy 82.1%). 216 patients (73.8 % of women and 79.2 % of men) had complaints, of them patients 161 (57.6 % women and 61 % men) had specific to HP (galactorrhea, menstrual disorders, reduced libido, infertility, gynecomastia, breast pain), 80 patients (25.3 % of women and 30 of men) had non-specific complaints (weight gain, acne, headache, dizziness, scrotum pain, fatigue). The main presenting symptom was gynecomastia in 40.3% of man, and menstrual irregularities in 36.2% of the women.
Conclusion
The cannulated prolactin test was useful in excluding pathological HP, stress-induced HP (negative CPT) was determine in 62.5% of patients. Patients with stress-induced HP (negative CPT) and patients with pathological HP (positive CPT) had no statistically significant differences in age and frequency of occurrence of specific and non-specific complaints and symptoms for HP. Determination of PRL in CPT with reference to pathological HP result in a moderate sensitivity and high specificity.

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EP1076

JOINT3034

Celebral salt wasting syndrome in a patient with known central diabetes insipidus on the background of mcap overgrowth syndrome

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Introduction
Salt-wasting syndrome constitutes a significant disorder of sodium and water homeostasis, commonly observed in individuals with intracranial pathology, such as central nervous system infections, cerebral ischemia, elevated intracranial pressure, or following neurosurgical procedures. Central diabetes insipidus is another disorder affecting sodium homeostasis and is associated with these conditions. The coexistence of these two disorders poses a substantial challenge for pediatric endocrinologists, particularly in critically ill patients.
Aim/Methods
We present the case of a patient with MCAP overgrowth syndrome who developed salt-wasting syndrome on the background of pre-existing central diabetes insipidus.
Results
The patient had a known history of MCAP syndrome (megalencephaly, macrocephaly, polymicrogyria), with genetic testing revealing a mutation in the PIK3CA gene. At 13 months of age, the patient underwent ventriculoperitoneal shunt placement. Postoperatively, he developed central adrenal insufficiency, central hypothyroidism, and central diabetes insipidus, and treatment with hydrocortisone, levothyroxine, and desmopressin was initiated. Six months later, due to Chiari type 1 malformation, a decompressive laminectomy at the A1 level was performed. At 20 months of age, the child presented with fever of central origin, and brain CT revealed the presence of subdural hygromas. The patient was treated with prednisolone. Laboratory findings demonstrated hyponatremia, mildly elevated urea, low urine specific gravity (SG = 1001), and natriuresis (urinary sodium = 49 mmol/L). The diagnosis pointed towards salt-wasting syndrome, and treatment included oral sodium supplementation and fludrocortisone.
Conclusions
Salt-wasting syndrome is an important cause of hyponatremia and clinical dehydration, particularly in the setting of structural and functional abnormalities of the central nervous system. It must be differentiated from syndrome of inappropriate antidiuretic hormone secretion (SIADH). The pathophysiology of salt-wasting syndrome involves both sympathetic nervous system dysfunction and the secretion of natriuretic peptides in response to brain pathology. The coexistence of salt-wasting syndrome with central diabetes insipidus is rarely reported in pediatric populations. Nevertheless, progressive central nervous system damage or repeated neurosurgical procedures are risk factors that warrant heightened vigilance by treating physicians.

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EP1077

JOINT2458

Challenging management of electrolyte imbalances in neurosurgical patient: cerebral salt wasting case report

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Introduction
Electrolyte disorders are common in central nervous system (CNS) diseases, including subarachnoid hemorrhage, traumatic brain injury, cerebral tumors, infections and postoperative neurosurgical setting. These conditions can be associated with both the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and to cerebral salt wasting (CSW). Hypothalamic-neurohypophyseal system affections instead, can lead to central diabetes insipidus (CDI). CSW is characterized by hyponatremia and hypovolemia due to excessive sodium loss in urine. SIADH presents as euvolemic hyponatremia due to inappropriate ADH secretion. CDI is primarily characterized by polyuria due to insufficient ADH. The table below summarizes the key differences among these

	Urine volume	Urine Na concentration	Plasma Na concentration	Extracellular fluid volume	Fluid balance
SIADH	↔ or ↓	↑	↓	↑	↔ or ↑
CSW	↔ or ↑	↑	↓	↓	↓
CDI	↑	↓	↔ or ↑	↓	↔ or ↓

syndromes to avoid misdiagnosis and inappropriate therapy. We present a case of a child with chiasmatic-hypothalamic tumor who developed post-surgery fluid and electrolyte imbalance, detailing the initial neurosurgical and intensive care approach and subsequent endocrine management.
Case presentation
A 3-years-old girl with chiasmatic-hypothalamic astrocytoma underwent lesion debulking surgery. Intraoperatively and postoperatively, she presented polyuria (5 mL/kg/h) with normal natremia. Desmopressin and sodium chloride infusion were administered. The next day she developed hyponatremia (Na 130 mEq/l) with persistent polyuria, prompting a second desmopressin bolus. On post-operative day two, diuresis increased (10 mL/kg/h) and laboratory tests showed: Na 125 mEq/l,K 3.2 mEq/l,urinary Na 164 mEq/L. Suspecting CSW, endocrinologist specialist recommended stopping desmopressin, initiating hypertonic saline and administering fludrocortisone (0.05 mg twice daily). Strict fluid balance monitoring and electrolyte surveillance were emphasized. Hypokalemia, likely due to mineralocorticoid therapy, was corrected with potassium infusion. As fluid and electrolytes stabilized, sodium and potassium supplementation were gradually discontinued, and fludrocortisone was reduced.
Discussion
Accurate determination of the patient's volume status is the key to diagnose CSW and to differentiate from SIADH, while natremia and urine concentration can help to rule out CDI. Hyponatremia in CSW must be corrected gradually to prevent osmotic demyelination. Fludrocortisone therapy may induce hypokalemia, requiring frequent monitoring of sodium and potassium levels. Proper diagnosis and management are key to avoid complications.

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EP1078

JOINT1837

Pituitary apoplexy: epidemiology, presentation and outcomes - a population-based study in malta

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Aims and Objectives
To determine the prevalence, incidence and outcomes of pituitary apoplexy patients presenting acutely in Malta.
Methodology
Twenty-nine patients presenting with pituitary apoplexy between 1980 and 2023 were retrospectively identified. The prevalence and incidence rates were calculated. Clinical presentation, endocrinological, radiological findings and outcomes of all patients with pituitary apoplexy were analysed and compared between the two cohorts who were treated conservatively or with early surgical intervention, taking into consideration serum prolactin levels at diagnosis. The Pituitary Apoplexy Score (PAS) was applied retrospectively.
Results
Five from 29 patients had a known pituitary adenoma. The prevalence for pituitary apoplexy was 4.61/100,000 individuals (NFPA 3.69/100,000; functional adenoma 0.92/100,000) and the overall SIR was 0.19/100,000/year (NFPA 0.144/100,000/year; functional adenoma 0.047/100,000/year). Prevalence rates and SIR were higher amongst males (prevalence 8.08/100,000 in males vs 0.78/100,000 in females). 92% of the patients who presented with apoplexy were macroadenomas, whilst 8% were microadenomas. The median age for apoplexy was found to be 51 years (IQR 42-58); higher in the NFPA subtype; 55 (IQR 49.5-63) when compared to 43 (IQR 38.5-45.25) in the functional group. Visual field defects were more prevalent when baseline prolactin levels were less than 5ng/ml; 68.75% vs 42.86% ($P = 0.014$). Complete pituitary function was preserved in 7.18%, whilst 78.57% showed panhypopituitarism and 14.29% exhibited partial hypopituitarism. Whilst 72.41% were initially managed conservatively, 27.59% were surgically treated and underwent trans sphenoidal decompression of the sella, within 7 days of presentation. There was no difference in terms of endocrinological outcome at 3 or 12 months between the surgically and conservatively treated group. At 12 months, 7.14% retained pituitary function, whereas 75% experienced panhypopituitarism and 17.86% exhibited partial hypopituitarism. Three from 27 patients (11.11%) were reported to have regrowth post apoplexy and 1 patient had recurrence of apoplexy in the tumour remnant. Utilising a lower PAS threshold, a comparative analysis showed that 87.5% of patients who underwent early surgery had a PAS ≥ 4, whilst 26.32% of those treated conservatively had a PAS ≥ 4 ($P < 0.001$).
Conclusions
Through thorough case identification, this study provides both prevalence and incidence rates of pituitary apoplexy in a well-defined population in Malta. Clinical sequelae and various treatment modalities have been studied to better understand this rare condition.

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EP1079

JOINT2312

Clinical and hormonal features of prolactinomas in men

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Introduction
Pituitary adenomas account for approximately 15% of all brain tumors. The most common hormone-secreting pituitary tumors are prolactinomas, which represent nearly 40% of all pituitary adenomas. Prolactinomas are three times more frequent in women but exhibit different features in men.
Methods
We reviewed clinical and hormonal data of 36 men followed for prolactinoma from 2000 to 2023 in a referral endocrine center of the region of Sfax, Tunisia.
Results
The mean age at diagnosis was 43.6 $\pm$ 15.1 years, with extremes ranging from 19 to 75 years, and a peak incidence at 41.5 years. The mean diagnostic delay varied between 2 weeks and 14 years, with an average latency of 15.3 $\pm$ 17.2 months. Pituitary tumor syndrome was the initial presentation for the majority of patients (94.4%). Headaches were the most common presenting symptom (86.1%). Visual disturbances were reported in 25 patients (69.4%). Pituitary apoplexy revealed the prolactin-secreting adenoma in 6 patients (16.7%), while incidental discovery was noted in 2 patients (5.6%). The endocrine hyperprolactinemia syndrome was dominated by sexual dysfunction, including erectile dysfunction and decreased libido in 17 patients (47.2%). Visual field examination was performed in patients with visual disturbances and was abnormal in 61.1% of cases (22 patients). Bitemporal hemianopia was identified in 22.2% of cases. The mean prolactin level was 18,662.18 $\pm$ 52,817.93 ng/ml, with extremes ranging from 46.7 ng/ml to 274,400 ng/ml. A positive and statistically significant correlation was observed between prolactin levels and prolactinoma size (rho $= 0.658$, $P = 0$). Regarding other hormonal assays, gonadotropic insufficiency was observed in 23 patients (63.88%), thyrotropic insufficiency in 16 patients (47.05%), corticotropic insufficiency in 22 patients (61.11%), and somatotropic insufficiency in 4 patients (11.11%). Additionally, 44.4% of patients had deficits in three axes, involving gonadotropic, corticotropic, and thyrotropic insufficiencies.
Conclusion
Although prolactinomas are rare in men, their clinical presentation can be more severe. It is therefore essential to consider this diagnosis in order to prevent significant impacts on quality of life, fertility, and visual disturbances.

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EP1080

JOINT923

Arginine vasopressin resistance - rare clinical cases

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Introduction
Arginine vasopressin resistance (AVR) is a rare disorder with both congenital and acquired causes. Primary AVR is linked to mutations in the *AVPR2* and *AQP2* genes, while secondary AVR can result from conditions such as ureteral obstruction, a rare yet potentially reversible cause that remains under-researched. We present two clinical cases of primary and secondary AVR. Despite differing etiologies, both patients exhibited similar symptoms from an early age.
Clinical Case 1
Patient P., a 24-year-old male, has had AVR since birth. Bilateral hydronephrosis was diagnosed in utero at 32 weeks of gestation. By age 7, urine output had reached 5 liters per day. His clinical diagnosis included bilateral megaureter, meatal stenosis, a

posterior urethral valve, and secondary pyelonephritis. He underwent a meatotomy and endoscopic resection of the posterior urethral valve. At age 7, AVR was confirmed via a water deprivation test and desmopressin challenge. Despite treatment with hydrochlorothiazide and desmopressin, he continued to experience persistent polyuria, nocturia, fatigue, and difficulty concentrating. At 22 years, he was diagnosed with chronic kidney disease (CKD) stage 4. Due to progressive renal decline, renal replacement therapy and placement on the kidney transplant waiting list were recommended.
Clinical Case 2
Patient G., a 37-year-old male, was first hospitalized in the neuroendocrinology department at age 23 with severe thirst, nocturia, and polyuria of up to 16 liters per day. His symptoms had begun in childhood, with urine output reaching 20 liters daily by age 7. Despite prior desmopressin therapy, his condition remained unresponsive. AVR was confirmed through a water deprivation test and desmopressin challenge. Genetic testing identified a hemizygous *AVPR2* mutation (c.539delA p.R180fsX211), confirming the diagnosis. Treatment with thiazide diuretics and potassium supplements led to a significant reduction in thirst and urine output, stabilizing at 4–5 liters per day.
Conclusions
AVR in childhood is rare, with often nonspecific clinical manifestations. Regardless of etiology, timely and accurate diagnosis is crucial, as affected patients are at risk for hypernatremic dehydration and developmental delays. Increasing awareness among healthcare providers, particularly pediatricians, is essential to ensure proper evaluation of polyuria-polydipsia syndrome and a systematic approach to diagnosing arginine vasopressin disorders.

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EP1081

JOINT1582

Clinical case of arginine vasopressin resistance associated with a new mutation in the AVPR2 gene

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Introduction
Arginine vasopressin resistance (AVR) is an orphan disease clinically characterized by severe polydipsia and the excretion of large volumes of dilute urine. Hereditary AVR is linked to mutations in the vasopressin receptor gene predominantly in 90% of cases, which is expressed in the renal collecting ducts (*AVPR2*). We present a clinical case of AVR in a patient with a mutation in *AVPR2* (hemizygous mutation c.587T>C p.Phe196Ser), which has not been previously described in the literature.
Clinical Case
Patient K., a 29-year-old male, presented to the Endocrinology Research Centre (ERC) with complaints of thirst, polyuria up to 15 liters per day, and nocturia. The diagnosis of arginine vasopressin disorder (AVD) was confirmed at age 3 against a water deprivation test. Desmopressin therapy was initiated without clinical effect. Magnetic resonance imaging (MRI) did not reveal any structural abnormalities of subcortical brain structures. At the ERC a desmopressin test was conducted, which showed no increase in urine osmolality. Genetic sequencing of the *AVPR2* revealed a hemizygous transition, resulting in a substitution of cytosine for thymine in exon 2 at position 587 (c.587T>C), leading to the amino acid substitution of phenylalanine (Phe) for serine (Ser) at position 196 of the receptor protein (p.Phe196Ser). This mutation has not been documented in medical literature. The patient was prescribed hydrochlorothiazide at a dose of 25 mg twice daily along with potassium supplements, while being monitored for diuresis and electrolyte levels. After two weeks, the patient reported a reduction in thirst, and urine volume significantly decreased. However, due to discomfort and "tingling" sensations behind the sternum, accompanied by hypokalemia, the patient independently discontinued medication, after which potassium levels normalized and the uncomfortable sensations subsided. AVR symptoms recurred. Given the development of hypokalemia despite potassium supplementation while on hydrochlorothiazide, therapy with non-steroidal anti-inflammatory drugs (NSAIDs) was initiated without significant clinical improvement. It was decided to resume hydrochlorothiazide treatment at a reduced daily dose (25 mg) alongside potassium supplements, while a potassium-sparing diuretic (amiloride) was also introduced at a dose of 5 mg daily. Patient monitoring continues.
Conclusions
AVR is a rare disease with social significance. Timely and accurate diagnosis not only prevents severe complications and initiates adequate treatment but also significantly enhances the patient's quality of life. The vigilance of primary care physicians in the presence of polydipsia-polyuria syndrome, competent patient routing, and an interdisciplinary approach are crucial in diagnosing and managing patients with AVR.

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EP1082

JOINT1344

Longitudinally assessed sex-typed play behaviour and its association with androgen levels during minipuberty in full-term and preterm children

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Context
Higher androgen levels during minipuberty have been associated with more masculine sex-typed play behaviour in full-term (FT) infants. On the other hand, reduced sex-typed play behaviour has been reported in preterm (PT) children at the age of five years.
Aim
To investigate the longitudinal development of sex-typed play behaviour and its association with testosterone and DHEAS levels during minipuberty in FT and PT children.
Methods
A standardized psychometric questionnaire Preschool Activities Inventory (PSAI) was used to measure the sex-typed play behaviour in 54 FT (boys $n = 26$) and 91 PT (boys $n = 44$) children at three time points: infancy (mean age (SD) 1.2 (0.1), $n = 117$), early childhood (EC, 3.1 (0.3), $n = 89$) and late childhood (LC, 9.1 (0.7) $n = 63$). Higher PSAI score indicates more masculine and lower score more feminine behaviour. Urinary testosterone and DHEAS levels during minipuberty were measured using HPLC-MS/MS. Spearman's correlation and mixed model were used for statistical analyses.
Results
Both testosterone and DHEAS levels in minipuberty were significantly ($P < 0.001$) higher in PT than in FT infants. DHEAS levels did not differ between sexes, but testosterone levels were higher in boys than in girls ($P < 0.001$). Notably, testosterone levels in PT girls were at the same level as in FT boys. In all the children, testosterone level correlated positively with PSAI in infancy (Spearman's rho 0.230, $P = 0.013$) and in EC (rho 0.339, $P = 0.001$), but not in LC (rho 0.194, $P = 0.132$). However, no significant associations were observed in the subgroups. In PT boys, DHEAS correlated negatively with PSAI in infancy ($P = 0.036$), but in the other multivariate analyses including the number of brothers and sisters and the age, neither testosterone nor DHEAS levels were associated with PSAI scores.
Conclusions
Prematurity seems to affect the longitudinal development of the PSAI score, but the differences are small. Urinary T or DHEAS measured during minipuberty were not associated with PSAI score after early childhood.

Table 1.

	Infancy		Early childhood (EC)		Late childhood (LC)	
Boys	FT	PT	FT	PT	FT	PT
PSAI	62.2 (4.4)	59.8 (7.8)	63.5 (8.7)	61.9 (7.4)	66.3 (7.0)	68.1(7.4)
Change from infancy to EC			not significant (NS)	NS		
Change from EC to LC					NS	$P < 0.001$
Girls	FT	PT	FT	PT	FT	PT
PSAI	44.1 (7.5)	44.7 (9.2)	33.6 (8.9)	32.0 (9.2)	34.1 (9.3)	39.2 (8.7)
Change from infancy to EC			$P < 0.001$	$P < 0.001$		
Change from EC to LC					NS	$P = 0.002$

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EP1083

JOINT853

MRI findings in girls with central precocious puberty: a comparative study with control group and their association with pubertal diagnosis and progression

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Context
Central precocious puberty (CPP) has a complex etiology that involves a variety of conditions. Although approximately 90% of cases in girls are classified as idiopathic, a subset presents additional imaging findings that may have clinical significance.
Objective
To compare the frequency of brain magnetic resonance imaging (MRI) findings between girls with CPP and a control group and analyze, in CPP patients, their relationship with pubertal diagnosis and progression.
Methods
Data were collected between April 2017 and November 2024 from 102 girls who exhibited clinical pubertal progression before the age of 8 and underwent brain MRI, as well as 25 girls and 72 boys with other conditions, the majority diagnosed with idiopathic short stature, who also underwent brain MRI. The data evaluated were chronological age (CA), height SDS (zH), body mass index SDS (zBMI), bone age (BA), LH levels at diagnosis and after follow-up.
Results
Abnormal MRI findings were observed in 38 girls (37.3%) from the CPP group and in 19 individuals (19.6%) from the control group (z test, $P < 0.05$). Among the 38 abnormalities in the CPP group, 33 (32.4%) where classified as indeterminate (I) (e.g., inter-hypothalamic adhesion, pars intermedia cyst, pineal gland cyst), while 5 (4.9%) were classified as pathologic lesions (PL) (e.g., hypothalamic-optochiasmatic glioma, hydrocephalus). In the control group, all 19 abnormalities were limited to I, with no cases of PL. Girls with CPP due to PL exhibited a shorter interval between the diagnosis and the start of pubertal suppression therapy ($P = 0.017$) and showed less advanced bone age relative to chronological age at diagnosis ($P = 0.035$). No significant differences were found among the CPP subgroups in terms of age at puberty onset, age at diagnosis, BA at diagnosis, bone age-corrected height SDS, baseline LH, LH peak after GnRH stimulation, CA at initiation and discontinuation of pubertal suppression therapy, or age at menarche.
Conclusions
It is essential to perform MRI on all girls with CPP, including those aged 6-8 years, since they may also have undiagnosed PL. There were no differences in CPP group patients with or without abnormal MRI findings in relation to clinical or laboratory data. While indeterminate findings are more frequent in girls with CPP compared to the control group, these cannot yet be established as a cause or indicative of a different progression of puberty.
Key words
precocious puberty; MRI; glioma; inter-hypothalamic adhesion.
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EP1084

JOINT1204

Novel score of autonomic dysregulation in children with hypothalamic syndrome

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Objective
Rapid-onset Obesity with Hypothalamic dysfunction, Hypoventilation and Autonomic Dysregulation (ROHHAD) is a rare syndrome manifesting in childhood. Diagnosis of ROHHAD syndrome remains challenging due to the diversity of symptoms that may be missed easily, especially for autonomic dysfunction. The diagnostic criteria for the hypothalamic syndrome (HS) (van Santen *et al*, 2023) are a novel tool for recognizing symptoms of hypothalamic dysfunction. However, symptoms of autonomic dysregulation are lacking in these criteria. They are therefore insufficient for use in ROHHAD patients. No other scoring system for autonomic dysfunction in ROHHAD syndrome exists. We aim to improve the diagnostic criteria for HS by including a score for autonomic dysregulation, supporting early diagnosis of ROHHAD syndrome.
Methods
A score for autonomic dysregulation in ROHHAD syndrome supplementary to the diagnostic criteria for HS was developed based on existing instruments to assess autonomic dysfunction symptoms adjusted for specific symptoms in ROHHAD syndrome, with a score ranging from 0-10. The diagnostic criteria for HS including our add-on were tested retrospectively in 4 ROHHAD patients.

Table 1. Suggested add-on score autonomic dysregulation.

Clinical symptoms	Score
Ophthalmological dysfunctionStrabismusOculomotor apraxiaAltered pupil reactions to lightPtosisAltered vision	0-1-2
Altered peripheral vaso- or secretomotor tonelce-cold extremitiesFacial flushing/rednessAberrant sweating Dry mouthDry eyes	0-1-2
Pain threshold Decreased Increased	0-1-2
Gastrointestinal or bladder dysmotilityConstipationDiarrhea Bladder dysfunction	0-1
Cardiovascular manifestationsBlood pressure regulationOrthostatic intolerance Decreased heart rate variabilityArrhythmiaExercise intolerance	0-1-2
Torticollis	0-1
Total (out of 10)	

0 = no or normal, 1= yes/minor, 2=major. Total score: 0-3 = no autonomic dysregulation 3-6 = mild autonomic dysregulation 7-10 = severe autonomic dysregulation .

Table 2. Suggested updated hypothalamic score.

Clinical criteria
Hyperphagia
Hypophagia
BMI
Behavior
Sleep
Core temperature regulation
Pituitary function
Autonomic dysregulation
Pre-test probability
Presence of HS (yes/no)

Presence of HS is assessed by combining the clinical criteria using cut-off as presented by van Santen et al (2023).

Results
Four ROHHAD patients, median age 9.4 years (range 4.6-25.7), were assessed regarding signs and symptoms of HS and autonomic dysfunction. All patients had HS and scored on at least 3 different domains of autonomic dysregulation. Median score was 7 out of 10 (range 4-9).
Conclusions
The diagnostic criteria for HS are not sufficient to recognize autonomic dysfunction due to hypothalamic dysfunction in ROHHAD syndrome. Our add-on score may help in early recognition and follow-up in ROHHAD syndrome and other causes of hypothalamic syndrome.
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EP1085

JOINT2113

Decoding insulinomas: clinical insights and treatment pathways

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Introduction
Insulinomas are rare, typically benign neuroendocrine tumors of the pancreas that cause hypoglycemia due to excessive insulin secretion. Malignancy can occur, particularly with local invasion or metastasis. These tumors are often associated with Multiple Endocrine Neoplasia type 1 (MEN 1), a genetic syndrome that predisposes individuals to various endocrine tumors. This work presents the experience of our department with a series of 12 insulinoma cases over a 22-year period, from 2003 to 2025.
Methods and results
The cohort consisted of 11 females and 1 male, yielding a female:male ratio of 11:1, with a median age at diagnosis of 38.58 years (range: 10–69 years). The diagnosis was confirmed through biochemical testing, such as measuring fasting plasma glucose, insulin and C-peptide levels, with a documented hypoglycemic episode in all patients. The tumors were localized using CT or MRI in 11 cases (91.7%), with intraoperative echographic exploration in one (8.3%). All patients underwent surgery, except for one who refused and is currently being treated with somatostatin analogs. The most common localization of insulinomas was in the pancreatic tail (58.3%), followed by the pancreatic head (25%), and multiple localizations in MEN 1 syndrome (16.7%). The benign insulinomas comprised 9 lesions (75%), with 7 classified as NET-G1 (58.3%) and 2 as NET-G2 (16.7%), both occurring in the context of MEN 1 syndrome. Three patients experienced recurrent hypoglycemic symptoms following surgery: one was lost to follow-up, while the other two, diagnosed with MEN 1 syndrome, are being managed with somatostatin analogs and diazoxide. It is important to note that, within the MEN 1 syndrome group, the mean

age at diagnosis was 18.6 years, with the youngest patient being 10, having a family history of MEN 1. These findings are consistent with the literature. We included 3 malignant insulinomas (25%). All presented with secondary hepatic metastases and were treated with chemoembolization, chemotherapy, or hepatic resection. One patient also had adrenal and kidney metastases receiving chemotherapy and PRRT. All patients with malignant insulinomas received treatment with somatostatin analogs.
Conclusion
Our findings are consistent with the literature, indicating that insulinomas are mostly benign, with a strong link to MEN 1 syndrome in younger patients. Malignant insulinomas, though rare, are frequently metastatic and require a comprehensive treatment strategy.
Key words
insulinoma, neuroendocrine tumors, insulin, multiple neuroendocrine neoplasia.
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EP1086

JOINT3626

Neurohypophysitis in a pediatric patient with autoimmune hepatitis

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Introduction
Hypophysitis is a rare condition in pediatrics, considered an autoimmune phenomenon, with the most common form being lymphocytic hypophysitis. It frequently presents as central diabetes insipidus (CDI) or growth hormone deficiency (GHD). The diagnosis is clinical and radiological, though in some cases, a biopsy may be required to exclude other systemic or neoplastic diseases. The treatment includes the use of immunosuppressive therapy, with corticosteroids being the first-line therapy.
Case Description
A 15-year-old male patient was admitted for acute liver failure (abdominal pain, vomiting, and jaundice, associated with hyperbilirubinemia, hypertransaminasemia, hypoalbuminemia, and coagulopathy). Endocrinology was consulted due to the finding of hypernatremia. Upon directed questioning, he reported polydipsia, polyuria, and enuresis for 3 weeks. He denied headache or visual disturbances. On physical examination, his weight and height were in the 75-90th and 25th percentiles, respectively, with normal growth velocity, euthyroid status, Tanner stage G4 P4, and testes 15/15 cc. Given the suspicion of CDI, a water deprivation test was performed, confirming the diagnosis with a good response to oral desmopressin. Further studies were conducted, including hypothalamic-pituitary axis evaluation, with sufficient cortisol levels, low thyroid hormone levels consistent with euthyroid sick syndrome, growth hormone resistance (GH 11.1 ng/ml with undetectable IGF1 levels), and arrested puberty (LH 1.4 mUI/ml, FSH 2.16 mUI/ml, and Testosterone 1.12 ng/ml). Alpha-fetoprotein and β-hCG were negative, and skeletal radiographs were normal. A magnetic resonance imaging (MRI) scan revealed the absence of the spontaneously hyperintense signal in T1 of the neurohypophysis. No alterations were observed in the adenohypophysis or the pituitary stalk. During hospitalization, autoimmune hepatitis was confirmed with hypergammaglobulinemia, positive antinuclear antibody (ANA), and anti-smooth muscle antibody (ASMA), prompting the hepatology team to initiate methylprednisone 0.6 mg/kg/day orally. After 72 hours, desmopressin requirements decreased, and was finally discontinued after 10 days due to the development of hyponatremia. Normal sodium levels were maintained after 8 months of follow-up. Thyrotropin, somatotropin, and gonadotropin and testosterone levels normalized, considering previous alterations a transient phenomenon due to systemic disease.
Conclusions
We describe an adolescent who presented with CDI in the context of liver failure, later diagnosed with autoimmune hepatitis. The MRI only revealed the absence of the bright spot, without involvement of the pituitary stalk. Although this finding is present in 20% of the normal population, the clinical presentation, the association with autoimmune disease, and the excellent response to corticosteroid treatment increase the suspicion of a clinical picture compatible with neurohypophysitis.
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EP1087

JOINT109

Tolosa-Hunt syndrome?

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Introduction
Tolosa-Hunt syndrome (THS) represents a rare inflammatory disease of unknown etiology that affects the cavernous sinus, superior orbital fissure or orbital apex. It most commonly occurs in patients over the age of 40. The clinical presentation is characterized by unilateral headache and paresis of the oculomotor (III), trochlear (IV), and/or abducens (VI) cranial nerves, leading to painful ophthalmoplegia of the ocular muscles. Contrast-enhanced magnetic resonance imaging (MRI) usually reveals lesions in the cavernous sinus corresponding to inflammatory infiltrative changes. Histologically, granulomatous inflammation with fibroblast proliferation, lymphocyte infiltration, and the presence of plasma cells and giant cells is typically observed. Treatment primarily relies on glucocorticoids; however, in the case of recurrence, alternative immunosuppressive therapy or radiotherapy should be considered. THS is a diagnosis of exclusion.
Case Report
A 43-year-old female patient with a history of migrainous headache and an endocrinologically inactive pituitary adenoma noticed a worsening of her vision and diplopia in December 2023. Due to the sudden onset of symptoms and the known sellar lesion, she was urgently examined by an endocrinologist. On physical examination, there was a left-sided abducens nerve (VI) paresis and the development of convergent strabismus. MRI revealed progression of the sellar lesion, necessitating endoscopic transsphenoidal resection. Histological examination of the resected tissue confirmed a PitNET tumor of the corticotropic lineage (T-pit positive), with a secondary finding of granulomatous inflammation with necrosis of unclear etiology. Sarcoidosis, granulomatosis with polyangiitis, mycobacterial infections, and other etiologies were subsequently excluded. The diagnosis of THS was made of exclusion, and it was consistent with the pathological findings.
Therapy
Given the diagnosis of THS, intravenous corticosteroid therapy was initiated, followed by oral corticosteroid therapy, with gradual dose reduction. The patient's symptoms gradually improved with corticosteroid treatment.
Conclusions
The presented case corresponds to a combined finding of a PitNET and the rare Tolosa-Hunt syndrome.
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EP1088

JOINT1998

The iron key to adolescence: impact of chronic iron deficiency anemia on pubertal hormones, timing, and growth"

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Background
Iron deficiency anemia (IDA) is a common nutritional deficiency worldwide, particularly among adolescents due to increased iron requirements during periods of rapid growth and physiological changes. Adolescence is a critical period marked by pubertal development, hormonal changes, and the pubertal growth spurt, all of which may be adversely affected by chronic IDA.
Objective
To examine the impact of chronic IDA on pubertal hormones, pubertal timing, and the pubertal growth spurt, drawing on research findings from 2000 to 2024.
Methods
A literature review was conducted to identify studies focusing on the relationship between chronic IDA and pubertal hormones and growth. Data from over 20 studies were synthesized into a structured table, including author, year, patient characteristics, interventions, and outcomes.
Results
1. Hormonal Impact: Chronic IDA suppresses gonadotropin-releasing hormone (GnRH) secretion, leading to reduced levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This results in lower estradiol in females and testosterone in males, delaying pubertal progression (Beard *et al*., The Journal of Nutrition, 2000).

2. Timing of Puberty: Adolescents with chronic IDA experienced delayed onset of puberty compared to peers with normal iron levels. Female adolescents were particularly affected due to menstrual blood loss (Iron Deficiency in Adolescence, The Journal of Pediatrics, 2017).
3. Pubertal Growth Spurt: IDA was associated with reduced growth velocity and impaired attainment of peak height during the pubertal growth spurt. This was attributed to diminished oxygen transport capacity and decreased energy metabolism, critical for growth processes (Santos *et al*., Journal of Human Growth and Development, 2012).
4. Intervention Outcomes: Iron supplementation was effective in restoring hormonal balance, improving growth velocity, and normalizing the timing of puberty. Early detection and treatment were emphasized for optimal outcomes (Iron Deficiency Anemia in Children, Johns Hopkins Medicine, 2024).
Conclusion
Chronic IDA during adolescence has profound implications for pubertal development, including disruptions in LH, FSH, estradiol, and testosterone levels, leading to delayed puberty and reduced growth velocity. Addressing IDA through early diagnosis and effective intervention is crucial to ensure normal growth and development during this critical period. Further research is needed to explore the long-term implications of IDA on reproductive and overall health.

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EP1089

JOINT1724

Osilodrostat use in severe pediatric cushing's syndrome: short term outcomes in a case of pituitary adenoma

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Background
Osilodrostat is an inhibitor of steroidogenesis approved for treatment of Cushing's disease in adults. It acts against 11β-hydroxylase (CYP11B1) which catalyzes the last step in cortisol synthesis. A trial in the pediatric population is ongoing to assess its pharmacodynamics, pharmacokinetics and tolerability (NCT03708900) but data about its efficacy in pediatric Cushing's disease are lacking.
Case presentation
A 10-years-9months old boy was transferred to the Intensive care Unit (ICU) of our center for refractory hypokalemia and sinus bradycardia with U waves. Upon clinical examination he presented facies lunaris, acne, central obesity and striae rubrae. Laboratory tests showed ACTH 139.7ng/l,serum cortisol 118 µg/dl (2.4-15), urinary free cortisol (UFC) 45 585.2 nmol/24h (upper reference range, URR, 124) at the first 24 h urine collection and 21 877.5 on the second collection. Considering UFC, Brain MRI was performed and revealed a hypophyseal mass: diagnosis of Cushing's disease was confirmed. Surgery to remove the hypophyseal adenoma was performed but it was complicated by meningitis requiring antibiotic therapy and a further period of recovery in ICU. Despite initial reduction, both ACTH and cortisol progressively increased up to 969 ng/lfor the former and 149 µg/dl for the latter, within three weeks after surgery. After 24 hours of treatment with Metyrapone, Osilodrostat was started at a dose of 1 mg twice daily. Due to swallowing issues, the tablets had to be shredded. After two weeks of treatment with Osilodrostat, UFC was within the URR with serum cortisol 53.8 µg/dl and ACTH 134.7 ng/L. One month later, with a dose of 1 mg + 1.5 mg, serum cortisol remained at 53 µg/dl. After three months, UFC was 179.1 µg/24h, slightly above the URR (176). PET scan using gallium-DOTATATE confirmed a residual pituitary adenoma, suspected due to lack of laboratory tests after surgery. No adverse events from Osilodrostat were observed.
Discussion
We described a case of pediatric Cushing's disease with recurrence after surgery, which demonstrated a laboratory response to Osilodrostat. This outcome was achieved starting with the minimal dose approved for adults in Europe, then increased by 0.5 mg (2.5 mg/day). Treatment was effective despite the need of shredding the coated tablets. Further studies are required to confirm the efficacy of Osilodrostat in pediatric patients to widen the therapeutic spectrum of Cushing's disease in this age group.

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EP1090

JOINT1770

Pituitary abscess as a rare cause of multi-hormonal pituitary insufficiency and vasopressin deficiency (AVP-D, diabetes insipidus)

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We present a case of a 39-year-old immunocompetent woman who developed a purulent pituitary infection, most likely secondary to recurrent sinusitis, that led to anterior pituitary insufficiency and vasopressin deficiency (AVP-D). The first symptoms appeared nine months postpartum and included severe headaches, vomiting, secondary amenorrhea, polydipsia, and polyuria. Multi-hormonal pituitary insufficiency and AVP-D were diagnosed. Pituitary MRI revealed an enlarged pituitary gland with a well-demarcated solid-cystic lesion measuring 22×14×16 mm, causing expansion of the sella turcica. Due to the suspicion of a pituitary adenoma, the patient underwent transsphenoidal surgery. During the procedure, upon incision of the lesion's capsule, thick yellow purulent-like content was released. Histopathological examination revealed features of chronic inflammatory exacerbation with necrosis, likely originating from the abscess wall. However, the patient did not receive further treatment apart from hormone replacement, owing to no improvement in pituitary function. She was admitted to our Department a year after an initial surgery due to gradually worsening symptoms, including headaches, nasal obstruction, and olfactory disturbances. MRI revealed an extensive infiltration involving the enlarged pituitary gland and sphenoid sinus. Due to symptomatic progression a second transsphenoidal surgery was performed. Histopathological analysis again revealed an inflammatory infiltrate, and Staphylococcus aureus was cultured from the sample. Targeted antibiotic therapy was initiated. Follow-up MRI scans showed no recurrence of the focal lesion. Based on clinical presentation, MRI findings, and histopathological and microbiological results, a diagnosis of pituitary abscess, leading to permanent multi-hormonal pituitary insufficiency and AVP-D, was established.
Discussion
Pituitary inflammation is a rare disease. The most common type is lymphocytic hypophysitis, while bacterial pituitary infections are exceedingly rare. The most frequently reported symptoms include headache, vomiting, visual disturbances, and signs of anterior or posterior pituitary insufficiency. MRI imaging typically shows a symmetrically enlarged gland with homogeneous contrast enhancement. Additionally, the characteristic "bright spot" of the neurohypophysis in T1-weighted images is usually absent, and the pituitary stalk may appear thickened. In some cases, the MRI appearance may resemble a pituitary adenoma or cyst. The treatment of choice for autoimmune-related hypophysitis in patients with neurological symptoms (e.g., severe headaches, cranial nerve palsies, and visual disturbances) is high-dose glucocorticoid therapy. However, other etiologies, such as infectious causes—like in the presented patient—should also be considered, and treatment should be tailored accordingly. In bacterial pituitary infections, obtaining cultures and an antibiotic susceptibility profile is crucial for implementing targeted antibiotic therapy.

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EP1091

JOINT2191

Age-related differences in clinical features of central precocious puberty: insights from a portuguese cohort

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Background
Central precocious puberty (CPP) presents age-dependent diagnostic and therapeutic challenges. This study aims to analyze the clinical, laboratory, and radiological features of CPP across age clusters and evaluate their impact on treatment decisions.
Methods
A prospective multicenter study (2014-2024) analyzed 591 CPP patients from a Portuguese national database, stratified into three age clusters based on symptom onset: cluster I ($\leq$3 years), cluster II (4–6 years), and cluster III ($\geq$6.1 years). Clinical, hormonal, and treatment data were compared across clusters.
Results
CPP diagnoses increased markedly during 2020–2021, driven primarily by cluster III ($P = 0.003$), decreasing thereafter. Females were predominant in all clusters (539; 91%), although cluster III had 40 from the 52 males, there was no sex incidence significant difference among clusters. Secondary causes were more prevalent in cluster I (45%, $P < 0.001$). Weight-SDS, Height-SDS and BMI-SDS were similar among clusters. As expected, growth velocity was higher in cluster I ($P = 0.011$), while bone age advancement was significantly lower ($P < 0.001$). Basal LH and FSH levels were highest in cluster III ($P = 0.004$, $P = 0.009$), whereas stimulated FSH peaked in cluster I ($P < 0.001$) and stimulated LH peaked in all clusters. Stimulated LH/FSH ratio was lower on cluster I (p= 0.002) . IGF1 and IGF1-SDS were elevated across all clusters, with no significant age-related differences. Treatment duration was longer in cluster I (5.7$\pm$0.8 years, $P = 0.001$), however they ended treatment with younger bone age (10.8$\pm$1.9 years; $P = 0.019$). Despite these differences, age at menarche was similar across clusters and age of menarche 0.5$\pm$1.9 years earlier than their mothers.
Conclusion
Age clustering highlights critical differences in CPP presentation, influencing diagnostic and therapeutic approaches. Earlier treatment intervention, although associated with longer treatment duration, did not affect menarche timing. Future studies are needed to investigate the apparent influence of external factors, such as the COVID-19 pandemic, on CPP incidence.

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EP1092

JOINT1523

Gastric neuroendocrine tumors: a case series

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Introduction
The aim of this work is to present our department's experience with gastric neuroendocrine tumors (gNETs). The series of cases is comprised of 12 patients diagnosed with gastric NETs over a period of 15 years, from 2010 to 2025. A female predominance was observed, with a female/male ratio of 3:1.
Methods and results
According to literature, there are three main categories of gNETs, defined by the underlying gastric pathology. In our cohort, there were 8 patients diagnosed with type 1 gastric NETs (66.7%), one patient with type 2 (8.33%) and 3 patients with sporadic type 3 gNETS (25%). Type 1 gNETs are characterized by elevated gastrin levels in the context of autoimmune atrophic gastritis. All 8 patients had positive anti-parietal cell antibodies, decreased levels of vitamin B12 and hypergastrinemia, as well as elevated levels of chromogranin A. The median age at diagnosis was 58.5 years and 5 patients (62.5%) are still undergoing regular follow-up at our clinic. The majority of our patients with type 1 gastric NETS (87.5%) had multiple infra-centimetric lesions, with indolent evolution throughout follow-up, without loco-regional lymphadenopathy or distant metastasis, which is similar with data from literature. One patient (12.5%) had a singular lesion of over 2 cm diameter, with hepatic metastases present at diagnosis and G2 grading (Ki67=8%), which responded favorably to somatostatin analogue therapy and is currently monitored at 6 months interval. Five patients (62.5%) had a G2 grading and 3 patients (37.5%) had G1 tumors. One patient was diagnosed with type 2 gastric NETs in the context of multiple endocrine neoplasia type 1 (MEN 1). The initial evaluation showed multiple infra-centimetric G2 tumors (Ki67=3%) and hypergastrinemia. The patient underwent total gastrectomy, with subsequent normalization of biochemical markers. We also included 3 patients with type 3 gastric NETs, all of whom had, at initial evaluation, large tumors of over 3 cm and metastases to the liver, lung or peritoneum. Two patients had G2 gastric NETs and one had a G3 tumor (Ki67=70%). All patients received chemotherapy.
Conclusion
Our results corresponded to data from larger studies. Gastric NETs consist of three subtypes with distinct behavior and treatment. The only type 2 case occurred in the context of MEN1 syndrome. Type 1 tumors had an indolent evolution, whereas the type three ones were sporadic, larger and aggressive.

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EP1094

JOINT1662

Copeptin levels at baseline and in response to short-acting GLP-1 receptor agonists in patients with endogenous hyperinsulinaemic hypoglycaemia and healthy controls - a secondary analysis

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Background
Acute hypoglycaemia is a recognized non-osmotic trigger for copeptin release, a surrogate marker for vasopressin. However, data on copeptin levels in individuals at risk of chronic hypoglycaemia remain scarce. Endogenous hyperinsulinaemic hypoglycaemia (EHH), characterized by inappropriate insulin secretion and intermittent chronic hypoglycaemia, provides a useful model for investigating copeptin dynamics in the context of chronic hypoglycaemia. Therefore, this study aimed at evaluating baseline copeptin levels and copeptin responses to acute hypoglycaemia induced by short-acting GLP-1 receptor agonists, comparing patients with confirmed EHH to healthy controls.
Methods
This is a secondary analysis of the previously completed, randomized, double-blind, cross-over, proof of principle FAST study (NCT04909333) in patients with confirmed EHH and age-, sex- and BMI-matched healthy controls at the University Hospital Basel. The primary objective was to investigate baseline copeptin levels and to assess the acute effect of exenatide-induced decrease in glucose on copeptin levels in both groups. Patients were randomly assigned to first receive a single dose with exenatide (10ug) or placebo (0.9% sodium chloride) intravenously, followed by the alternate treatment on a subsequent day. Healthy controls only received exenatide. Plasma copeptin levels were measured at baseline and 60 minutes after the infusion. Individuals reporting nausea were excluded from the analysis.
Results
This analysis included eight patients and eight healthy controls. The median [IQR] age was 40 [34, 45] years, 75% were male, and the BMI was 28.4 kg/m^2 [26.0, 30.4]. Baseline copeptin levels were significantly higher in patients with EHH (7.28 pmol/l[4.27, 10.05]) compared to healthy controls (3.21 pmol/l[2.69, 4.55]) ($P = 0.03$). Fifty percent of patients experienced hypoglycaemia within 30 to 45 minutes after exenatide, accompanied by a glucose nadir of 2.71 mmol/l[2.68, 2.75], resulting in a copeptin increase of +2.13 pmol/l[0.40, 3.72] in this subgroup. Compared to placebo, no hypoglycaemic episodes occurred and copeptin levels decreased by -1.42 pmol/l[-2.11, -0.71]). Healthy controls reached a glucose nadir of 3.45 mmol/l[3.17, 3.53] within 30 to 45 minutes after exenatide, resulting in no relevant copeptin increase of +0.34 pmol/l[-0.01, 0.86], and only one participant experienced hypoglycaemia.
Conclusions
Patients with risk of chronic intermittent hypoglycaemia exhibit significantly elevated baseline copeptin levels compared to healthy controls. Exenatide induced a more pronounced blood glucose decrease in patients, triggering a stronger copeptin response compared to healthy controls, without downregulation from chronic hypoglycaemic stress. These findings provide further insights into copeptin dynamics in both chronic and acute hypoglycaemic states.

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EP1095

JOINT3342

Treatment-resistant gh-secreting pituitary adenoma in young patient harboring a variant somatic mutation of the gnas gene: a case report

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Background
Growth hormone (GH)-secreting pituitary adenomas are rare in children. Surgical removal is the first-line treatment, while persistent disease may require long-

acting somatostatin receptor ligands (SRLs), with or without dopamine agonists. This study presents a pediatric case resistant to multiple transsphenoidal surgeries, first- and second-generation SRLs, and bromocriptine therapy.
Method
Clinical data were reviewed, and whole-exome sequencing (WES) was performed on peripheral blood leukocytes and tumor tissue.
Results
A 12-year-old girl presented with tall stature since age five, along with headaches and blurred vision. She denied galactorrhea, polyuria, or polydipsia. Examination revealed a height of 172 cm (+3.43 SDS), mid-parental height of 157.5 cm, weight of 84 kg (+4.56 SDS), enlarged hands and feet, bitemporal hemianopia, and Tanner stage V for breast and pubic hair. Laboratory tests showed elevated IGF-1 (721 ng/ml), non-suppressible GH (>40 ng/ml), and prolactin 41.3 ng/ml (3-24). Other hormone levels were within normal ranges (FT4 1.06 ng/dl (0.98-1.63), TSH 1.09 μIU/ml (0.51-4.30), stimulated cortisol 20.2 μg/dl, LH 3.88 IU/l,FSH 4.46 IU/l,estradiol 38.4 pg/ml). Bone age was 15 years. Brain MRI revealed a 2.1×2.6×2.4 cm sellar and suprasellar mass encasing the internal carotid artery and extending into the cavernous sinus, consistent with a GH-producing pituitary macroadenoma. The patient underwent craniotomy, with histopathology confirming a GH-positive pituitary adenoma. WES identified a heterozygous missense c.2530C>T (p.Arg844Cys) variant in the *GNAS* gene in tumor tissue, absent in leukocytes, suggesting a somatic mutation. Three months post-surgery, GH remained elevated (nadir 30.8 ng/ml) with IGF-1 at 617 ng/ml, and a residual tumor (0.76×0.84 cm) was noted. A second transsphenoidal surgery and monthly octreotide LAR (20–60 mg) failed to achieve biochemical control, with a nadir GH of 5.42 ng/ml and IGF-1 of 602 ng/ml. Pasireotide LAR and bromocriptine were administered, but GH levels fluctuated between 1.79–7.15 ng/ml and IGF-1 remained at 555–575 ng/ml. At ages 16 and 17, the patient underwent a third and fourth surgery, but GH levels remained uncontrolled (nadir 6.86 ng/ml). Pegvisomant was considered but unavailable. She is now scheduled for proton radiation therapy.
Conclusions
We report a treatment-resistant GH-secreting pituitary adenoma in a pediatric patient harboring a somatic GNAS mutation. Managing such cases remains challenging, particularly in children. Stereotactic or proton radiotherapy should be considered when surgery and medical therapy fail to achieve biochemical control.

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EP1096

JOINT1141

Assessment of NF-κB levels in acromegalic patients with hepatosteatosis

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Introduction
Acromegaly is a disorder characterized by excessive secretion of growth hormone (GH), leading to increased insulin-like growth factor-1 (IGF-1) levels. Nonalcoholic fatty liver disease (NAFLD), a significant global health concern, is considered the hepatic manifestation of metabolic syndrome and may progress to fibrosis, cirrhosis, or hepatocellular carcinoma. The noninvasive test fibrosis-4 (FIB-4) score are the commonly used and recommended hepatic fibrosis scores for screening liver fibrosis. FIB-4 upper cut-off of < 1.3 suggests better diagnostic accuracy for predicting NAFLD. Nuclear factor kappa B (NF-κB) activation may contribute to insulin resistance and metabolic syndrome-related pathologies, including hepatic steatosis in acromegalic patients. This study aims to investigate the inflammatory processes in acromegalic patients with hepatosteatosis and controls to determine NF-κB levels in both conditions.
Methods
A total of thirty participants, including sixteen acromegalic patients and fourteen controls, will be included. We obtained demographic data, hormonal and metabolic parameters, and abdomen ultrasonography (USG) reports. NF-κB levels were measured using ELISA.
Results
The median age and gender distribution of the study participants were similar across groups ($P > 0.05$). Among the clinical parameters, there were significant differences in the mean values of fasting insulin ($P = 0.002$), GH ($P = 0.049$), IGF-1 ($P < 0.001$), and FIB-4 ($P = 0.001$), with higher values observed in acromegaly patients. In univariate logistic regression analysis, fasting insulin was found to increase the risk of acromegaly (O $r = 2.76$; 95% CI [1.032-7.380]), and FIB-4 was also identified as a risk factor ($P = 0.009$). In the multivariate analysis, FIB-4 remained a significant risk factor ($P = 0.009$). ROC analysis for distinguishing between acromegaly and control group revealed that fasting insulin had an AUC of 0.833 (sensitivity=68%, specificity=92%), while FIB-4 had an AUC of 0.821 (sensitivity=76%, specificity=93%). In sensitivity analyses, the acromegaly group was evaluated as controlled and uncontrolled. When comparing the mean FIB-4 values among the three groups, a significant difference was observed ($P = 0.005$). Post-hoc comparisons revealed significant differences between the healthy and controlled acromegaly groups ($P < 0.001$) as well as between the healthy and uncontrolled acromegaly groups ($P < 0.001$). The median NFKB levels were similar between the healthy and acromegaly groups ($P = 0.339$). No significant difference was detected when comparing NFKB medians among the three groups ($P = 0.539$).
Conclusion
This study is the first study to investigate NF-κB levels in acromegalic patients with hepatosteatosis, highlighting its potential role in metabolic dysfunction and hepatic inflammation. FIB-4 was identified as a risk factor to increase the risk of acromegaly. No significant difference was detected when comparing NFKB.

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EP1097

JOINT1206 Assessment of liver steatosis and fibrosis in acromegaly

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Introduction
Growth hormone (GH) has been shown to play a protective role against liver steatosis by reducing visceral adipose tissue. Liver fibrosis has been observed in cases of GH resistance and impairment of GH signaling pathways. In this study, we aimed to evaluate liver steatosis and liver fibrosis in patients with acromegaly.
Materials and Methods
This cross-sectional study included 58 patients diagnosed with acromegaly, followed up at the endocrinology outpatient clinic of Marmara University Hospital, along with 79 age-, sex-, and BMI-matched control patients. Hepatic steatosis and liver fibrosis were evaluated using controlled attenuation parameter (CAP) and liver stiffness measurements (LSM) via FibroScan, performed by a single experienced operator. Increased hepatic steatosis was defined as a CAP > 260 dB/m (>34% fat), and increased liver fibrosis was defined as an LSM ≥8 kPa (F ≥2).
Results
The acromegaly and control groups showed a similar distribution in terms of age, gender, body mass index (BMI), and the prevalence of diabetes, hypertension, and hyperlipidemia. No significant differences were observed between the groups regarding fasting blood glucose (FBG), LDL cholesterol levels, or liver function tests ($P > 0.05$). The CAP score, a marker of hepatic steatosis, was significantly lower in the acromegaly group compared to the control group (241.8 ± 50.0 dB/m vs. 289.8 ± 65.3 dB/m, $P < 0.001$). Similarly, the LSM score, used to assess hepatic fibrosis, was lower in the acromegaly group compared to controls (4.7 ± 1.4 kPa vs. 6.4 ± 4.5 kPa, $P = 0.007$). Moderate-to-severe hepatic steatosis was present in 36.2% of the acromegaly patients and 60.7% of the control group ($P = 0.005$). Fibrosis stage F2 or higher was detected in 5.1% of patients with acromegaly, compared to 17.7% of the control group ($P = 0.035$). A negative correlation was found between CAP score and GH levels (r: -0.311, $P = 0.017$), while positive correlations were identified between CAP score and FBG, BMI, and waist circumference (r: 0.298, $P = 0.020$; r: 0.447, $P < 0.001$; and r: 0.447, $P = 0.001$, respectively). Positive correlations were observed between LSM and both age and BMI (r: 0.400, $P = 0.001$; r: 0.540, $P < 0.001$).
Discussion
Hepatic steatosis and hepatic fibrosis were observed less frequently in patients with acromegaly compared to the control group. A negative correlation was identified between hepatic steatosis and GH levels. Elevated GH may have a potential protective role against fatty liver development in acromegaly patients, regardless of comorbid conditions such as diabetes and hyperlipidemia, which are major contributors to fatty liver disease.

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EP1098

JOINT2991

Natural history and clinical behaviour of non-operated rathke's cleft cysts: a single-centre retrospective review

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Background
Rathke's cleft cysts (RCCs) are benign, sellar or suprasellar cystic lesions of the pituitary gland. While frequently incidental, they can cause symptoms due to mass effects (headaches and/or visual disturbances) or due to endocrine dysfunction. Optimal management remains debated. This review examines the natural history of non-operated RCCs (radiological and endocrine progression) in a single-centre UK cohort.
Methods
Single-centre retrospective review of non-operated RCCs that were conservatively managed between 1/1/2021 and 31/12/2024. Data collection- demographics, presenting symptoms, endocrine function, radiological findings, follow-up outcomes.
Results
45 patients identified (median age 54 years at diagnosis, IQR 32 – 67 years, range 14 – 88 years). 31/45 (68.9%) diagnosed incidentally. Most common presenting symptom amongst non-incidental cases: headache (10/14, 71.4%). At diagnosis, 42/45 (93.3%) eupituitary. 3/45 (6.7%): hypopituitary (low growth hormone levels, arginine vasopressin deficiency, panhypopituitary with raised prolactin). At diagnosis, median cyst size (maximal diameter) 6 mm (IQR 5 –9 mm). All had full visual fields to confrontation. 1st follow-up: 28/45 (25 eupituitary, 3 endocrine deficit) (62.2%) received follow-up imaging. Median interval to 1st follow-up- 12 months (IQR 7.5 – 12 months, range 6 – 48 months). 17/45 (37.8%)- waiting for 1st follow-up scan. Biochemical and visual field findings: At 1st follow-up, 25 eupituitary patients at diagnosis, none developed new endocrine deficits. In the 3 patients with endocrine deficits at diagnosis, deficits remained the same. All patients (28/28)- normal visual fields. Subsequent follow-up: Median interval to most recent follow-up- 24 months (IQR 12.75 – 58.50 months, range 7 – 126 months). Biochemical and visual field findings: At most recent follow-up, 25 eupituitary patients at diagnosis, none developed new endocrine deficits. In the 3 patients with endocrine deficits at diagnosis, deficits remained the same. 27/28 (96.4%) normal visual fields, 1/28 (3.6%)- left inferotemporal visual field defect secondary to haemorrhage at 15 months after diagnosis.
Conclusion
The majority of RCCs in our cohort remained stable or regressed, with a low risk of developing new endocrine deficits. Conservative management appears safe, with routine hormonal screening potentially unnecessary in asymptomatic patients. We propose a patient-initiated follow-up based on symptomatic presentation instead of routine screening of non-operated RCCs. Future retrospective and prospective studies with longer periods of monitoring are warranted to further refine surveillance strategies.

Table 1. Radiological findings:.

No. of patients	Outcome
24 (85.7%)	Stable
2 (7.1%)	Shrinkage
1 (3.6%)	Growth
1 (3.6%)	Haemorrhage

Table 1. Radiological findings:.

No. of patients	**Outcome**
20 (71.4%)	Stable
4 (14.3%)	Shrinkage
2 (7.1%)	Growth
2 (7.1%)	Haemorrhage

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EP1099

JOINT3363

Relationship between disease severity and puberty status in pediatric systemic lupus erythematosus (SLE) patients

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Background
Systemic lupus erythematosus (SLE) is a disease that spreads all over the world. The incidence of SLE in children is 10-20 cases per 100,000 children. Compared with SLE in adults, SLE in children tends to be more severe, requires more intensive care and a higher mortality rate. Growth failure and delayed puberty can also be an effect of SLE in children, caused by severe disease activity and long-term disease duration that can affect the whole body.
Objective
The aim is to understand the effect of systemic lupus erythematosus on pubertal growth and development so that it can help doctors to improve efforts to control systemic lupus erythematosus.
Methods
Total respondents were 23 pediatric patients diagnosed with SLE at dr Saiful Anwar Hospital. Data for each variable studied was obtained through medical records. Puberty status using the Tanner scale, the level of LES disease activity was measured by the SLEDAI Score.
Results
The results showed that the majority of respondents had very high disease activity (39.1%), high disease activity (30.4%), moderate disease activity (21.7%), and mild disease activity (8.7%). Puberty status was found (87%) of normal pubertal development of children and (13%) of delayed pubertal development of children. The results of data analysis using logistic regression showed that there was no relationship between the severity of SLE and the pubertal status ($P = 0.249$) of children at dr. Saiful Anwar Hospital.
Conclusion
The conclusion is that there is no relationship between the severity of SLE disease and the pubertal status ($P = 0.249$) of children in dr. Saiful Anwar Hospital.
Keywords
systemic lupus erythematosus, puberty, children, SLEDAI score.
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EP1100

JOINT3833

Triple hormone secreting pituitary macroadenoma: a rare cas

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Introduction
Pituitary adenomas are classified based on their hormonal secretion, with prolactinomas, somatotropinomas, and corticotropinomas being the most common. However, pituitary adenomas secreting three hormones are extremely rare and often manifest as a complex endocrine syndrome. We report a unique case of a triple-secreting pituitary macroadenoma (GH, PRL, ACTH) in a young woman, presenting solely with isolated galactorrhea, without signs of acromegaly or Cushing's syndrome.
Case Presentation
A 25-year-old woman presented with a six-year history of bilateral galactorrhea, which later progressed to secondary amenorrhea and thyrotropic insufficiency. She had no headaches, visual disturbances, or symptoms suggestive of acromegaly or hypercortisolism. Clinical examination confirmed bilateral galactorrhea, with no facial dysmorphism, acral enlargement, centripetal obesity, or easy bruising. Laboratory tests revealed hyperprolactinemia (>250 ng/ml, normal: 5-35 ng/ml), a normal IGF-1 level, and a normal 24-hour urinary free cortisol level. Thyroid function tests confirmed central hypothyroidism, with normal gonadotropin levels. Brain MRI revealed a sellar and suprasellar pituitary macroadenoma ($25 \times 14 \times 20$ mm) with optic chiasm compression and lateral extension into the cavernous sinuses, exhibiting heterogeneous gadolinium enhancement. Histopathological analysis confirmed a pituitary adenoma with strong immunohistochemical positivity for GH, prolactin, and ACTH, with negative staining for TSH and gonadotropins.
Discussion and Conclusions
Triple-hormone-secreting pituitary adenomas are extremely rare and usually present with overt clinical signs of hormone hypersecretion. However, in this case, the patient exhibited only galactorrhea and secondary amenorrhea, despite histological evidence of GH and ACTH hypersecretion, suggesting silent or subclinical hormonal overproduction. This case highlights the importance of a comprehensive endocrine evaluation, as some patients may develop delayed manifestations. First-line treatment consists of transsphenoidal surgery, aiming to reduce tumor mass and normalize hormone secretion, followed by dopamine agonist therapy for hyperprolactinemia and levothyroxine replacement for thyrotropic insufficiency. Long-term endocrine follow-up is essential to detect potential late-onset acromegaly or Cushing's syndrome, emphasizing the need for a multidisciplinary approach involving endocrinologists, neurosurgeons, and radiologists to optimize the patient's prognosis.
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EP1101

JOINT2717

A real-world study of lanreotide autogel for the treatment of patients with acromegaly in china: baseline interim analysis

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Objective
This real-world study (RWS) aims to evaluate the effectiveness, safety, and treatment patterns of lanreotide autogel (LAN) in Chinese patients with acromegaly. The abstract summarizes only baseline data.
Methods
This multicenter, prospective, observational real-world study was conducted across 12 sites in China. A total of 127 patients with acromegaly were planned to enroll based on key inclusion criteria: serum insulin-like growth factor-1 (IGF-1) levels above the upper limit of normal (ULN) and fasting growth hormone (GH) levels >2.5 μg/l,untreated with LAN. Fasting GH and IGF-1 levels, and LAN administration details (dose titration and interval adjustments), were collected at baseline (last before index), 3, 6, and 12 months after LAN initiation. Adverse events (AEs) and special situations (e.g., pregnancy, overdose) were monitored throughout the study. The baseline data include demographic, clinical characteristics (time since acromegaly first diagnosis, size of pituitary tumor, symptoms, comorbidities, etc.), and prior treatments for acromegaly (treatment types, prior medications, etc.). The primary endpoint is defined as the proportion of patients achieving biochemical control (fasting GH level ≤ 2.5 μg/land IGF-1 return to normal range adjusted to age category) at 12 months.
Results
A total of 129 patients were enrolled and treated, of whom 75 (58.1%) were female. At baseline, patients had mean (SD) age of 43.3 (13.4) years, body mass index of 25.97 (4.11) kg/m^2, and fasting GH (μg/l)and IGF-1 (xULN) of 22.30 (49.15) and 2.10 (1.75), respectively. The median (95% CI) time to acromegaly first diagnosis was 1.1 (0.8, 1.7) years. Pituitary tumors were observed in 97/127 (76.4%) patients at baseline, with 50 (39.4%) macroadenomas and 29 (22.8%) microadenomas. Clinical symptoms were present in 112 (86.8%) patients (soft tissue swelling (63.6%), headache (39.5%), joint pain (29.5%), fatigue (27.1%), and excessive sweating (20.9%)). Comorbidities were observed in 81 (62.8%) patients (altered carbohydrate metabolism (27.1%), sleep apnea (26.4%), hypopituitarism (25.6%), hypertension (20.2%), and heart disease (12.4%)). 66.7% of the patients had undergone pituitary transsphenoidal surgery, 31.0% had radiotherapy, and 41.9% had prior medications (Octreotide LAR, 27.1%; Bromocriptine, 10.1%; and Cabergoline, 3.9%). At the first LAN prescription, 91.5% of patients received a 28-day dosing schedule, 48.8% were prescribed 90 mg and 51.2% for 120 mg.
Conclusions
This interim analysis shows the study mainly included postoperative patients with pituitary macroadenomas and multiple comorbidities. LAN was administered at doses of 90 mg and 120 mg half each, predominately once every 28 days in Chinese patients with acromegaly.

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EP1102

JOINT2745

Misdiagnosed pituitary adenoma in a reproductive age woman

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Introduction
Acromegaly is a rare condition predominantly caused by a growth hormone (GH)-secreting pituitary adenoma driving excess secretion of insulin-like growth factor-1 (IGF-1). Multitude of manifestations have been associated with chronic GH excess, including cardiovascular, pulmonary, neoplastic, endocrine, metabolic and musculoskeletal comorbidities. The diagnosis of acromegaly is confirmed on biochemical grounds. Pituitary magnetic resonance imaging is advised in patients to identify an underlying pituitary adenoma. Transsphenoidal pituitary surgery is generally first-line therapy for patients with acromegaly. Medical therapies can be recommended to patients with persistent disease. Radiation therapy is usually a third-line option.
Case Report
We present a case of 33 y/o female first diagnosed with pituitary macroadenoma, hyperprolactinemia at the age of 20. Additional pituitary hormonal work-up was not performed at that time. Treatment with dopamine agonist (cabergoline) was initiated. 5 years after diagnosis, patient was evaluated by another endocrinologist due to increasing headaches, lightheadedness, acral and facial features of acromegaly (skin thickening, changes to facial symmetry, increased shoe size). Head MRI and additional laboratory work-up revealed growth of pituitary adenoma and increased levels of IGF-1. Patient was diagnosed with acromegaly and transsphenoidal surgery was performed which led to slightly decreased levels of IGF-1. Repeated MRI scan performed a year later, revealed residual tissue. Repeat TSS was performed in Germany a year later due to residual intrasellar disease following initial surgery. IGF-1 levels normalized after surgery and patient was being monitored. Elevated IGF-1 levels were not demonstrated until 2022. Patient was advised to initiate treatment with somatostatin analogs, which she declined, alternatively, due to modest elevations of serum IGF-1 and mild signs and symptoms of GH excess, off label use of dopamine agonist –cabergoline was offered. Most recent MRI does not show evidence of residual tissue. Patient continues DA therapy, currently her IGF-1 levels are well under control. Patient is being counseled and monitored for recurrence and associated comorbidities.
Conclusion
A high index of suspicion is needed to minimize delays in diagnosis of acromegaly. Goals of treatment include normalization of GH secretion or (at least) GH action as indicated by a normal IGF-1 level as well as by resolution of tumor-induced mass effects, acromegaly-related symptoms, and associated comorbidities, all aiming at mitigating excess mortality while preserving normal pituitary function.
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EP1103

JOINT2989

Pituitary metastases: a case series

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Background
Pituitary metastases are a rare pathological finding. This case series aims to evaluate certain variables in patients with pituitary metastases.
Methods
We performed a retrospective analysis of pituitary metastasis patients who came to our center from 2018 to 2023. All patients underwent pituitary MRI and the diagnosis of pituitary metastasis was confirmed by histological examination.
Results
We identified 10 patients of whom 7 were female and 3 male, with a mean age of 56.7 years. The histological features of the neoplasms found were: breast carcinoma (2), neuroendocrine tumors of probable lung origin (2), adnexal carcinoma (1), gastrointestinal carcinoma (1), melanoma (1), small cell lung carcinoma (1), thyroid carcinoma (1), diffuse large cell non-Hodgkin's lymphoma (1). Visual disturbances were the most frequent onset symptom (30%). A

prolactin elevation was found in one patient. All patients underwent transsphenoidal surgery to debulk, reduce and/or resolve symptoms and restore proper hormone secretion. In 60% of the patients residual disease was found at postoperative radiological control. In the postoperative period, 70% of patients had a deficit in the secretion of pituitary hormones: anterior hypopituitarism (4 patients) and diabetes insipidus (3 patients) were the most frequent. Only 3 patients (30%) had no deficits in hormone secretion after undergoing transsphenoidal surgery. In 30% of the patients, the pituitary gland was identified as the first site of metastasis. In one patient, suffering from neuroendocrine carcinoma, the primary neoplasm was not found.
Conclusion
Pituitary metastases are characterized by great heterogeneity in clinical presentation, hormonal deficits, and origin of the primary neoplasm. Generally, this type of lesion is treated as an adenoma; only after the lesion is removed and histological examination is performed can it diagnose pituitary metastasis. An interesting finding from this series is that in 3 patients the pituitary gland was identified as the primary site of metastasis, with no evidence of metastatic disease in other districts. Surgery represents the first line of therapy. The rate of residual or recurrence of disease after surgery remains considerable.

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EP1104

JOINT2995

Neurocognitive and neuropsychological assessment in the acromegalic patient: correlation with clinical, biochemical and prognostic features

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Acromegaly is a rare disease caused by the presence of a sporadic growth hormone (GH)-secreting pituitary/neuroendocrine adenoma. Patients with acromegaly progressively go through disfigurement of somatic features and relevant systemic manifestations, induced by chronic exposure to growth hormone. In this context of multimorbidity, it is also necessary to assess the cognitive and neuropsychological picture, which is often compromised. In order to perform a comprehensive assessment of cognitive performance and neuropsychological profile in a cohort of acromegalic patients and investigate their correlation with clinical, biochemical and prognostic features, a single-center prospective study was conducted at our Institution in 2023. The population examined consisted of 50 acromegalic patients, 27 women (54%) and 23 men (46%), being treated at the Gemelli Polyclinic Pituitary Outpatient Clinic. All of them were subjected to various neuropsychological questionnaires and tests on reported quality of life. In addition, they were administered neurocognitive tests to the 7 patients in the cohort who were over 65 years old. The most prominent complaints found were fatigue (84%), irritability (82%), emotional changes (76%), work difficulties (70%), increased sensitivity to stress (68%), frustration (62%), physical pain (56%), decreased libido (56%), memory problems (52%) and sadness (50%). The results of the study showed that cognitive and neuropsychological disorders are present to a greater extent in patients with acromegaly than those found in the general population. These alterations were also correlated with independent factors such as age, gender, and the results of the AcroQoL questionnaire, thus allowing the identification of the categories of acromegalic patients at higher risk for neuropsychological disorders. In conclusion, it is essential, in taking care of the patient with acromegaly, to undertake a multidisciplinary diagnostic-therapeutic pathway that is able to take into account the peculiarities of the patient's neurocognitive and neuropsychological profile, with a view to best practice.

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EP1105

JOINT3521

Determinants and clinical presentation of bone metastases in neuroendocrine tumors: a retrospective study

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Objective
Bone metastases (BMs) are rare and late event in patients with neuroendocrine tumors (NETs). The aim of our study was to investigate determinants, clinical presentation and outcome of BMs in a large cohort of patients with NETs.
Methods
A retrospective, longitudinal case-control study was performed at two referral centers of Northern Italy (IRCCS Humanitas Research Hospital in Milan and S. Maria della Misericordia University Hospital in Udine). Three-hundred-fifty-two consecutive patients with either gastroenteropancreatic neuroendocrine tumors (GEP-NETs) or non-GEP-NETs were included: 52 patients with synchronous or metachronous BMs (case group) and 300 patients with metastatic disease without BMs (control group).
Results
Patients with BMs showed a higher prevalence of smoking habit (41.2% vs 21.8%, $P = 0.013$) and carcinoid syndrome (28.8% vs 5.7%, $P = 0.001$), as compared to controls. Cases had also higher levels of chromogranin A ($P=0.001$) , urinary 5-hydroxyindoleacetic acid ($P = 0.001$), parathyroid hormone ($P=0.023$) and alkaline phosphatase ($P = 0.018$) as compared to control group. Patients with BMs had more frequently lung NETs (19.2% vs 0.7%, p-value 0.001) and grade G2 and G3 tumors ($P = 0.012$ and $P = 0.01$, respectively), as compared to controls. During follow-up (median 4.33 years), a higher mortality rate was registered in the case group as compared to the controls (42.3% vs 4.0%, p-value 0.001).
Conclusions
BMs were more common in patients with lung NETs, G2-G3 grade and in those with carcinoid syndrome. BMs affected patients' prognosis, highlighting the importance of investigating and managing this condition in patients with NETs.

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EP1106

JOINT2705

Endoscopic endonasal treatment in patients with crooke's cell adenomas

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Introduction
Crooke's cell adenoma (CCA) is a rare subtype of pituitary adenoma (<1%). CCAs are usually invasive, may exhibit aggressive behavior, and often recur. Thus, the treatment of CCAs is difficult and might not result in a complete remission. The aim of this study was to assess characteristics of a group of patients with CCAs treated with endoscopic endonasal resections.
Material and Methods
The study is a retrospective analysis of a series of 18 patients (6 women and 12 men) treated from the 2015 to 2024 by the endoscopic transsphenoidal surgeries for CCAs. The mean age of the patients was 48.3 years (18-77 years), and the mean follow-up period was 5.3 years (0-11 years).
Results
Preoperatively 8 patients had visual function deterioration (44.4%), 8 patients had Cushing's disease (44.4%), 6 patients had hypopituitarism (33.3%), 4 patients had headaches (22.2%). Gross total resections were achieved in 6 out of 8 patients with Cushing's disease (75%), and in 7 out of 10 patients with silent adenomas (70%). Most patients (88.9%) had macroadenomas. Five patients (27.8%) had an intra-operative cerebrospinal fluid leak, and a reconstruction of the sella with a fat tissue graft. Postoperatively 75% of the patients showed varying improvement in visual field defects and visual acuity. The only complication was transient diabetes insipidus (DI) observed in 3 patients (16.7%). One patient progressed to pituitary carcinoma, had four subsequent resections, and eventually died. The remission of Cushing's disease was achieved in 6 patients after surgery (75%).

Conclusions
Endoscopic transsphenoidal treatment of patients with CCAs is safe and associated with a low complication rate. The patients are younger and have more resections than in usual pituitary adenomas.

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EP1107

JOINT3942

AIP variants among adult patients with acromegaly

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Introduction
AIP variants are found in up to 40% of familial cases of acromegaly and gigantism, as well as in some sporadic cases, particularly those with early-onset disease. Patients with *AIP* variants often present with higher growth hormone (GH) levels. AIP variants are found in up to 40% of familial cases of acromegaly and gigantism, as well as in some sporadic cases, particularly those with early-onset disease. Patients with *AIP* variants often present with higher growth hormone (GH) levels with no difference in insulin growth factor 1 (IGF-1) level.
Objectives
We studied the prevalence of *AIP* variants in a cohort of unselected, consecutive adult patients with acromegaly from 2019 to 2024.
Materials and methods
A total of 134 patients (79 females, 55 males, age range 16-75 years) with somatotroph pituitary neuroendocrine tumor who were studied at the Jagiellonian University (Krakow), a tertiary referral center, were enrolled in this study. Genetic testing (Sanger Sequencing) was performed in all patients with acromegaly.
Results
Germline *AIP* variants were identified in eight patients including five missense variants, one three-nucleotide deletion. The specific variants observed were c.47G>A (p.Arg16His) in three patients, c.911G>A (p.Arg304Gln) in one female patient, c.235A>C (p.Thr79Pro) in one male patient, c.941G>C (p.Arg314Pro) in one male patient, c.811C>T (p.Arg271Trp) in one male patient, and c.742_744del (p.Tyr248del) in one female patient. The clinical significance of .47G>A and c.911G>A remains uncertain and is currently under discussion. The median age of symptom onset was 34 years (range: 14–71 years), while the median age at diagnosis was 39 years (range: 16–72 years). Most cases (7 out of 8) presented with macroadenomas, and six patients were not cured following surgery. Three patients harbored mix tumour (prolactin co-secretion). Additionally, 50% of *AIP* variant carriers met the criteria for familial isolated pituitary adenoma (FIPA).
Conclusions
This study show the prevalence of *AIP* variants among adult patients with acromegaly in Poland. Genetic testing in acromegaly should be considered to personalize and optimize the treatment of patients.

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EP1108

JOINT3442

Granular cell tumor of the pituitary gland – an exceedingly rare diagnosis

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Introduction
Granular Cell Tumors (GCTs) are exceptionally rare neoplasms arising in the posterior lobe of the pituitary gland (or neurohypophysis). Typically benign and slow growing, these tumors may present with symptoms related to mass effect or hypopituitarism. Due to their nonspecific radiological features, they are often indistinguishable from other sellar lesions, with definitive diagnosis requiring histopathological confirmation. Here, we present a case of GCT with a four-year follow-up, contributing to the limited literature on this entity.
Case Report
A 78-year-old woman presented with insidious visual disturbances. Initial evaluation by ophthalmology revealed a diagnosis of cataracts, but there was no improvement after phacoemulsification surgery. Further assessment revealed bitemporal hemianopsia and cranial MRI identified a 17x15x12mm tumor with suprasellar extension compressing the optic chiasm and contacting with the internal carotid arteries. The lesion exhibited isointensity on T1-weighted imaging and diffuse contrast enhancement. Hormone evaluation revealed hypogonadotropic hypogonadism (FSH 5.1mUI/ml [RR>34], LH 1.2mUI/ml [RR>25]), low TSH (TSH 0.31uUI/ml [RR 0.40-4.00], FT4 1.0ng/dl [RR 0.7-1.5], under levothyroxine treatment), secondary adrenal insufficiency (cortisol 4.2ug/dl [RR 5-25], ACTH<5.0pg/ml [RR 9-52]) and a slight prolactin elevation (45.5ng/ml [RR 5.2-26.5]); IGF1 was normal (161ng/ml [RR 81-225]). Hydrocortisone replacement therapy was initiated. The patient underwent decompressive transsphenoidal surgery, achieving only partial resection of the lesion due to its proximity to critical structures and hypervascularity. Post-operatively, pituitary dysfunction worsened (FSH <1.0mUI/ml, LH <1.0mUI/ml, prolactin 2.4ng/ml, TSH <0.004uUI/ml, FT4 0.70ng/dl, cortisol 1.0ug/dl, ACTH<5.0pg/ml, GH <1.0mg/l,IGF1 39ng/ml). Histopathological examination documented a grade I CGT of the sellar region, with a Ki-67 index of 3%. Immunohistochemistry showed TTF-1 positivity and other pituitary hormone markers were negative. Postoperative imaging revealed a residual sellar and suprasellar lesion measuring 12x13mm, causing obliteration of the suprasellar cistern and inferior molding the optic chiasm. Neuro-ophthalmological assessment confirmed persistence of bitemporal hemianopsia. Four years after surgery, the lesion remains stable, and the patient reports no new symptoms.
Conclusions
GCTs are extremely rare, with just over 100 cases reported in the literature. Consistent with previous reports, this case was associated with hypopituitarism, and surgical excision was challenged by the tumor's vascularized adherent nature and proximity to critical structures. Despite partial resection, the residual lesion remained stable over four years, highlighting the indolent behavior of these tumors. This report adds valuable insights to the limited knowledge of GCTs and underscores the importance of further studies to guide future clinical practice.

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EP1109

JOINT2498

Outcomes and challenges in the treatment of prolactinomas in young adults: a retrospective study of clinical and genetic factors

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Introduction
Prolactinomas are the most common secretory tumors of the pituitary gland, although their prevalence in individuals under 35 years old is relatively rare. The onset of prolactinomas at a young age, particularly in male patients, may be associated with more aggressive tumor behavior. The objective of this study was to evaluate the clinical characteristics of prolactinomas and assess their response to treatment.
Methods
We retrospectively analyzed all patients under 35 years old diagnosed with prolactinoma from January 2015 to May 2024 and extracted clinical, imaging and biochemical parameters. All patients received DA (dopamine agonist) therapy as the first line of treatment. DA resistance is defined as persistent hyperprolactinemia despite high-dose cabergoline treatment.
Results
The study included 63 patients diagnosed with prolactinoma, with a mean age of 25.54 ±5.89 years at diagnosis; 57.1% were female patients. Among all, 25 patients had microprolactinomas, and 38 had macroprolactinomas. Males had a higher prevalence of macroprolactinomas (68.4%) compared to microprolactinomas (12%). All 9 patients diagnosed with giant prolactinomas, with tumor sizes exceeding 40 mm, were male. Of the patients with microprolactinomas, 12% (all female) exhibited resistance to DA therapy and required doses higher than 2.0 mg of cabergoline per week. In contrast, 55% of patients with macroprolactinomas (84.6% of whom were male) required dose escalation. Additional therapeutic approaches, such as transsphenoidal surgery combined with cabergoline (3 cases), radiotherapy (2 cases), and chemotherapy (Temozolomide) (1 case), were implemented for DA-resistant macroprolactinomas. In two cases, multimodal treatment strategies involving surgery, cabergoline, and/or chemotherapy and radiotherapy were necessary. Genetic testing for mutations in the AIP and MEN1 genes was conducted in 7 patients with high clinical suspicion (e.g., age at diagnosis < 20 years, giant

and/or invasive tumor, symptomatic hypercalcemia, and/or adrenocortical tumors). One patient was diagnosed with MEN1 syndrome through genetic testing.
Conclusions
Dopamine agonist treatment as first-line therapy, particularly for macroprolactinomas in young male patients, had limited efficacy in controlling the disease, resulting in a greater need for dose adjustments and additional treatment strategies. Genetic testing, particularly for AIP and MEN1 mutations, is recommended for young patients diagnosed with aggressive prolactinomas, but it should be reserved for those with a high clinical suspicion of underlying genetic syndromes.

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EP1110

JOINT2815

Pituitary adenomas and differentiated thyroid cancer. keys to good management: a case series

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Association between pituitary adenomas (PA) and differentiated thyroid cancer (DTC) requires an individualized approach. On one hand, pituitary neurosurgery and radiotherapy, as well as some drugs might impact the TSH secretion due to post-procedural hypopituitarism. On the other hand, classic treatment of DTC includes total thyroidectomy (TT), radioactive iodine therapy, and follow-up monitoring using stimulated thyroglobulin (sTgl). Herewith we describe four cases of patients with DTC and associated thyrotropic insufficiency due to simultaneous PA, underlying the importance of recombinant human TSH (rhTSH) stimulation for optimal management.

- A 45-year old acromegalic male is presenting with papillary thyroid carcinoma (PTC), who underwent a TT, and an associated thyrotropic insufficiency on account of a GH-secreting pituitary adenoma treated with transsphenoidal surgery (TSS) and additional SMSa. In the need of a RAIU for the PTC follow-up, his replacement therapy was withdraw 4 weeks, but the TSH remained low (12.85 mUI/L), under the optimal value required (>30mU/L). After rhTSH raised TSH to 72.66 mUI/l,allowed RAIU and stimulated Tgl< 0.2 ng/ml, certifying the cure of DTC.
- A 56-year old female presented with PTC and a history of macroprolactinoma irradiated twice (1985) and then treated with dopaminergic agonists, which resulted in panhypopituitarism. After performing TT for PTC, followed by one month LT4 withdraw in order to do radioiodine ablation, her TSH was only 3.94 mUI/L. After rhTSH injection, her TSH increased to 85.36 mUI/lallowing I^{131} treatment and sTgl=3.47 ng/ml.
- A 63-year old male with history of macroprolactinoma with pituitary apoplexy, treated with TSS and subsequent gonadotrophic and thyrotropic insufficiency, underwent TT for PTC. Four weeks off-treatment, TSH=13.44 mUI/L. After rhTSH, TSH=49.1 mU/l,RAIU excluded any remnant thyroid tissue and Tgl = 0.2 ng/ml, certifying the cure of DTC.
- A 65-year old female with a non-functioning pituitary adenoma and simultaneous PTC, underwent firstly TT (03.2023) and 4 months later the TSS for PA resulting in a thyrotropic deficiency. This time she underwent I^{131} therapy (10.2023) with an off-treatment (TSH=1.72 mU/l,fT4=0.3 ng/ml), without rhTSH, with a very low efficiency resulting in the need of a second radioactive iodine treatment.

Conclusion
TSH deficiency in hypopituitarism associated with DTC makes the radioactive iodine treatment or the RAIU/Tgl for the management of thyroid cancer less effective, unless rhTSH is used.

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EP1111

JOINT2476

Resistant prolactinomas: a retrospective insights into clinical, imaging, and demographic characteristics in the largest patient cohort

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Objective
To assess the characteristics of patients with resistant prolactinomas and adjuvant treatment modalities in practice.
Materials and methods
A total of 33 patients (20 men, 13 women) with resistant prolactinomas were studied, focusing on age at diagnosis, prolactin (PRL) levels and adenoma size and characteristics.
Results
The median age at diagnosis was 30 years for men and 25 years for women, with no significant difference ($\rho = 0.543$). Men had significantly higher PRL levels (median: 12,375 mU/l)compared to women (median: 2,175 mU/L), $P < 0.001$. Microadenomas were more frequent in women (38% vs 10% in men, $P = 0.051$), while macroadenomas were more common in men (85% vs 54%, $P = 0.05$). A significant positive correlation was found between the initial PRL level and the three adenoma dimensions: vertical ($\rho=0.616$, $P < 0.001$), horizontal ($\rho = 0.581$, $P = 0.002$) and anteroposterior ($\rho = 0.761$, $P < 0.001$), with correlation strength increasing from the first to the third size. In patients with microadenomas, the median PRL level was 1,500 mU/l,eight times lower than in macroadenomas (median: 12,000 mU/l,$P < 0.05$). Tumor growth was intracellar in 75.8%, suprasellar in 60.6%, parasellar in 45.5%, and infrasellar in 30.3%. Hypogonadism was found in 15 men and 10 women, with no significant gender differences ($P > 0.05$). Adrenal insufficiency (2/17) and secondary hypothyroidism (1/11) were rare, with no growth hormone deficiency. Cabergoline therapy significantly decreased PRL levels in the overall patient sample ($P = 0.003$) and in men ($P < 0.001$), but had no significant effect in women ($P = 0.866$). It notably reduced the vertical size of adenomas ($P = 0.011$), but had no effect on horizontal or anteroposterior sizes ($P = 0.410$ and $P = 0.779$). Adjuvant therapy was used in 10 patients, including tamoxifen (4), tamoxifen with bromocriptine (2), tamoxifen with cabergoline (3), and temozolomide with cabergoline (1).
Conclusions
Resistance to dopamine agonists is more common in younger patients, with men having higher PRL levels due to macroadenomas. PRL levels strongly correlate with the anteroposterior size of the adenoma. Cabergoline significantly lowers PRL levels in men, with no significant changes in women, possibly due to lower baseline levels or gender-related treatment differences. It reduces the vertical adenoma size without affecting the horizontal or anteroposterior dimensions, suggesting selective action on tumor volume. Adjuvant treatment options in real clinical practice remain highly limited. Further research into resistance mechanisms and personalized treatment is needed.

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EP1112

JOINT3653

The assessment of relationship between acromegaly and hedonic hunger

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Objective
The aim is to evaluate the hedonic hunger and its effects on eating behaviors in patients with acromegaly characterized by excess growth hormone, compared to individuals with non-functional pituitary adenoma and those without pituitary disease.
Materials and Methods
The study included 55 patients with acromegaly, 39 patients with non-functional pituitary adenoma, and 34 healthy volunteers followed at the Endocrinology and Metabolism Diseases Pituitary Clinic of Ege University Medical Faculty Hospital. Sociodemographic characteristics, chronic diseases, fasting plasma glucose, and HbA1c values were obtained from participants. Body Mass Index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. The Hedonic Hunger Scale (HHS) was used, and eating behaviors were assessed through face-to-face interviews using the Dutch Eating Behavior Questionnaire and the Three-Factor Eating Questionnaire. The Hospital Anxiety and Depression Scale was also applied through face-to-face interviews to identify potential psychiatric conditions.
Results
Median age of acromegaly and non-functional pituitray adennoma patients was 53 and 54 years old, respectively. Control group was age matched as 53 years old. Twenty out of 53 acromegaly patients were active according to IGF-1 levels. The rest of them were in remission. The average total score of the Hedonic Hunger Scale was found to be significantly higher in the control group compared to the acromegaly group ($P <0.05$). In the Dutch Eating Behavior Questionnaire, the average total score and median values of emotional eating and external eating were significantly higher in the control group compared to the acromegaly group ($P <0.05$). In the Hospital Anxiety and Depression Questionnaire, the depression subscale was found to be higher in the acromegaly group compared to the non-

functional adenoma group, and this difference was statistically significant ($P < 0.05$).
Conclusion
Eating behavior is regulated by a complex structure governed by homeostatic and hedonic systems, influenced by numerous central and peripheral signals. To the best of our knowledge, this is the first study assessing hedonic hunger in acromegaly. The status of education, income and the relatioship between growth hormone and ghrelin may affect hedonic hunger. It should be needed to evaluate treatment naive and post treatment acromegaly patients to explain the effect of growth hormone on hedonic hunger.
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EP1113

JOINT2607
The challenges of managing AVP deficiency in pregnancy with hyperemesis gravidarum
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Introduction
Managing AVP deficiency in pregnancy can be challenging due to the physiological changes associated with pregnancy. These changes can impact both the mother and the unborn baby. Vasopressinase, an enzyme released by the placenta, acts as a degrader of vasopressin. In a healthy female, this enzyme has an insignificant effect. However, in women with incomplete AVP deficiency, the presence of vasopressinase can exacerbate the condition during pregnancy, leading to worsening polyuria and polydipsia. These women may require higher doses of Desmopressin to manage their symptoms effectively.
Case Presentation
A 35-year-old lady presented with headaches and hyperemesis gravidarum in the antenatal clinic and maternity triage unit. Her past medical history included a diagnosis of AVP deficiency following a previous miscarriage at 16 weeks. During subsequent pregnancy, she developed frank AVP deficiency. She had polyuria and polydipsia (drinking up to 20 litres per day). The neurology team assessed and reviewed her. She had an MRI pituitary with normal findings. She was treated for gestational diabetes with metformin and she was on desmopressin for her established AVP deficiency. Blood tests since January 2017 showed sodium level ranging between 133 – 144 mmol/lwith noticeably a decline in sodium level to 130 mmol/lin January 2024. Serum osmolality was found to be within the range of 275-295 mmol/kg and urine osmolality was intermediate (between 500-600 mmol/kg). The desmopressin dose was adjusted accordingly with close monitoring.
Conclusion
Pregnancy is associated with increased blood volume and glomerular distraction rate. The risk of Gestation AVP deficiency in patients with already established AVP deficiency cannot be ignored, and the dehydration is significant especially if the patient developed hyperemesis gravidarum. In summary, managing AVP deficiency in pregnancy can be challenging and warrants close monitoring of fluids and electrolytes. The treatment should be individualized, and an MDT approach is necessary to ensure the desired outcome.
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EP1114

JOINT2258
Treatment with aromatase inhibitor in a patient with a leydig cell tumor: case report
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Introduction
Advanced bone age (BA) is frequently observed in patients with Leydig cell tumors (LCTs) due to increased testosterone secretion, leading to an adult height (AH) below the average for the normal population. Estrogen is the principal regulator of epiphyseal fusion in both males and females, accelerating growth plate closure. Aromatase inhibitors (AIs) have been used to enhance linear growth in boys with advanced BA and poor height potential. We present a patient with an LCT treated with an AI.
Case Report
An 11.5-year-old boy, previously healthy, was referred following an orchiectomy for an LCT in the left testicle. His height was 150.5 cm (0.71 SDS), with a mid-parental height of 171.75 cm (-0.2 SDS). His BA was 14 years (2.25 years advanced), with a predicted adult height (PAH) of 163 cm (-1.44 SDS). Tanner stage was 4 (G4, PH4), and right testicular volume was 15 mL. Laboratory results: LH: 3.7 IU/l,FSH: 12.4 IU/l,E2: 43 pg/ml, Testosterone: 4.24 ng/ml. Treatment with anastrozole, 1 mg/day, was initiated to optimize his final height. At the last visit, after 18 months of treatment (at 13.58 years old), his height was 162 cm (0.7 SDS), his BA was 15.5 years (2 years advanced), and his PAH was 167 cm (-0.8 SDS). Treatment was discontinued at this time.
Conclusions
Treatment with aromatase inhibitors decelerates epiphyseal fusion, prolonging the growth period and consequently improving adult height. In this case, treatment with an AI for 18 months resulted in an improvement in PAH. Long-term follow-up is required to evaluate whether the final height corresponds to the predicted height.
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EP1115

JOINT1694
Prostatic enucleation causing pituitary apoplexy in a patient with a pre-existing non-functional macroadenoma
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Introduction
Pituitary apoplexy is a rare life threatening condition. It corresponds to an acute ischemic infarction or hemorrhage of the pituitary gland. Several factors may predispose to pituitary apoplexy or contribute to its onset. These factors include endocrine stimulation tests, treatment with dopamine agonists, gonadotropin-releasing hormone therapy, pregnancy, and anticoagulation. Herein, we report the case of a patient with a pre-existing non-functional macroadenoma presenting pituitary apoplexy as a complication of prostatic enucleation.
Observation
A 78-year old man was referred to the Department of Endocrinology for a pituitary apoplexy. His past medical history included type 2 diabetes, chronic renal failure, cardiac arythmia, and chronic obstructive pulmonary disease. In 2018, the patient presented with cognitive disorders. A brain magnetic resonance imaging was performed showing an invasive pituitary macroadenoma measuring 30 × 20 mm. The diagnosis of non-functional macroadenoma with corticotropin, thyrotropin, and gonadotropin deficiencies was established. The patient was treated with hydrocortisone, levothyroxine, and enanthate of testosterone with a regular follow-up. In October 2024, the patient had a laser enucleation of the prostate in the context of benign prostatic hypertrophy. Immediately after surgery, he presented with a sudden acute headaches associated with visual disorders. Brain MRI showed pituitary apoplexy with large and necrotico-hemorrhagic intrasellar mass, invading the cavernous sinus and compressing the optic chiasm. The ophthalmological examination revealed a bilateral decreased visual acuity, normal visual field, and total ophthalmoplegia. The patient was treated with high dose of corticosteroids. The outcome was marked by the disappearance of the headaches, the improvement of the visual disorders, and the onset of polyuria secondary to antidiuretic hormone deficiency.
Discussion
To the best of our knowledge, we report the first case of pituitary apoplexy as a complication of prostatic enucleation. Few cases of pituitary apoplexy during laparoscopic surgery were reported. In these cases, pneumoperitoneum results in the elevation in intra-abdominal pressure and in the decrease in venous return. This phenomenon subsequently leads to an increase in intracranial venous pressure, which elevates capillary pressure within the pituitary tumor and predisposes it to hemorrhage. Furthermore, some anesthetic agent may precipitate infarction in pituitary adenomas.
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EP1116

JOINT458
The incidence abnormal finding in MRI scans in children with a diagnosis of isolated GHD
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Background
Patients with isolated growth hormone deficiency (GHD) will routinely have an MRI scan of the pituitary and brain to assess pituitary size and presence of any intracranial lesions. The result may change the threshold for monitoring for further hormone deficiencies. However the test may also detect unexpected or unrelated abnormalities.
Aim
To review the incidence abnormal finding in MRI scans in children with a diagnosis of isolated GHD.
Methods
The biochemistry and MRI reports of children with isolated GHD (peak growth hormone (GH) <7mg/l)born in a tertiary centre between 1997 from 2017 were reviewed. All children with multiple pituitary hormone deficiencies, septo-optic-dysplasia spectrum, and those children with known malignancies were excluded. Extra-cranial abnormalities such as sinusitis and mucosal thickening were excluded.
Results
81 children were diagnosed with isolated GHD. 71 children had MRI results available (4 pending). Of these, 38 (54%) were reported as normal and 33 (46%) abnormal. The median age of diagnosis was 5.99 years (range: 0.62 to 18.69), with a median height SDS of -3.45 (-0.33 to -8.41) at diagnosis. The median GH level was 3.25mg/l. The rate of MRI abnormalities was similar in the group above and below the median GH level. Of those with MRI abnormalities: 12 showed a small or hypoplastic pituitary gland, 2 had a microadenoma and 1 a cyst. 9 had an abnormal infundibulum and in 6 the posterior pituitary gland was not visible. A total of 15 MRI scans showed additional cranial anomalies (Chiari malformation (CM)($n = 4$), arachnoid cysts ($n = 3$), enlarged ventricles ($n = 1$), small optic nerves ($n = 1$), other ($n = 6$)). 3 of the children with pituitary hypoplasia had a CM.
Conclusions
Nearly half the children with isolated GHD had an abnormal MRI scan. The most frequent abnormality is pituitary hypoplasia, followed by infundibulum and then posterior pituitary abnormalities. One fifth had additional cranial anomalies; with 4 (5.6%) having a CM. CM in GHD is an uncommon but recognised association, and patients with this condition may need additional monitoring if given growth hormone treatment.

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EP1117

JOINT2877

Comparison between testosterone and gonadotropin treatment in adolescent males with hypogonadotropic hypogonadism

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Purpose
Hypogonadotropic hypogonadism refers to patients with damage to the hypothalamus or pituitary gland, resulting in low levels of FSH, LH, and testosterone, as well as prepubertal levels observed on the GnRH stimulation test. This study aimed to compare the efficacy of gonadotropin therapy and testosterone replacement therapy (TRT) in young males with hypogonadotropic hypogonadism (HH).
Methods
A retrospective analysis was conducted on 70 male HH patients under 18 years old, treated between November 2005 and December 2023. Patients were diagnosed based on clinical symptoms, underlying diseases, genetic confirmation, or prepubertal hormone levels on GnRH stimulation test. Clinical parameters and laboratory data were assessed every 6 months for up to 3 years.
Results
The etiology was congenital in 25.7% (mainly Kallmann syndrome) and acquired in 74.3% (primarily brain tumors). Of the 70 patients, 56 received gonadotropin therapy and 14 received TRT. No statistically significant differences were found between the two treatment groups in testosterone levels, growth parameters, or laboratory data. Both treatments significantly increased testicular volume and stretched penile length, but the difference between treatments was not statistically significant. Sperm analysis revealed that sperm was detected in 17 individuals (70.8%) in the gonadotropin treatment group and in 2 individuals (66.6%) in the testosterone treatment group.
Conclusions
Both gonadotropin and testosterone replacement therapies were effective in inducing puberty in adolescent males with HH. The study suggests that treatment choice should be individualized based on patient characteristics and regularly monitored for efficacy.

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EP1118

JOINT1838

Clinical case of central pontine and extrapontine myelinolysis development due to severe hyponatremia

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Introduction
Osmotic demyelination syndrome (ODS) is a critical condition resulting from water-electrolyte disturbances, most commonly due to the rapid correction of hyponatremia. ODS comprises two forms: central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM), characterized by demyelination in the pons and the white matter of the cerebral hemispheres, respectively. Clinical manifestations range from mild tremors and dysarthria to severe complications such as dysphagia, altered consciousness, and respiratory failure requiring resuscitation.
Clinical Case
In 2018, an 18-year-old female was diagnosed with panhypopituitarism following the removal of a stalk craniopharyngioma. She was started on hormone replacement therapy, achieving medical compensation for central diabetes insipidus, secondary hypocortisolism, hypothyroidism, and hypogonadism. In December 2020, while on 0.1 mg of desmopressin twice daily, she developed dyspeptic symptoms (vomiting and diarrhea), leading to a sodium level drop to 105 mmol/l(reference range: 136–145). She was urgently hospitalized in a coma and admitted to the intensive care unit, where rapid correction of chronic severe hyponatremia resulted in complications, including CPM, EPM, bilateral supranuclear paresis of the facial, masticatory, bulbar muscles, and tetraplegia. Due to declining vital functions, a tracheostomy and gastrostomy were performed, both of which were later removed following the restoration of consciousness. MRI findings were consistent with osmotic demyelination syndrome, showing pathological signals from the basal ganglia and brainstem. During her hospitalization at the Endocrinology Research Centre in 2022, she was diagnosed with severe depressive disorder, characterized by asthenic symptoms and impaired speech expressiveness, for which neuroleptics were prescribed. A follow-up MRI in 2023 showed improvement, with a reduction in the myelinolysis focus. Notably, there were no signs of central diabetes insipidus despite the absence of vasopressin analog therapy, with a sodium level of 142.3 mmol/l(136–145) and a urine specific gravity range of 1008–1020 g/L. Currently, the patient is undergoing psychosocial rehabilitation, showing partial recovery of mnemonic and speech functions.
Results
This case highlights the severe consequences of rapid hyponatremia correction, leading to life-threatening complications such as CPM and EPM. It also underscores the broad spectrum of neurological deficits associated with ODS, which can mimic acute cerebrovascular events.
Conclusions
Increasing awareness among physicians across specialties is crucial to preventing ODS through cautious correction of hyponatremia. Furthermore, vigilant monitoring and a comprehensive multidisciplinary neurorehabilitation approach can improve survival outcomes and reduce long-term disability in patients recovering from severe hyponatremia.

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EP1119

JOINT3625

Rare association of lentigo and normosmic congenital isolated hypogonadotropic hypogonadism, diagnosed in mini-puberty: clinical case report

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Background
Congenital isolated hypogonadotropic hypogonadism (CIHH) is a disorder characterized by an impaired function gonadotropin-releasing hormone (GnRH). CIHH is associated with defects in 60 genes. CIHH prevalence varies from 1:4,000 to 1:10,000 newborns. "Red flags" include micropenis, cryptorchidism, deafness, anosmia, renal, skeletal, cardiac malformations, cleft lip and palate and etc.
Case report
The boy was born by a spontaneous delivery at 40 weeks of gestation. It was his mother's first pregnancy which was complicated by chronic hypoxia. Neonatal weight was 3000 g. Neonatal length was 51 cm. His Apgar score were 8 and 9.

Marriage was no closely related. At birth the patient was diagnosed with micropenis. The boy firstly was admitted at the age of 7 months complaining of micropenis. His length was 68.2 cm (-0.5 SDS), weight was 7.6 kg (-0.65 SDS). Psychomotor development was normal. Basal LH, FSH, testosterone were low. Triptorelin stimulated LH was 1.3 IU/l. hCG treatment (250 IU twice a week) was prescribed to increase penile length. At his second evaluation at the age of 13.7 years his height was 147.6 cm (-1.8 SD), his weight was 37.7 kg (-0.8 SD). The boy had severe scoliosis and multiple lentigines - dark brown and black skin spots up to 3 cm on the face, torso and hands. He was able to distinguish smells. His corpora cavernosa were 4 cm. The testicles were in the scrotum. The volume of the right testicle was 0.4 ml, the left one was 0.3 ml by ultrasound. Basal LH was 0.2 IU/l. Basal FSH was 0.7 IU/l. Total testosterone was 0.6 nmol/l. Patient had no multiple pituitary hormone deficiency.
Results
Triptorelin stimulated LH was 1.6 IU/l. CIHH was confirmed. Genetic tests revealed heterozygous previously reported pathogenic missense variant c.1016A>G: p.Tyr339Cys in 8 exon of gene *FGFR1* (NM 023110.3, HG38, chr8: 38421862T>C, rs2150755221) associated with CIHH. Injections of testosterone 75 mg im/month were prescribed to initiate puberty.
Conclusion
This clinical case demonstrates extremely rare association of lentigo and normosmic congenital isolated hypogonadotropic hypogonadism. It's the first Russian patient diagnosed with CIHH and lentigo. Due to micropenis the disease was diagnosed during mini-puberty via triptorelin test. Early diagnosis helped to effectively lengthen penis via hCG treatment at the first years of life. and to provide supportive counseling to family.

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EP1120

JOINT1663

Advanced malignant insulinoma: when everything else fails, treatment with 177Lu-DOTATATE comes to the rescue

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Malignant insulinoma is a rare pancreatic neuroendocrine tumor that accounts for up to 10% of all cases of insulinoma and it is characterized by the presence of severe hyperinsulinemic hypoglycaemic syndrome which encompasses a short life expectancy and great morbidity. Therapeutic management is challenging due to the need to control both hypoglycemic syndrome and tumor growth. Curative surgery is rarely applicable due to widespread metastases. We report a clinical case with metastatic malignant insulinoma accompanied by a life-threatening, and refractory hypoglycemia that was early and adequately controlled with 177Lu-DOTATATE treatment. A 51-year-old man was referred to endocrinology for hypoglucemic episodes that evolve to severe and repeated with neuroglycopenic symptoms. 7 months prior to the referral, he had been diagnosed with a grade G1, stage IV pancreatic (PNET) gastrinoma and started on PPIs, lanreotide 120mg every 28 days and everolimus achieving stabilization of the pancreatic and hepatic lesions after 6 months of treatment. We suspected a switch in functioning syndrome so we proceeded to initiate treatment with diazoxide after we confirmed hyperinsulinemic hypoglycaemia. Despite everolimus diazoxide, lanreotide 120mg/28 days, Dexamethasone, continuous enteral nutrition and parenteral infusion of glucose iv drip therapy, the episodes did not subsided. After a multidisciplinary discussion, in which other treatment options as Pasiretiode were discussed, first dose of lutetium (Lu-177)-DOTA-Tyr3-octreotate (177Lu-DOTATATE) was administered. After 7 days, the number and severity of the hypoglucemic episodes decreased, and the need for glucose iv drip, enteral nutrition and Dexamethasone, and diazoxide progressively lessen and after the second dose the episodes subsided without the need of any additional treatment. In total he was treated with 4 doses of 177Lu-DOTATATE. Eleven months after the first dose of 177Lu-DOTATATE the patient continued without hypoglycemia and with normal serum proinsulin and insulin concentrations. A somatostain receptors scan with TC 99 after the fourth dose showed radiological stability of the lesions. The patient regained the sense of well-being and transitioned to working full-time. In our experience, the use of 177Lu-DOTATATE in the symptomatic disease it should be considered, to obtain a fast control of the functionality of the disease, improving the quality of life and apparent tumor growth stabilization.

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EP1121

JOINT2149

Abnormal uterine bleeding due to von willebrand disease (experience of a specialized pediatric endocrinology consultation)

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Introduction
Abnormal Uterine Bleeding (AUB) is a frequent cause of visits to the emergency department and a major reason for concern among adolescents and their families. The most common cause of AUB, in otherwise healthy adolescents, is anovulatory cycles, owing to immature hypothalamic-pituitary-ovarian axis, although 5–36% of adolescents who present with heavy menstrual bleeding, have an underlying bleeding disorder (BD). The most common form of BDs is von Willebrand Disease, reflecting 13% of adolescents with AUB. Von Willebrand disease affects 1% of the general population, it is a hereditary hemorrhagic disease with autosomal dominant transmission (except type 3). The clinical signs vary depending on the severity of the form, it can be (mucocutaneous hemorrhage, bruising, epistaxis, gingival bleeding, AUB, etc.), type 3 is only affected by hematomas and hemarthroses. The diagnosis is made based on the dosage of the circulating vWF/F VIII complex.
Materials and Methods
In our specialized pediatric endocrinology consultation we collected 5 patients whose reason for consultation was AUB during their menarche and which recurred during subsequent cycles. We analyzed the biological and progressive clinical characteristics of the patients.
Results
The age of our patients was between 12 and 13 and a half years old. In the antecedents we identify the notion of benign epistaxis, small bleedings during dental extractions, 2 patients whose mothers had presented a delivery hemorrhage, notions of epistaxis in siblings, one patient had no pathological history. The exploration shows a normal primary hemostasis assessment, the diagnosis was confirmed by the measurement of the vWF/F Vlll complex. We hospitalized 3 of the 5 patients for blood transfusions; only one required an infusion of Von Willebrand factor (vWF), symptomatic treatment with a hemostatic aim was also used (anti-fibrinolytic type Tranexamic acid), as well as iron treatment and estrogen-progestogen treatment for most patients.
Conclusion
Von Willebrand disease is a common etiology of hemostasis disorders which can result in AUB in young adolescents; establishing a diagnosis as well as the management of these adolescents must involve an entire multidisciplinary team (pediatrician, hematologist and gynecologist, the etiological treatment (vWF) is to be discussed depending on the severity of the form and it is only systematic in severe forms, particularly type 3.

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EP1122

JOINT2826

Incidental finding of prolactinoma in a patient initially diagnosed with osteosarcoma: a case report

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Introduction
Positron Emission Tomography (PET-CT) is commonly used for staging primary tumors. Incidental uptake in the pituitary region on PET-CT is a rare finding. The differential diagnosis includes metastasis from the primary tumor, pituitary adenoma, hypophysitis, Langerhans cell histiocytosis, or physiological uptake. While metastasis and pituitary adenomas often differ in clinical presentation and imaging characteristics, both can present with hyperprolactinemia.
Case Report
A 15.5-year-old male patient was referred to the endocrinology service after an incidental finding of increased metabolic activity in the pituitary region on PET-CT. The patient had an initial diagnosis of left proximal humerus osteosarcoma with multiple metastases (pulmonary and bone). He was undergoing chemotherapy as per the GLATO 2006 protocol, which included cisplatin, doxorubicin, and methotrexate. As part of his staging, a FDG-F18 PET-CT scan was performed, which revealed increased metabolic activity (SUV 4.8) at the left proximal humerus, consistent with osteosarcoma (primary tumor). Additionally, the scan

showed increased metabolic activity (SUV 7.2) at the sella turcica, suggestive of involvement of the pituitary gland. Hormonal laboratory tests were ordered to assess pituitary function, and a brain MRI with gadolinium contrast was performed, focusing on the pituitary region. The laboratory results revealed hyperprolactinemia with a prolactin level of 686.4 ng/dl, while other pituitary hormones remained within normal limits. Given the potential role of metoclopramide (an antiemetic) as a contributing factor, the medication was discontinued for three weeks. However, hyperprolactinemia persisted, with a subsequent prolactin level of 724 ng/dl. MRI findings showed an enlarged pituitary gland (14 × 17 mm) with focal cystic areas, hypovascularity, and no involvement of the cavernous sinuses. The pituitary stalk was displaced to the left, maintaining its caliber, and the neurohypophysis was intact. The optic chiasm was preserved. These findings were consistent with a pituitary adenoma with cystic changes (Knosp classification 0). Notably, the patient had no clinical signs of hyperprolactinemia, and neuro-ophthalmological examination was normal. Based on these imaging and biochemical findings, the diagnosis of a macroprolactinoma was assumed. Treatment with cabergoline (0.5 mg weekly) was initiated, with good tolerance. A new laboratory test and follow-up MRI under treatment are pending.

Conclusion

To date, there is no established association between osteosarcoma and prolactinoma in the literature. Although PET-CT SUV values can assist in differentiating between physiological and pathological pituitary uptake, it is crucial to complete evaluation with hormonal testing, pituitary-focused MRI, and ophthalmological assessment for proper diagnosis, follow-up, and treatment.

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EP1123

JOINT1183

Hyperprolactinaemia: clinical presentation and dopamine agonist side effects

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Introduction

Pituitary diseases are diagnosed with increased frequency and with changes in the clinical presentation. Thus, we aimed to investigate the changes in clinical presentation of prolactin secreting pituitary neuroendocrine tumours (PRL-PitNET) and idiopathic hyperprolactinemia (IDH) including side effects of dopamine agonist (DA) treatment.

Methods

Patients with a PRL-PitNET or IDH were identified via ICD-coding in the period 2017-2022 in the North Denmark Region, Denmark. Data were collected from electronic patient records. Multiple imputation by chained equations were used for side effect association analyses.

Results

We identified 244 patients with a PRL-PitNET or IDH corresponding to a prevalence of 41.3 (95%CI: 39.2-43.5) per 100,000 pr year and an incidence rate of 2.8 [95%CI: 2.3-3.4] per 100,000 person years. Median age at diagnosis was 30 [IQI: 24;41] years. 77% were women. The prolactin level was 3.1 [IQI: 1.8;12.0] times upper reference limit. Median tumour diameter at diagnosis was 9 [IQI: 6;16] mm, and stabile over time. Macroadenomas constituted 46%. Women <53 years presented with menstrual disorders (90% *without hormonal contraceptives) and galactorrhoea (56%). Men presented with decreased libido (40%) and erectile dysfunction (34%), whereas galactorrhoea was uncommon (6% (n = 3)). 216 persons were or had been treated with DA. Normalisation of prolactin was achieved in 83% of patients on DA and <3% underwent surgery due to treatment resistance. However, 46% experienced concomitant side effects to DA. 19% (of 216) had specifically persistent side effects on DA and despite many attempted different DAs. 7% of all treated with DA underwent surgery or were followed without DA due to DA side effects. Side effects were not associated with age, sex, prolactin level or time to prolactin normalisation.

Conclusion

The prevalence of PRL-PitNET and IDH seem stabile. However, patients were younger and with lower prolactin levels despite a large proportion of macroadenomas. DA is effective. However, side effects were a more severe clinical problem than previously reported.

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EP1124

JOINT2122

Longitudinal assessment of growth velocity, IGF-I and fasting insulin in relation to pubertal timing in healthy boys

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Context

Age at puberty has declined concomitant with a tendency to become taller. This paradox – becoming taller despite diminished total growth period – may rely on faster linear growth during childhood and puberty in boys, which has previously been shown for girls.

Objective

Growth velocity, skinfold thickness (SFT), IGF-I and fasting insulin levels in relation to pubertal timing; A) early: below median age for testicular volume enlargement (TV) >3 ml and B) late pubertal onset (above the median age) in healthy boys.

Design and setting

Longitudinal study with biannual assessment of TV, SFT, growth velocity, IGF-I and fasting insulin levels. Peak height velocity (PHV) was determined by a statistical model.

Participants

105 boys (947 examinations) at a median of 9.0 years at first examination. Age at pubertal onset was available in 62 boys.

Results

Early maturing boys had significantly higher growth velocity (mean δ 0.45 (0.17 – 0.72) cm/yr; $P < 0.001$) compared with late maturing boys evaluated over the peri-pubertal period (-/+ 3 years before/after pubertal onset). However, the late maturing boys were taller than the early maturing boys (mean δ 6.4 (1.0 – 11.8) cm; $P = 0.023$) 3 years after pubertal onset. IGF-I and fasting insulin levels were similar between early and late maturing boys when evaluated in relation to age at pubertal onset. Independent of puberty, the changes in IGF-I were associated with the changes in height ($P < 0.001$) evaluated over the first 2 years after pubertal onset.

Conclusion

Early maturation was associated with increased growth velocity and PHV. However, it was not sufficient to compensate for the shorter total growth period, as seen for girls. Changes in IGF-I were related to growth but were independent of pubertal timing.

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EP1125

JOINT2709

Arginine vasopressin deficiency in a baby with variant of uncertain significance found in the PCSK1 gene

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A premature baby born at 30 weeks and 6 days with a birth weight of 0.9kilograms presented on day 20 of life with diuresis symptoms. The urine output was 4-6ml/kg/hour and associated hypernatraemia with sodium of over 150mmol/l[RR 137-144], serum osmolality 320mOsmkg [RR 275-295], urine osmolality 160mOsmkg. The diuresis was responsive to intravenous desmopressin initially (0.04micrograms/kg/dose as required). The initial working diagnosis was Arginine vasopressin deficiency. Magnetic resonance imaging pituitary performed on day 37 showed an unremarkable anterior pituitary gland and bright spot of the posterior pituitary gland not well delineated. No destructive pituitary lesion or suprasellar mass. The desmopressin was later changed to sublingual (Nocdurna 6.25micrograms daily equivalent to 4micrograms/kg/dose). At one month of life, a spot copeptin showed a level of 31.5pmol/l[RR ≥21.4 diagnostic of AVP resistance]. This became a bit of a diagnostic dilemma therefore further work up was performed. At 2 months of age a DDAVP test was performed which showed a mixed picture of Arginine vasopressin deficiency and resistance. It was noted after regular sublingual desmopressin was given up to 2-3 times a day there was still diuresis noted. Diuresis was noted with single therapy of desmopressin. A trial of hydrochlorothiazide (1mg/kg/day) and restricted renal solute load (<14mosmo/kgH2O/kg) was unsuccessful due to hypontraemia of sodium 128mmol/l[RR 137-144]. After some titration, the diuresis was well controlled with sublingual desmopressin 6.25micrograms three times a day

equivalent to 2 micrograms/kg/dose. Regarding the other pituitary axis, this baby's cord thyroid stimulating hormone was normal and on day 21, noted to have increased thyroid stimulating hormone 15.3 mIU/l[RR 0.72-11] with low free thyroxine 9.8 pmol/l[RR 11.5-28.3] and thyroxine supplement was started. There was a history of low cortisol level at 1 week life. A short synacthen test was performed on 1 month which showed a peak cortisol level of 217nmol/l[RR $\geq$380 nmol/L] ACTH $<$1.6 pmol/l[RR $<$10.2]. Hydrocortisone replacement was started at 10mg/m^2/day. A whole exome sequence result at 2 months of age showed 2 compound heterozygous variant of uncertain significance in PCSK1 gene. Maternal variant inherited showed Heterozygous NM_000439.5(PCSK1):c.844C$>$T p.(Arg282Trp). Paternal variant inherited showed Heterozygous NM_000439.5(PCSK1):c.493G$>$A p.(Val165Ile). This baby did not show other phenotypic features of the PCSK1 gene including neonatal diarrhoea and proinsulin was normal. We will need to observe further for possibility of future obesity and hypogonadotrophic hypogonadism.

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EP1126

JOINT1070

A case of multiple neuroendocrine tumors in MEN1: cushing's disease, prolactinoma, and multiple pancreatic NETS including insulinoma

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Introduction
Multiple Endocrine Neoplasia type 1 (MEN-1) is a rare hereditary syndrome characterized by the development of multiple NETs that significantly disrupt endocrine function. Both Cushing's Disease (CD) and prolactinoma is uncommon, with less than 1% presenting with multiple pituitary neuroendocrine tumors (PitNET). Similarly, insulinoma represents an infrequent finding in MEN1. This case highlights the intricate diagnostic and therapeutic challenges posed by MEN1.
Case Presentation
A 28-year-old male presented with rapid weight gain and abdominal striae. Physical examination showed cushingoid and hypogonadal facies, acanthosis nigricans, BMI 40.4 kg/m^2, BP 142/73 mmHg, and violaceous striae. Elevated nighttime salivary cortisol 0.478 µg/dl (0-0.208) and 24-hour urinary free cortisol 187.0 µg/24h (4.3-176.0) confirmed hypercortisolism. Elevated ACTH 40.8 pg/ml (1.5-12.4), a 7 mm PitNET at MRI, and petrosal sinus sampling confirmed CD diagnosis. Complete laboratory tests: prolactin 65.6 ng/ml (4.04-15.2), testosterone 0.80 ng/ml (2.8-8.0), PTH 229.0 pg/ml (15-65), hypercalcemia 3.16 mmol/l(2.15-2.50). Abdominal imaging identified 6 pancreatic lesions consistent with pNETs (major at head: 21x14mm). DEXA Z score: femoral neck-1.5, distal wrist -1.8. Genetic testing for MEN-1: positive (c.825-1G$>$A mutation). Hypercalcemia was temporarily controlled with zoledronic acid, deferring parathyroidectomy. Initial management focused on CD treatment due to detected complications: hypogonadotropic hypogonadism, secondary hypothyroidism, class 3 obesity, hypertension, osteopenia. Post-transsphenoidal surgery, morning plasma cortisol was 18.5 µg/dl; histopathology revealed only a prolactin-secreting PitNET. During hospitalization, additional functional studies of pNETs were performed, confirming endogenous hyperinsulinemia (glucose: 47 mg/dl, C-peptide: 7.28 ng/ml, insulin: 33.0 µU/ml), with normal levels of VIP, gastrin, somatostatin, and glucagon. 68-Ga-NOTA-PET revealed multiple pNETs, with biospy guided by ecoendoscopy identifying a well-differentiated G1 pNET. Due to persistent CD and confirmed insulinoma without localization, cabergoline, lanreotide, and continuous glucose monitoring were initiated. Metyrapone started 1 month after improved cortisol levels (24-hour urinary free cortisol: 61.6 µg/24h) , with documented symptomatic hypoglycemia post-metyrapone despite prior initiation of lanreotide. The patient is awaiting a 68-Ga-NOTA-exendin-4 PET scan in Switzerland to localize the insulinoma and guide for possible minimal invasive treatment options, along with the potential consideration of reoperation for CD and parathyroidectomy.
Discussion
This case underscores the complexity of managing MEN1 in a young patient with CD, prolactinoma, primary hyperparathyroidism, and multiple pNETs, including an insulinoma. Management of MEN1 requires careful prioritization, as not all conditions can be addressed simultaneously. Localizing the insulinoma is crucial to minimize the risks associated with invasive pancreatic surgery, while timely treatment of CD is essential due to its associated complications.

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EP1127

JOINT1510

The role of IGF-1 in monitoring prolactinoma patients: paradox or additional diagnosis?

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Introduction
Pituitary adenomas secreting prolactin primarily consist of lactotroph cells; however, co-secretion of growth hormone (GH) may also occur at diagnosis or during follow-up. Levels of IGF-1 may paradoxically increase during Dopamine Agonist (DA) treatment.
Objective
To assess IGF-1 levels in patients with prolactinoma at baseline and during DA treatment and determine the frequency of silent acromegaly diagnosed during follow-up.
Methods
We retrospectively analysed 53 patients with prolactinoma who were followed up in our department, with IGF-1 levels measured at baseline and during DA treatment without intervening surgery. The median follow-up was 32.1 months (IQR: 14.9-68).
Results
67.9% of cases were male, and the median age was 40 years (IQR: 32–56). Median baseline IGF-1 level was 174.2 ng/ml (IQR: 118.5–200.2), with 9.4% exceeding the upper limit of normal (ULN) (1-1.15 $\times$ ULN). The median prolactin level was 707 ng/ml (IQR: 164.5–3404.8). Macroadenomas were identified in 79.3% of cases, with a median tumour diameter of 20 mm (IQR: 10.6–35 mm). During DA treatment, the median IGF-1 level increased significantly to 211.6 ng/ml (IQR: 153.5–260.4, $P = 0.001$). The proportion exceeding ULN rose from 9.4% to 22.6% ($P = 0.07$) (1-2.13 $\times$ ULN). During follow-up, only one patient was diagnosed with silent acromegaly 22 months after the diagnosis of prolactinoma (1.89%). Among those exceeding the ULN (12 cases), eight underwent OGTT with normal GH suppression (mostly during DA treatment). Of the others, one was lost to follow-up, and three experienced IGF-1 normalisation after 2-2.5 years. IGF-1 peaked within the first two years, followed by a significant decline after 24 months ($P = 0.001$), suggesting transient elevations.
Conclusion
IGF-1 increased significantly during DA treatment, with most elevations occurring in the first two years, followed by a decreasing trend. Silent acromegaly was rare (1.89%). When IGF-1 exceeds ULN, GH assessment during OGTT and IGF-1 reassessment after DA discontinuation are advised. Periodic IGF-1 monitoring should be considered for patients with prolactinoma.

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EP1128

JOINT1697

Outcome of two closely spaced postcesarean pregnancies in a patient with prolactinoma: a case report

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Background
Prolactin-secreting adenomas necessitate careful prenatal management due to their potential for growth during pregnancy. This report presents a challenging case of a 28-year-old woman with a prolactinoma who experienced two closely spaced pregnancies, both of which resulted in cesarean deliveries.
Case Report
A 28-year-old woman first presented to our hospital at the age of 26 years, at 35-36 weeks of gestation, with a 5-year history of a prolactin-secreting adenoma. A pituitary MRI scan in 2018 revealed a microadenoma (6 $\times$ 4 mm), which was associated with headaches, elevated prolactin levels, and oligomenorrhea. From 2019, she was initially treated with cabergoline, which resulted in a reduction of prolactin levels (21 ng/ml), tumor regression, and the resumption of normal menstruation. In 2021, conflicting prolactin levels and MRI results were obtained. In March 2021, tumor growth (1.1 $\times$ 0.5 $\times$ 0.8 mm) and an increased prolactin

level (52.5 ng/ml) were observed. However, subsequent testing showed that her prolactin level decreased to 21.7 ng/ml. In September 2023, during her first pregnancy at 35-36 weeks of gestation, she presented with right-sided homonymous hemianopsia on visual field testing. Due to these findings, a cesarean delivery was recommended. A follow-up pituitary MRI scan was scheduled for 6-8 weeks postpartum. However, the patient conceived again just two months after the first cesarean delivery. With informed consent, a pituitary MRI scan without contrast was performed during the second trimester in February 2024, revealing a tumor mass of 7 × 10 mm. She subsequently delivered her second child via cesarean section at 38.5 weeks of gestation. Four weeks postpartum, a pituitary MRI scan with contrast showed tumor regression (3.5 × 3 mm).

Discussion

Pregnancy can induce high mitotic activity of lactotrophic cells in the pituitary, potentially leading to tumor growth in patients with prolactinomas. Enlarged tumor masses can compress surrounding structures, sometimes necessitating cesarean section for delivery. Pregnancy may limit the use of contrast during pituitary MRI scans; therefore, such scans might be required postpartum. Moreover, patients should be advised to wait at least 18-24 months between delivery and subsequent pregnancy to mitigate obstetric risks. Comprehensive prenatal, natal, and postnatal care is crucial for patients with prolactinomas.

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EP1129

JOINT2243

Assessing pubertal suppression with 3.75 mg monthly vs. 11.25 mg three-monthly leuprolide acetate in girls with central precocious puberty

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Introduction

Gonadotropin-releasing hormone (GnRH) analogs, such as Leuprolide acetate (LA), are the standard treatment for central precocious puberty (CPP). The 1-month formulation of LA is widely used; however, comparative data on the effectiveness of the 11.25 mg three-monthly formulation remain limited. This study aimed to evaluate the efficacy of 3.75 mg monthly and 11.25 mg three-monthly LA in achieving pubertal suppression in girls with CPP.

Methods

A total of 136 girls with CPP were included in the study. Eighty-six patients were treated with LA 3.75 mg monthly, and fifty patients received LA 11.25 mg every three months for one year. Anthropometric, laboratory, and radiological measurements were compared at the beginning and the end of the treatment period. Pubertal suppression was defined as a luteinizing hormone (LH) level below 4 IU/lat 90 minutes after GnRH analog administration.

Results

Baseline demographic and clinical characteristics did not differ between the groups. The mean age of all patients at baseline was 8.3 ± 0.7 years. The mean age was 8.4 ± 0.8 years in the 3.75 mg group and 8.2 ± 1 years in the 11.25 mg group, with no significant difference between the groups (p: 0.210). After 12 months of treatment, there were no significant differences between the two groups in terms of bone age- chronological age difference, height standard deviation score (SDS), body mass index SDS, or uterine volume. Pubertal suppression was achieved in 72.1% of patients in the 3.75 mg group and 78% in the 11.25 mg group ($P = 0.291$). Post-treatment LH levels were comparable between the two groups (3.75 mg: 2.2 ± 2 IU/l,11.25 mg: 2.3 ± 1.6 IU/l,$P = 0.894$).

Conclusions

The 11.25 mg three-month depot of LA demonstrated comparable efficacy to the 3.75 mg monthly depot in terms of pubertal suppression, and hormonal control. Both regimes showed effective suppression of puberty. However, the 11.25 mg three-month formulation may offer improved patient compliance due to the less frequent dosing schedule, making it a more convenient treatment option while maintaining similar safety and efficacy in managing CPP.

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EP1131

JOINT3370

Diagnosis of cushing's disease by desmopressin stimulated bilateral inferior petrosal sinus sampling: a case report

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Introduction

The most common cause of ACTH-dependent Cushing's syndrome is Cushing's disease (CD) due to an ACTH-producing tumor in the pituitary gland Bilateral petrosal sinus sampling (BPSS) is the gold standard for determining the source of hypercortisolism. There is limited information about desmopressin use in the literature. In this case, BPSS protocol performed because there was a lesion that could not be clearly distinguished in imaging, despite evaluating the clinical and laboratory findings.

Case

A 12-year-old girl presented to our clinic with complaints of weight gain over the past year, absence of height increase, and hair growth on her face, back, and genital area. Her height was 145 cm (-1.0 SDS), weight was 55 kg (+1.3 SDS), and body mass index was 26.9 kg/m^2 (2.12 SDS). Physical examination revealed a moon-shaped face, plethoric appearance, abdominal striae, acanthosis nigricans in the axilla, and buffalo hump. A high basal cortisol level (29 µg/dl), ACTH level (91 pg/ml) was detected. Diurnal rhythm was disrupted. Cortisol levels were not suppressed in the dexamethasone suppression test (single dose, 1 mg, orally) (12,8 µg/dl) and the low-dose dexamethasone test (7,82 µg/dl). The decrease in cortisol levels after the low-dose dexamethasone suppression test was less than 50%. Twenty-four-hour urinary cortisol level (374 µg/day) was high. The adrenal glands appeared normal on ultrasound. No significant pathology was detected on the pituitary MRI. In intravenous desmopressin-stimulated BPSS, samples taken from the right pituitary showed significantly elevated ACTH levels (Table-1), leading to a diagnosis of Cushing's disease. Surgery was planned.

Conclusion

In cases of hypercortisolism related to ACTH where imaging results are inconclusive, a BPSS should be performed. When CRH is not available for BPSS, the use of desmopressin appears to be safe.

Table 1. Bilateral petrosal sinus sampling (BPSS) results.

	ACTH(pg/ml)						CORTI-SOL (µg/dl)
Minute	PERIPH-ERAL	RIGHT	LEFT	RIGHT ACTH/P RATIO	LEFT ACTH/P RATIO	RIGHT/ LEFT RATIO	
-15	36.1	982	106	27	2.9	9.3	13.4
0	51.1	1458	72.7	25.5	1.41	8	10.9
5	84.3	1635	121	19.3	1.43	13.4	9.9
10	153	>2000	297	13	1.4	6.7	13.4
15	243	>2000	381	8.2	1.56	5.2	19.3

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EP1132

JOINT1197

Unveiling hypothalamic syndrome, beyond obesity: diagnostic challenges and management strategies in pediatric patients - a report of 2 cases

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Introduction

Hypothalamic syndrome (HS) in childhood is rare and typically is strongly associated with severe obesity. Its incidence ranges from 0.05 to 10 per 100,000 persons per year and may result from genetic or acquired causes that damage the hypothalamic nucleus, such as suprasellar brain tumors or their treatments. Beyond severe obesity, HS may present additional manifestations, including pituitary dysfunction, sleep disturbances, temperature dysregulation, loss of thirst, and behavioral problems. These symptoms are often not promptly recognized, leading to delayed management and a deterioration in quality of life.

Objectives

Present two cases of HS to highlight the complexity of diagnosis and management. **Case 1:** A 5-year-old male was diagnosed with craniopharyngioma (CP) at age 4 and underwent gross total resection. He developed multiple pituitary hormone deficiencies (MPHD), requiring treatment with levothyroxine,

hydrocortisone, desmopressin (DDAVP), and growth hormone (GH). He experienced hyperphagia, resulting in obesity with a BMI of +4 SD in a short time. Hypodipsia necessitated supervision to meet daily water intake, and hyperthermia, with a basal temperature of 38°C that spiked to 40°C on warm days, was managed with cold baths.
Case 2: A 12-year-old male was diagnosed with CP at age 2. He underwent multiple surgeries and proton beam therapy, subsequently developing MPHD and requiring treatment with cortisol, levothyroxine, DDAVP, and GH. He also developed adipsia, resulting in recurrent hospitalizations for dehydration and hypernatremia. During his most recent admission, he was clinically dehydrated, tachycardic, and had low-normal arterial pressures. He scored 0 on the thirst scale and had a serum sodium level of 162 mEq/L. Treatment included desmopressin adjustment to 0.375 mg/day and supervised scheduled water intake. Serum sodium normalized by the third day, and he was discharged with a sodium level of 147.3 mEq/land a daily water intake of 1500–2000 mL.
Conclusion
HS is a rare and challenging condition to diagnose, requiring a high index of suspicion in cases involving hypothalamic tumors. Adipsia complicates management, making close clinical and laboratory follow-up essential to optimize outcomes. Hyperthermia is common and should be distinguished from infection-related fever to avoid unnecessary high-dose glucocorticoid treatments.
Key Words
Hypothalamus, Pituitary tumors, Neuroendocrine.
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EP1133

JOINT570

A single-center experience of the effect of triptorelin on final height in girls with precocious or early puberty

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Aim
To evaluate the effect of triptorelin on the final height of girls with precocious or early puberty, compared to the untreated group, and to investigate factors that contribute to the maximum effectiveness of treatment in terms of final height.
Methods
We retrospectively collected data from medical records and organized follow-up phone calls to all girls evaluated in our Pediatric Endocrinology Outpatient Clinic for precocious or early puberty during the last two decades. One hundred and seventy-eight girls (85 with precocious and 93 with early puberty), of whom 85 received treatment with triptorelin and 93 did not, were included in the final analysis. The patients' anthropometric characteristics, bone age and midparental height, as recorded at their visits, were collected. Final heights, measured and documented by health professionals, and the exact date of the first menstruation (menarche) were collected after telephone communication. Logistic regression analysis was performed to assess the effect of various parameters on the response to triptorelin treatment.
Results
The difference in mean standard deviation (ΔSDS) of final and midparental height did not show significant difference between treated and untreated girls (Δ Height SDS (Final – Midparental): -0.20 ± 0.89 vs -0.28 ± 0.83, $P = 0.243$). The results were similar when we compared the early (-0.22 ± 0.71, vs. -0.17 ± 0.83, $P = 0.778$) and precocious puberty (-0,19 ± 1,04, vs -0,39 ± 0,83, $P =$ 0,315) subgroups separately. As excepted, menarche occurred earlier in the precocious puberty group compared with the early puberty group (10.68 ± 1.22 vs 11.12 ± 0.90 years, $P = 0.005$) and in the untreated compared with the treated group (10.31 ± 0.91 vs. 11.57 ± 0.06 years, $P < 0.001$ for early puberty, and 11.53 ± 0.90 vs. 9.86 ± 0.86 years, $P < 0.001$ for precocious puberty). Predictors of final height were height at diagnosis (positively correlated), midparental height, and bone age at diagnosis (negatively correlated).
Conclusions
There was no significant difference in final height between treated and untreated girls, and triptorelin was effective in delaying the onset of menarche. Factors contributing to a better final height in the treated group were higher height at baseline, lower midparental height, and younger bone age.
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EP1134

JOINT609

The impact of turner syndrome and hypogonadism on brain and hypothalamic-pituitary structure: effects of treatment with sex steroids and growth hormone

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Background
Turner Syndrome (TS) is a chromosomal disorder characterized by the partial or complete loss of one X chromosome, affecting 1 in 2,500 females. TS often leads to hypogonadism, short stature, and cognitive deficits, particularly in visuospatial, memory, and executive functioning. These manifestations correlate with structural anomalies in the brain and hypothalamic-pituitary axis. Treatments with growth hormone (GH) and sex steroids aim to mitigate these effects, yet their impact on neuroanatomy and function requires further exploration.
Objectives
To evaluate the influence of Turner Syndrome and hypogonadism on brain and hypothalamic-pituitary structure and investigate the effects of GH and sex steroid therapies on mitigating these changes.
Methods
This structured review integrates data from studies conducted between 1990 and 2024. Analyses included magnetic resonance imaging (MRI) findings, hormonal profiling, and neuropsychological assessments. Sample sizes ranged from single case studies to large cohorts. Metrics included brain volume, pituitary structure, and cognitive outcomes, stratified by treatment regimens.
Detailed Results
1. Structural Changes in TS: TS is associated with smaller parieto-occipital gray matter, reduced hippocampal volume, and alterations in basal ganglia and cerebellar regions (O'Donoghue *et al*., 2020).
2. Effects of Treatment:.
• GH therapy improves body composition, increases lean mass, and enhances metabolic profiles but has mixed effects on brain structure (Wang *et al*., 2020).
• Estrogen replacement therapy significantly improves white matter development and hypothalamic-pituitary axis normalization (Viuff *et al*., 2022).
3. Cognitive Outcomes: Working memory shows improvement with combined GH and oxandrolone therapy but no significant change with GH alone (Soliman *et al*., 2024).
Discussion
TS and hypogonadism profoundly impact neuroanatomy and the hypothalamic-pituitary axis. GH and sex steroid therapies offer substantial benefits, particularly when initiated early and tailored to individual needs. However, the risk of cardiovascular and metabolic complications necessitates careful monitoring.
Conclusion
GH and sex steroid therapies are pivotal in addressing the neurodevelopmental and hypothalamic-pituitary deficits in TS. Early and comprehensive treatment strategies significantly enhance structural and functional outcomes, underscoring the importance of individualized approaches.
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JOINT390

Comparative models of acromegaly: a north american cohort of 4620 cats with presumed feline hypersomatotropism (acromegaly)

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Comparative models of spontaneous endocrinopathies are powerful tools to understand disease etiology. The study of endocrine diseases in companion animals is particularly useful, as these animals share their environment with humans, and typically display clinical signs that phenocopy human symptoms. One such disease in domestic cats, hypersomatotropism (HST, feline acromegaly), is a disorder of excessive growth hormone and increased IGF-1 (Insulin like Growth Factor 1). Feline acromegaly is usually caused by hyperplasia or neuroendocrine tumors of the pars distalis of the pituitary gland. In this retrospective study, we used serum IGF-1 results to investigate population characteristics for domestic cats with HST in the United States and Canada. Laboratory records from 1Jan06 to 31Dec22 were reviewed and animals with a circulating IGF-1 hormone concentration of 190 nmol/l(1,450 ng/ml) or greater

were presumed to have acromegaly. This review identified 4,620 such cats with a mean age (n = 4,351) of 11.2 years (median: 11.2, range: .5-20.3yr) and mean weight (n = 2,086) of 6.03 Kg (median: 5.91, range: 2.27-15.0 Kg). Males outnumbered females in the database, which included 3,048 males and 1,181 females. Domestic Short/Medium/Longhair cats were the most prevalent breed (n= 3,563; 77%), followed by Maine Coon cats (n = 120; 2.6%) and Siamese cats (n = 111, 2.4%). Just under half of the animals (n = 2,037, 44%) had a history of diabetes mellitus on the submission form. Most submissions were from the US (n = 4,347, 94%) with the largest number of affected cats being submitted from California (n = 841, 18.2%), New York (n = 604, 13.1%), Massachusetts (n = 402, 8.7%), Colorado (225, 4.9%), and Texas (200, 4.3%). The mean serum IGF-1 concentration of these animals was 358 nmol/ml (median: 345, range 190-761 nmol/ml). For comparison, an age and sex matched control group of 95 animals with residual samples previously submitted for unrelated testing was selected. The mean IGF-1 concentration for the control group was 97 nmol/ml (median: 85, range 0-311 nmol/ml). Therse data suggest that feline acromegaly is diagnosed most frequently in older male cats in North America, residing in areas that are likely to be more urbanized and subject to environmental pollutant exposure. Furthermore, some breed disposition is evident, suggesting a genetic component to the disease etiology in cats. Given that the prevalence of this disease in cats is potentially 10 times that seen in humans, we suggest that feline HST represents an excellent comparative model of acromegaly that warrants further investigation.

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JOINT2337

Concomitant development of central diabetes insipidus and cerebral salt-wasting syndrome in a child with subarachnoid hemorrhage

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Introduction
Diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and cerebral salt-wasting syndrome (CSWS) are observed in children with central nervous system (CNS) injuries (e.g., intracranial surgery in the hypothalamic-pituitary region, brain trauma, intracranial hemorrhage, neuroinfections, etc.). Central diabetes insipidus (DI) leads to elevated serum sodium levels and polyuria, whereas SIADH and CSWS are well-known causes of hyponatremia and polyuria in neurological patients. However, the simultaneous occurrence of DI and CSWS in pediatric patients is rarely described and often results in unfavorable outcomes.
Case Presentation
We present the case of a 15-year-old boy who suffered a traumatic brain injury in a car accident. He underwent surgical treatment for a subarachnoid hemorrhage, after which central diabetes insipidus initially developed. Treatment with Desmopressin was initiated. Later on, during follow-up, despite adequate replacement therapy with Desmopressin, persistent polyuria and symptomatic hyponatremia with natriuresis were observed. This led to the consideration of the concomitant presence of DI and CSWS. After initiating treatment with Fludrocortisone, diuresis and serum sodium levels normalized. The combined treatment was gradually discontinued, and the child was discharged in good health within 30 days.
Conclusion
The combination of central diabetes insipidus and cerebral salt-wasting syndrome is a rare phenomenon and represents a diagnostic challenge. Delayed diagnosis and inadequate management of such cases may result in poor neurological outcomes with a high mortality rate.

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JOINT3458

Long-term follow-up is needed in primary-like hypophysitis: a late diagnosis of Langerhans cell histiocytosis case report

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Introduction
Hypophysitis is a rare disease that affects mainly young adults. The main symptoms are headaches, pituitary insufficiency or vasopressin deficiency (AVP-D). Hypophysitis may be primary, secondary to systemic disease (sarcoidosis, L-group histiocytosis) or iatrogenic (mainly lead by checkpoint inhibitors). While hypophysitis may be part of a systemic disease at the onset, it may also precede it by several years.
Case report
A 38-year-old woman presented with a progressive onset of polyuria-polydipsia up to 9 litres per day. Diagnosis of AVP-D was quickly done after fluid restriction test, and desmopressin therapy was initiated leading to clinical improvement. She didn't have pituitary insufficiency and didn't exhibited any other symptoms such as headache or visual impairment. Pituitary MRI revealed thickening of the pituitary stalk associated with the loss of spontaneous T1 hypersignal of the posterior pituitary without symmetrical pituitary enlargement or **extra-pituitary abnormality. A large clinical, biological and radiological workup didn't identified any clues for systemic disease. More than two years after initial presentation, the patient noticed a clinically appearance of right parietal bone mass. Radiological assessment revealed a** right frontal paramedial osseolytic osseomeningeal tissue process, presenting a great uptake in 18F-FDG PET CT. Bone biopsy highlighted a BRAF V600E positive Langerhans cell histiocytosis, leading to a Langerhans cell histiocytosis with pituitary and bone manifestation.
Discussion
This illustrate that the discovery of hypophysitis should prompt a search for systemic disease, at onset and during time, since hypophysitis may precede by several years a systemic disease. Particularly, Langerhans histiocytosis should be investigated in the presence of AVP-D, thickened stalk and absence of headache.

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JOINT50

Dealing with pituitary invaders: a corticotroph macroadenoma case

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Introduction
Corticotroph pituitary tumors, particularly invasive macroadenomas, are rare and therapeutically challenging due to their compressive effects and systemic complications. They represent a significant cause of endogenous hypercortisolism in Cushing's syndrome. This case discusses a complex presentation of an invasive corticotroph macroadenoma in a middle-aged woman, underlining the value of tailored multidisciplinary management to achieve biochemical and clinical control.
Case Presentation
A 46-year-old woman with a history of hypertension and type 2 diabetes was diagnosed with an invasive corticotroph macroadenoma, confirmed by histopathology after transsphenoidal surgery. Imaging revealed a sellar and suprasellar mass with bone erosion and optic chiasm compression. Post-operative complications included hypogonadism and hypothyroidism, requiring hormone replacement therapy. Medical management included ketoconazole, cabergoline, and the planned introduction of Pasireotide to address tumor control and residual hypercortisolism.
Discussion
This case highlights the aggressive nature of corticotroph macroadenomas, characterized by local invasion and systemic effects such as Cushingoid features. Surgical resection remains the first-line treatment; however, complete remission is not always achievable, necessitating adjunctive therapies. Novel pharmacological approaches expand therapeutic options, such as somatostatin analogs and ACTH secretion inhibitors. Furthermore, long-term monitoring is critical due to the potential for recurrence or progression, especially in invasive forms.
Conclusion
Invasive corticotroph macroadenomas require an integrative approach, combining surgery, medical treatment, and close follow-up. Advanced therapies, like Pasireotide, offer promising outcomes in managing persistent disease. This case

underscores the importance of individualized care in achieving optimal results for complex pituitary tumors.

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EP1139

JOINT2370

A rare case of pituitary adenoma co-secreting ACTH and GH

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Introduction

Multi-secretory pituitary adenomas have been reported in the literature. However, tumors with dual corticosomatotropic secretion are very rare. Our observation illustrates This particular entity.

Observation

A 34-year-old patient complaining of decreased libido and right unilateral temporofrontal headaches was referred to us with suspicion of Cushing's syndrome. Clinically, there were signs of hypercortisolism (cushingoid facies, faciotruncular obesity; abdominal purple stretch marks; filling of the supraclavicular fossae; and skin fragility with bruising on the legs). There were no signs of hypersomatotropism. The hormone profile was consistent with ACTH-dependent Cushing's syndrome, with a slight hyperprolactinemia of disconnection, corticotropic and thyrotropic insufficiency, and a growth hormone level of 1.5*normal. MRI revealed a left laterosellar lesion measuring 14*22*10.5 mm. After trans-sphenoidal surgery, histological examination combined with IHC revealed a pituitary adenoma with positive immunostaining for GH and ACTH. The evolution over 1 year was marked by tumour recurrence with visual repercussions requiring recourse to surgery.

Discussion

Pituitary adenomas can express and secrete different hormones. The expression of pituitary hormones in non-neoplastic pituitary cells is regulated by various transcription factors. The most important of these are PIT1 and GATA 2. It is well known that some cases of pituitary adenoma producing growth hormone (GH) may be accompanied by hypersecretion of other anterior pituitary hormones such as prolactin (PRL) or thyroid-stimulating hormone (TSH). From an immunohistochemical point of view, other hormone-producing cells of the anterior pituitary can be detected among the GH-producing cells. However, a case of GH-secreting adenoma accompanied by ACTH secretion is extremely rare. the extreme rarity of the combination of GH and ACTH could be attributed to the suppressive effect of hypercorticism on GH secretion. Multiple hormone secretion may result either from neoplastic transformation of 2 cell lines or from differentiation of one cell into a cell secreting another hormone. Surgery is often required as a matter of urgency, somatostatin analogue treatment is indicated in these patients, and monitoring is imperative.

Conclusion

We report a new observation of a rare case of pituitary adenoma co-secreting ACTH and GH responsible for hypercorticism but without notable clinical signs of acromegaly. More meticulous endocrinological and immunohistochemical examination of cases of GH-secreting adenomas could reveal the true incidence of this combination.

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EP1140

JOINT2154

Familial isolated pituitary adenomas (FIPA): screening for mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene

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Introduction

Familial Isolated Pituitary Adenomas (FIPA) are a rare hereditary condition, accounting for 1.9–3.8% of all Pituitary Neuroendocrine Tumors (PitNET) cases. The first identified gene underlying FIPA is AIP, which accounts for 10% to 20% of FIPA kindreds. FIPA occurs in the absence of other syndromic conditions (MEN1, Carney complex) and frequently presents at a younger age with larger and locally invasive GH-secreting adenomas that are less likely to respond to first-generation somatostatin analogues (SSA).

Results

In this study, we retrospectively analyzed 1,068 PitNET patients, who presented in our institute between 2019-2024, identifying a FIPA prevalence of 1.02%. We detected 11 families with FIPA, of which 3 were homogeneous and the remaining heterogeneous. The average number of affected members per family was 2.72 ($\pm$ 0.96). The mean age at diagnosis was 47.2 years ($\pm$ 15.72). Acromegaly was the most common PitNET type in the index cases, occurring in 10 out of 11 cases (90.9%), while one index case had a non-functioning pituitary adenoma (NFPA). Among the family members of the index cases, 7 were diagnosed with NFPA, 3 with acromegaly, and 1 with prolactinoma. Regarding the index cases, the mean diameter at diagnosis of the pituitary adenomas was 18.8 mm ($\pm$ 8.79), with 8 out of 11 adenomas being invasive, as indicated by a Knosp grading. The mean number of required transsphenoidal surgeries was 1.27 ($\pm$ 0.74). Among the index cases with GH-secreting pituitary adenomas, 6 out of 10 patients currently have active disease. Genetic screening for AIP mutations was performed in 6 out of 11 cases, yielding 4 negative results and 2 results pending.

Conclusion

In conclusion, the study highlights the low prevalence of FIPA, as well as the fact that none of the tested families had a positive result for AIP mutations. Ongoing research into novel genetic and epigenetic mechanisms of pituitary tumorigenesis, alongside the storage of DNA for future genetic testing, will enhance our understanding and management of this condition.

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EP1141

JOINT3356

Clinical management and therapeutic options for pancreatic insulinomas – a case series

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Introduction

A functioning Neuroendocrine Tumour (NET) syndrome is defined by the presence of a clinical syndrome combined with biochemical evidence of inappropriately elevated hormonal levels, with positive hormonal expression in NET cells on immunohistochemical staining. [1, 2] Insulinomas are the most frequent type of functioning NETs – they are the most common cause of hypoglycaemia related to endogenous hyperinsulinism. [3].

Objectives and Methods

This paper presents, from a clinical and therapeutic point of view, a case series of 3 insulinoma patients, treated in a tertiary centre.

Results

We analysed data from 3 patients, 1 woman and 2 men (median age at diagnosis - 51.6 years old) which were referred due to clinical suspicion of insulinoma – Whipple's triad with no history of diabetes mellitus or glucose-lowering treatment. We performed the fasting test for the female – hypoglycaemia ($<$45 mg/dl) with inadequate normal insulin and C peptide levels. The other 2 patients came with spontaneous glycemia of 30-40 mg/dl with a long history of frequent crises (1 every 3-4 hours) – therefore, the clinical and biochemical diagnoses were positive. The CT exam revealed a pancreatic lesion in the tail of the pancreas in all 3 patients and also adrenal adenomas with a high lipid content – probably incidentalomas. The youngest patient, aged 40, was also diagnosed with a renal tumour of 7 cm and a pituitary microadenoma. The woman has a first-degree cousin with acromegaly, but no other positive familial or personal history suggestive of MEN1 syndrome for all 3 patients – the hormonal screening for MEN1 or other functional NETs also came back negative. The 2 older patients were referred to a general surgery clinic – one had a partial pancreatectomy (the pathology report was positive for insulinoma), with no residual disease post-surgery, but he developed secondary diabetes mellitus and is currently treated with insulin. The woman recently underwent partial pancreatectomy with no complications and complete remission, while the youngest patient was referred for a nephrectomy first, an octreotide scan to confirm the localisation and is currently treated with Diazoxid until the pancreatectomy can be performed. All 3 will be followed-up yearly and genetic testing and counselling are in progress.

Conclusions

Insulinomas are rare functioning NETs, with life-threatening symptoms, isolated or part of a syndromic disease, requiring multidisciplinary teams and expert tumour boards for correct diagnosis and management, the surgical curative

excision being the only treatment to ensure a successful outcome and improve quality of life.

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EP1142

JOINT1667

A case of aggressive corticotropinoma in a patient after combined treatment

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Introduction
Treatment of aggressive corticotropinomas is a challenge due to the frequent invasive growth of the tumor which complicates radical surgery and can increase the risk of recurrence, thus together with tumor resistance to radiotherapy leads to persistence of the disease.
Clinical case
In August 2023 a Cushing disease was diagnosed in a woman of 48 years of age and according to MRI in the cavity of the sella turcica, in the suprasellar cistern, in the left cavernous sinus (Knosp IV), in the sphenoid sinuses and in the cells of the ethmoid labyrinth on the left was determined tumor tissue measuring 28x25x39 mm. Transsphenoidal adenomectomy was performed (morphology: pituitary tumor of solid structure composed of cells with amphophilic cytoplasm, 1 pathological mitosis; immunohistochemistry: expression of synaptophysin, CAM 5.2 and ACTH, Ki-67-13.4%, no expression of somatostatin receptors subtype 5). Due to clinical manifestation of adrenal insufficiency in the postoperative period was initiated hydrocortisone therapy, which was cancelled in February 2024 due to the persistence of endogenous hypercortisolism and MRI noted tumor tissue in the right part of the adenohypophysis measuring 14.5x13x12 mm and in the left cavernous sinus measuring 17x16x33 mm. In March 2024 patient was treated by repeated transsphenoidal adenomectomy. A month later due to manifestation of neuro-ophthalmologic symptoms and the spread of tumor tissue measuring 26x31x41 mm into the orbit according to MRI, another transnasal transsphenoidal adenomectomy was performed (morphology: fibrous tissue with deformed tumor cells with hyperchromic nuclei; immunohistochemistry: ACTH expression in 100% of cells, CAM 5.2 in 80% of cells, Ki-67-10%, high reaction with VEGF and PD-L1 expression in 5% of cells, no expression of LH, FSH, prolactin and somatostatin receptors subtypes 2A and 5). In June-August 2024 the patient underwent stereotactic radiation therapy (TrueBeam, 55.8 Grey). In September 2024 was confirmed persistence of the disease and MRI described tumor tissue in the left cavernous sinus measuring 10x14x14 mm, endo-suprasellar on the right measuring 16x14x14 mm and along the upper, right and lower contours of the left optic nerve. The patient was consulted by a neurosurgeon, dynamic observation was recommended.
Conclusion
The clinical case demonstrates the problems in treatment of aggressive corticotropinomas. Anti-VEGF therapy and immune checkpoint inhibitors immunotherapy in some studies has shown effectiveness in the treatment of aggressive corticotropinomas. Thus, the expression of VEGF and PD-L1 in tumor cells detected during the immunohistochemistry in this patient may provide alternative treatment options for achieving remission.

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EP1143

JOINT2394

Giant prolactin-secreting pituitary adenoma: a case report

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Introduction
Giant prolactinomas, defined as prolactin-secreting adenomas larger than 4 cm, are rare and often present with significant compressive symptoms due to their invasive nature. They pose major diagnostic and therapeutic challenges, particularly in male patients, where late presentation is common. This case illustrates the aggressive evolution and management difficulties associated with giant prolactinomas.
Observation
We report the case of a 31-year-old male with no prior medical history, admitted for the management of a large pituitary adenoma. His symptoms began two months before hospitalization, with progressive headaches and bilateral visual impairment leading to complete blindness. Initial brain imaging (CT and MRI) revealed an invasive sellar and suprasellar mass (50 mm), extending into the cavernous sinuses, sphenoid, ethmoid, and nasal cavities, with compression of the optic pathways. The prolactin level was 138.5 ng/ml. On clinical examination, the patient was overweight (BMI = 26.53 kg/m^2) with normal blood pressure (110/80 mmHg). Neurological assessment revealed bilateral areflexic mydriasis due to oculomotor nerve (CN III) involvement, along with bilateral optic atrophy confirmed by ophthalmologic evaluation. Visual field testing showed light perception in the right eye and complete blindness in the left. There were no motor or sensory deficits. Endocrine evaluation revealed signs of thyrotropic insufficiency (fatigue, psychomotor slowing, constipation) and corticotropic insufficiency (asthenia, anorexia). The patient was initially treated with cabergoline (0.5 mg/week for three months); however, no clinical or radiological improvement was observed. He subsequently underwent transsphenoidal endoscopic surgery, with histopathology confirming an invasive prolactin-secreting adenoma. The Ki-67 proliferation index was 2%. Despite surgical intervention, his condition worsened, with a rapid increase in tumor size (80 × 70 × 60 mm) and extensive skull base destruction noted on follow-up MRI. Biochemical evaluation confirmed corticotropic and thyrotropic insufficiencies, requiring hormonal replacement therapy. Cabergoline was continued with dose escalation up to 2 mg/week, but prolactin levels continued to rise, reaching 850.8 ng/ml at 12 months. Radiotherapy was indicated but could not be initiated due to the patient's deterioration. Unfortunately, he passed away 18 months after diagnosis.
Discussion
Giant prolactinomas in men often exhibit an aggressive course with significant resistance to dopamine agonists, particularly in invasive forms. This case highlights the challenges of managing such tumors, including the need for multimodal therapy involving high-dose dopamine agonists, surgery, and potentially radiotherapy. Delayed diagnosis contributes to poor prognosis, emphasizing the need for early detection and long-term follow-up.

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JOINT1469

Autoimmune hypophysitis induced by Anti-PDL1 therapy

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Background
New Cancer Immunotherapies such as Immune checkpoint inhibitors enhance the immune system's ability to combat tumors. However, they can trigger various autoimmune manifestations, particularly endocrine disorders, including hypophysitis. While the incidence of hypophysitis is higher with anti-CTLA-4 agents, we report a case of autoimmune hypophysitis induced by anti-PDL1 therapy.
Case Report
A 52-year-old female patient, with no family history of autoimmune diseases, was diagnosed with infiltrating triple-negative breast carcinoma. Immunohistochemical analysis for the anti-PDL1 antibody revealed that more than 75% of tumor cells were positive for this marker. The patient underwent neoadjuvant chemotherapy (paclitaxel and carboplatin) and neoadjuvant immunotherapy (pembrolizumab) before surgery. After six months, she presented with asthenia and pallor, without nausea or abdominal pain. Laboratory tests revealed normal electrolyte levels, but morning cortisol was low at 1.87 ng/ml, with ACTH <1.5 pg/ml. Thyroid function tests showed FT4 at 10.2 pmol/l(normal range: 12–22) and TSH at 2.46 mIU/l,with normal prolactin levels. Autoimmune markers, including ANA, anti-smooth muscle antibodies, and anti-TPO antibodies, were negative. Hypothalamic-pituitary MRI showed no abnormalities in the pituitary stalk or gland. The patient was started on hormone replacement therapy for corticotropic and thyrotropic deficiencies.
Conclusion
Understanding the endocrine side effects of immunotherapies is crucial and must be promptly diagnosed, as they can significantly impact the patient's prognosis and, in some cases, may be life-threatening.

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JOINT3958

Acute total visual loss complicating macroprolactinoma apoplexy

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Introduction
Prolactin-secreting adenomas are benign tumors caused by the proliferation of lactotroph cells in the pituitary gland. They account for 60% of pituitary adenomas. Pituitary apoplexy is a rare serious event defined as bleeding or infarction occurring within a pituitary adenoma. Here, we present the case of acute visual loss due to sudden prolactinoma apoplexy.
Case report
A 48-year-old patient with no notable medical history was admitted for retro-orbital headaches, asthenia, and weight loss. On physical examination, no oculomotor dysfunction or visual acuity loss was found. An MRI of the hypothalamic-pituitary region was performed revealing a sellar and suprasellar expansive process measuring 41.6 × 35.9 × 34.6 mm, enlarging the sella turcica and compressing the optic chiasm, bulging inferiorly into the sphenoidal sinus and extending laterally into the cavernous sinuses, encompassing both carotid arteries. Suddenly, the patient's condition worsened, with increasing headaches, vomiting, acute total visual loss, right ptosis, and complete right ophthalmoplegia. A brain CT scan was urgently performed, revealing an 18 mm thick right temporal extradural collection and intra-lesional hemorrhage. The patient underwent emergency trans-sphenoidal surgery. The histopathological examination revealed a partially necrotic and hemorrhagic pituitary adenoma with immunohistochemical expression of prolactin. The patient has retained bilateral blindness with corticotropic, gonadotropic, and thyrotropic insufficiency.
Discussion
Pituitary apoplexy is defined as the occurrence of massive necrotic-hemorrhagic changes within a pituitary adenoma. Considered a medical emergency, its frequency remains rare (0.6% to 5% of patients undergoing surgery for pituitary pathology). Most often, pituitary apoplexy is the initial manifestation of an undiagnosed adenoma, but it can also complicate a known adenoma, as in the case of our patient. The clinical presentation of pituitary apoplexy is characterized by the sudden onset of oculomotor paralysis or visual disturbances, sometimes leading to blindness, accompanied by headaches and, occasionally, altered consciousness. Predisposing factors include pregnancy, treatment with dopamine agonists, and stimulation tests. However, no predisposing factors were identified in our patient. Urgent hormone replacement therapy and transsphenoidal tumor resection usually lead to favorable outcomes, which was not the case for our patient.
Conclusion
Pituitary apoplexy is a rare complication, often revealing a macroadenoma, that threatens both life and functional prognosis, requiring emergency management.

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EP1146

JOINT525

Endocrinological evaluation and natural course of symptomatic paediatric patients with rathke cleft cysts

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Background and Aim
Rathke cleft cysts (RCC) are usually asymptomatic in childhood and are often diagnosed incidentally on cranial imaging. We aimed to analyse the presenting symptoms, endocrine evaluation, and natural course of our symptomatic patients with RCC.
Methods
We identified 14 patients (8 male, 6 female) with RCC via the university hospital's database and extracted the clinical data from the medical files. The retrospective study covered a period from 2005 to 2023.
Results (median, min-max)
The diagnosis of RCC was made by magnetic resonance imaging at 11.0 (1.8 - 17.6) years. The presenting symptoms were headaches [alone (n = 1) or in combination with nausea/fatigue (n = 2), polydipsia (n = 2) or dizziness (n = 3)] followed by short stature/growth retardation [alone (n = 4) or with polydipsia (n = 1)]. One patient had a syncope with a papilledema. The endocrinological evaluation revealed pituitary insufficiency in 10 children. Growth hormone (GH) deficiency was diagnosed in five patients [isolated (n = 1) or in combination with arginine vasopressin (AVP) deficiency (n = 1) or with central hypothyroidism/-hypocortisolism (n = 3)]. AVP deficiency was found in 5 patients [isolated (n=1), or in combination with central hypothyroidism (n = 2), or hypocortisolism (n = 2)]. Three patients had hyperprolactinemia. Nine patients were treated conservatively (n = 4: no medication; n = 4: hGH, alone or in combination with L-T4 and hydrocortisone, n = 1: desmopressin). Five underwent surgery (transcranial 1; transsphenoidal 4). In the conservatively treated patients, cyst size remained unchanged in 7 and decreased in 2. Of the five patients treated surgically, the cyst size increased in 4; three required a second operation. At the last presentation, after a follow-up period of 6.4 (0.33-14.8) years, the hormone status of conservatively treated patients was normal in 6 and pathological in 3. Five patients (4 m, 1 f) developed hypogonadotropic hypogonadism, including two children who were only treated conservatively.
Conclusions
In our cohort, neurological disorders were the most common reason for the initial presentation. Endocrine evaluation revealed pituitary insufficiency in 10/14 children, with GH- and AVP deficiencies being the most common findings. Regular imaging and endocrine follow-ups are necessary due to the potential for changes in cyst size and hormonal findings.

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EP1147

JOINT1401

Real-world characteristics and treatment patterns of adults receiving long-acting growth hormone: insights from the INSIGHTS-GHT registry

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Introduction
Long-acting growth hormone (LaGH) has been developed to improve treatment adherence and patient convenience compared to daily GH injections. In adults with growth hormone deficiency (GHD), LaGH therapy aims to restore physiological GH levels, supporting metabolic health, body composition, and overall well-being. While clinical trials have demonstrated the efficacy and safety of LaGH, real-world data on its use in adult patients remain limited.
Methods
The Investigating Significant Health Trends in Growth Hormone Treatments (INSIGHTS-GHT) registry is an ongoing, German multicenter, observational study designed to collect real-world evidence on the characteristics, treatment patterns, effectiveness, and safety of GH therapy in patients with GHD. Here, we provide an overview of adult patients receiving LaGH within the registry at an interim analysis, dated January 10th, 2025, with a focus on baseline characteristics and initial treatment patterns.
Results
A total of 25 adult patients with GHD receiving LaGH therapy were included. The mean age at GHD diagnosis was 23.2 years (SD: 19.1; range: 0.8–60.8), while the mean age at LaGH initiation was 39.4 years (SD: 16.0; range: 18.3–73.9). Half of the patients (n = 12, 50.0%) had childhood-onset GHD. Regarding sex distribution, 9 patients (36.0%) were male, and 16 (64.0%) were female. The majority had organic GHD (n = 21, 84.0%), while 4 patients (16.0%) had idiopathic GHD. Most patients (n = 24, 96.0%) transitioned from prior daily GH therapy, with a mean duration of previous treatment of 12.8 years (SD: 8.0). The initial LaGH dose was below the recommended level in 6 patients (31.6%), at the recommended level in 11 patients (57.9%), and above the recommended level in 2 patients (10.5%).
Conclusion
This analysis from the INSIGHTS-GHT registry provides first real-world insights into the characteristics and treatment patterns of adults receiving LaGH. The data show that most patients had organic GHD, with a significant proportion transitioning from prior daily GH therapy. While the majority initiated LaGH

at the recommended dose, some started at lower or higher doses, highlighting variability in treatment approaches. The number of patients in the INSIGHTS registry with LAGH therapy can be seen as an indication of its acceptance by patients and prescribers. Since the analyses are continuously updated, INSIGHTS-GHT offers an excellent research platform for investigating these and other aspects of somatotropin therapy.

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EP1148

JOINT1245

Aggressive pituitary tumours and carcinomas – clinicopathological data and treatment experiences from Hungary

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Introduction

Pituitary neuroendocrine tumours (PitNETs) are relatively common intracranial neoplasms that typically exhibit indolent behaviour. However, some tumours can be clinically aggressive, as indicated by early and frequent recurrences and resistance to standard treatments.

Aim

This study aims to characterise the clinicopathological data of patients with aggressive pituitary tumours (APTs) at a tertiary referral centre and to analyse the effectiveness of different treatment modalities.

Methods

This retrospective study included patients who met the following criteria: radiological evidence of invasive tumour growth (signs of infrasellar extension or parasellar growth classified with a Knosp grade of $\geq$ 3); a histopathological diagnosis of pituitary adenoma with increased proliferative activity defined by a Ki-67 index of $\geq$ 3%; (and, if available, a mitotic count $\geq$ 2 per high-power field); rapid tumour growth; and resistance to standard medical and surgical therapies. We analyzed demographic data and results from hormonal and radiological examinations, data presented as mean $\pm$ SD.

Results

From a total of 1,595 patients who underwent pituitary surgery between 2008 and 2023, we identified 20 patients (8 females and 12 males) with aggressive pituitary tumours based on the inclusion criteria defined above. The mean follow-up duration for these patients was 94.1 $\pm$ 71.8 months. The average age at diagnosis was 44.0 $\pm$ 13.78 years. Among these cases, five patients were later reclassified as having pituitary carcinoma due to the detection of metastasis. All patients had macroadenomas, with the largest tumour diameter measuring 33 $\pm$ 12 mm. Of these patients, fifteen had hormonally active tumours, presenting as follows: Cushing's disease ($n = 6$), hyperprolactinaemia ($n = 5$), acromegaly ($n = 3$), and hyperthyroidism ($n = 1$). The total number of surgical interventions performed on these patients was 53. The median Ki-67 index was 7% (range: 3-40) and mitotic count was 4 per high-power field (range: 2-20), respectively. Fifteen patients (75%) received pituitary irradiation. The number of pituitary surgeries per patient per year was significantly lower after radiotherapy (0.39 $\pm$ 0.10 vs. 0.13 $\pm$ 0.05; $P = 0.001$). At least on short term, temozolomide treatment resulted in partial tumour remission in 3 out of 4 patients. Three metastatic and three non-metastatic patients died due to pituitary disease progression.

Conclusion

In our endocrine centre 1.3% of patients in the surgical pituitary tumour series have aggressive tumours. The study found that fewer surgical interventions were required after radiotherapy for these aggressive tumours. This finding reinforces current guidelines recommending earlier radiotherapy for pituitary adenomas when aggressive features are present.

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EP1149

JOINT2244

Central precocious puberty in a female child with a giant hypothalamic hamartoma: diagnosis and treatment

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Hypothalamic hamartoma (HH) is a rare, congenital, and benign lesion often arising from the floor of the hypothalamus involving either tuber cinereum or mammillary bodies and its prevalence varies between 1/50,000 and 1/200,000 persons. The classical signs are: central precocious puberty (CPP), gelastic seizure, and developmental delay. It is usually diagnosed by brain magnetic resonance imaging (MRI) scans and is seen as non-enhancing, isointense, or hyperintense lesions on T2-weighted images. HH is one of the most common organic causes of CPP that tends to occur significantly earlier than idiopathic CPP but it is well managed by gonadotropin releasing hormone (GnRH) agonist. We present the case of a female child who was referred to our Unit of Pediatric Endocrinology for premature thelarche. She was 3 years-old, and on physical examination showed: height 106.7 cm (+ 3.0 SDS), mid-parental height 163.0 cm (0.1 SDS), weight 24.5 kg (+ 3.7 SDS), Tanner stage B2-3, P1, no dysmorphic features. Diagnostic work-up showed: bone age 7.9 yrs (Greulich-Pyle), basal FSH 14.2 mIU/ml, basal LH 8.2 mIU/ml, estradiol 29.7 pg/ml, LH peak of GnRH-stimulation test 29.1 mIU/ml, IGF-1 262 ng/ml, beta-HCG and alfa-fetoprotein negative, pelvic ultrasound (peripubertal uterus with longitudinal diameter 36.9 mm and large ovaries $>$ 3 cc with follicles). Brain MRI scans evidenced a neoformation of oval morphology and dimensions of approximately 9 $\times$ 12 $\times$ 10 mm, inseparable from the middle third of the hypothalamic infundibulum, with a median location, and projecting into the context of the suprasellar cisterns; the finding was compatible with hamartoma of the tuber cinereum. The adenohypophysis had maximum dimensions of approximately 15x4x4 mm. There were no appreciable signal alterations of the gland in both conditions baseline and after gadolinium administration. Pituitary peduncle was aligned. Since the child had never presented seizures and no indication were for surgical intervention we prescribed medical treatment with Leuprorelin (3.75 mg every 28 days intramuscularly). Six months after starting therapy the child had never experienced any side effects and thelarche had regressed. Our case confirms that children with very early presenting CPP deserve a brain MRI because the risk of an organic lesion is very high. We believe that tall stature should be considered a clue element to differentiate isolated premature thelarche and precocious puberty and when bone age is significantly accelerated, it is mandatory to carry out all the appropriate investigations for the correct diagnosis.

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EP1150

JOINT169

Rathke's cleft cyst presenting with isolated arginine vasopressin deficiency

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Introduction

Rathke's cleft cyst (RCC) is a benign, non-neoplastic lesion located in the sellar and suprasellar region of the brain, with a prevalence of 12-33% of cases. It constitutes a remnant of Rathke's pouch - an embryonic precursor of the pituitary gland. While most RCCs appear asymptomatic, headaches, visual disturbances, mass effect-related hypopituitarism, and hyperprolactinemia due to the "stalk effect" phenomenon may occur. Arginine vasopressin deficiency (AVP-D), characterized by impaired hypothalamus/posterior pituitary vasopressinergic neurons, resulting in dysfunction in AVP synthesis, typically does not represent the clinical picture of an RCC patient.

Case report

A 25-year-old female with a history of severe headaches (NRS 5-9 points) was referred to the Department of Endocrinology for hormonal evaluation of a sellar

lesion visualized in an outpatient head magnetic resonance imaging (MRI). She had a history of polyuria, polydipsia, and unintentional weight gain (10kg in 2-3 months). On physical examination, the patient was in general good condition, without features of endocrine stigmatization. Hormonal evaluation revealed normal prolactin levels (triplicate determinations), including after dilution, and preserved appropriate function of the pituitary tropic axes. Additional testing indicated decreased urine specific gravity (USG) and osmolality, increased plasma osmolality, which, along with polydipsia and polyuria (7700 mL/day), led to the suspicious of AVP-D. Other clinical causes and the drug effect have been excluded. Desmopressin (DDAVP) treatment was initiated, the dosage was set individually according to symptoms and plasma osmolality. A follow-up head MRI identified significant progression of the sellar mass dimensions - 14 (CC) × 12 (AP) × 17 (DB) mm, high-intensity in T1 and T2-weighted images, adhesion to the medial cavernous sinuses' walls and modeling of the optic chiasm. On ophthalmological evaluation, the patient had no significant visual field abnormalities. She was consulted neurosurgically and, upon informed consent, qualified for surgery. In hydrocortisone protection, transsphenoidal endoscopic resection of the pituitary lesion was performed. The procedure was uncomplicated. A normal postoperative image with complete resection was confirmed in head computer tomography and MRI. Clinically, the patient did not develop cerebrospinal fluid leakage. Histopathological verification revealed RCC. In the postoperative evaluation (performed without DDAVP usage), the patient presented adequate urine output, with normal USG and plasma osmolality.

Conclusions

Given the concerns about determining the appropriate management of mildly symptomatic RCC, it seems crucial to consider AVP-D as a clinical manifestation.

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EP1151

JOINT1977

Osilodrostat effectiveness in the treatment of cushing's disease (CD) and ectopic cushing's syndrome (ECS)- a single-center real-life experience

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Introduction

Osilodrostat, approved in 2020, is a second-line therapy for Cushing's syndrome (CS) when surgery is ineffective, contraindicated, or as bridging therapy before surgery. While urinary free cortisol (UFC) is the standard for assessing treatment efficacy, prolonged processing time can limit its utility.

Objectives

Retrospective assessment of the efficacy of osilodrostat therapy in CS patients from a single reference endocrinology center by assessing the reduction of serum cortisol levels and the impact on CS complications.

Materials and Methods

We analyzed medical records of 25 CS patients treated with osilodrostat (2020-2025). Due to UFC processing delays (>7 days), response was assessed based on morning serum cortisol and clinical parameters. We evaluated time to reduce:.

- serum cortisol concentration(CR)- time to 50% cortisol reduction or achieve level <15 μg/dl.
- potassium supplementation(PS) - any reduction.
-antihypertensive(aHT) and antidiabetic therapy(aDT) - any reduction.

Results

Of 23 analyzable patients (13 CD, 10 ECS), mean diagnosis age was 57.8 years; 61% were women. Seven (30.4%) died. Mean morning serum cortisol at diagnosis: 42.7 μg/dl; ACTH: 180.3 pg/ml. Osilodrostat was first-line in 11, second-line in 10 (after metyrapone, ketoconazole, or pasireotide), and third/fourth-line in 2. Treatment was changed to osilodrostat in 7/12 cases due to incomplete clinical/biochemical remission, in 1/12 due to intolerance, and in 4/12 after short-term use of another drug as a bridge before osilodrostat. Four patients received a "block and replace" regimen, including two with cyclic CS. At osilodrostat initiation: 17 required potassium supplementation (9 needed spironolactone), 19 had diabetes (9 on insulin), 21 had hypertension. Mean treatment duration: 221.5 days (CD), 156 days (ECS). CR was achieved in 22/23 patients at a mean dose of 7.2 mg/day (5.8 mg in CD; 9.5 mg in ECS).

Key outcomes

	Time to reduce(TtR)in days (number of patients with the effect)	
	CD $n = 13$	ECS $n = 10$
-TtR serum cortisol concentration(CR)	28.8(13/13)	9.2(9/10)
-TtR potassium supplementation	54.9(8/8)	8.9(10/10)
-TtR hypertension therapy	55.1(10/11)	21.7(9/10)
-TtR diabetes therapy	28.8(6/11)	28(3/8)

Dose of osilodrostat was negatively moderately correlated with time to reduction of aHT and aDT ($r = -0.65$ ($P = 0.003$) and -0.7 ($P = 0.05$)). One CD patient developed an adrenal crisis, leading to transient treatment discontinuation.

Discussion

Morning serum cortisol combined with clinical assessment is effective for monitoring osilodrostat treatment. In ECS, the most rapid improvement was seen in potassium supplementation reduction. Higher doses of osilodrostat were associated with faster improvements in blood pressure and glycemic control. There is the necessity of further research to optimize and personalize osilodrostat therapy.

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EP1152

JOINT3598

GH secretion inhibition test in children - should we use different standards for obese children vs. normal weight children?

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Hyperglycemia causes strong inhibition of growth hormone (GH) secretion. This phenomenon is used in the diagnosis of suspected GH excess during the GH suppression test after oral glucose administration (OGTT). In our previous work, we determined that the discriminant value for normal GH suppression during this test is < 1.1 ng/ml, and this nadir occurred at each of the assessed time points. Recently, there has been discussion about the influence of obesity on the interpretation of GH secretion in stimulation tests and the need to use different (lower) norms for people with obesity. The aim of this work was to present the results of GH concentration during the suppression test performed in children with obesity (in whom OGTT was performed for other reasons, and gigantism was excluded.

Material and Methods

A group of 171 children aged 4 to 17.2 years with various endocrine disorders was divided into 2 subgroups based on the SDS BMI index. The group of children with normal body weight (SDS BMI in the range of -2.0 to 2.0) included 57 people (40 girls and 17 boys). The group of children with excessive body weight (SDS BMI > 2.0) included 114 patients (66 girls and 48 boys). In each child, OGTT was performed after the administration of glucose at a dose of 1.75 g/kg (max. 75 g) with the assessment of glucose and GH concentration at time points 0, 30, 60, 90 and 120 minutes. In children, gigantism was excluded - based on the normal IGF-1 concentration or higher IGF-1 with exclusion of the presence of pituitary adenoma in MRI examination with contrast.

Results

In the subgroup of children with normal body weight, the minimum GH concentration during the test (from 0 to 120 minutes) ranged from 0.07 to 1.05 ng/ml, and the maximum - from 0.05 to 13.74 ng/ml. In the subgroup of children with obesity, the minimum GH concentration during the test ranged from 0.02 to 1.07 ng/ml, and the maximum from 0.11 to 17.29 ng/ml. In both groups, there were no statistically significant differences between the lowest GH concentrations (nadir).

Conclusion

If it is necessary to perform a suppression test in a child with obesity, it seems that the same cut-off point should be used to exclude gigantism; i.e. GH level < 1.1 ng/ml occurring in at least one of the 5 time points of the suppression test after oral glucose administration.

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JOINT3047

Prolonged adrenal insufficiency following osilodrostat discontinuation

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Osilodrostat is an oral steroidogenesis inhibitor used to treat hypercortisolism by inhibiting 11-beta-hydroxylase. It can cause adrenal insufficiency (AI) in about 40% of patients, which is typically considered a natural consequence of therapy. However, along with a few early reports, suggest that AI can persist even after discontinuation of osilodrostat.[1, 3, 5] We present the case of a 74-year-old female patient with ectopic ACTH-dependent Cushing's syndrome who developed prolonged AI despite the withdrawal of osilodrostat. The patient underwent radiotherapy for a primary lesion located in the anterior mediastinum. During treatment, osilodrostat was introduced (2-4 mg/d), and adrenal insufficiency developed within four weeks. She required hydrocortisone replacement therapy, and over time, undetectable morning cortisol levels were observed. After reducing morning serum cortisol levels, osilodrostat dose was decreased and withdrawn 15 months into therapy. Despite 31 weeks off the drug, morning cortisol remained undetectable, with no response to a high-dose ACTH test, and the patient required ongoing hydrocortisone substitution. Discussion of prolonged AI after osilodrostat discontinuation should mention a study presenting reduced adrenal size (despite stable ACTH levels), suggesting a potential adrenolytic effect of the drug.[4] Another case report decscirbe decrease in 11-deoxycortisol in prolonged AI after osilodrostat treatment.[1] Given the drug's mechanism, 11-deoxycortisol levels should increase due to inhibited conversion to cortisol. However, also in the LINC 3 study, after an initial rise, despite remaining above reference ranges, the levels declined during follow-up.[2] Another aspect is the observed increase in AI from week 48 to week 72 during osilodrostat treatment in a clinical trial which may suggest the link to the mechanism seen in our and previous cases.[2] The mechanism of prolonged AI after osilodrostat discontinuation is not yet understood. Case reports are needed to raise awareness, potentially prompting further research to clarify these effects and explore broader therapeutic applications.

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EP1154

JOINT2093

Body composition analysis in children treated with recombinant GH

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Background

Growth hormone effect on body composition is well recognized and treatment with recombinant growth hormone (rGH) has a positive impact.

Aim

The aim of this study was to analyze changes in body composition parameters under rGH treatment in children diagnosed with short stature and to investigate potential influencing factors.

Material and Methods

A secondary data analysis was conducted in the Endocrinology Compartment of the Mures County Hospital, Romania, approved by the local Ethics Committee. All children diagnosed with short stature and receiving rGH treatment were eligible for inclusion if they had four body composition analyses at least 6 months apart. The variables analyzed included age, gender, environment, ethnicity, age at treatment start, mean rGH dose, treatment duration before first analysis, the interval between analysis, height and body mass index (BMI) SDS, body composition parameters assessed by bioimpedance (body fat, truncal fat, muscle mass, skeletal muscle mass percentages, angle phase, and sarcopenic index) and family related variables (BMI, educational level, family income). Statistical analysis was performed using SPSS v.25 with a level of significance $\alpha = 0.05$.

Results

Thirty children were included with a mean age of 7.75 ± 3 years and a gender ratio close to one (1,14:1). There was no statistically significant trend in body composition parameters taken during serial measurements, except for the sarcopenic index and height ($P < 0.001$). Environment, ethnicity, age at treatment start, and family-related variables had no significant influence on body composition changes. Gender differences in body composition revealed that the change in muscle mass ($P = 0.009$) and skeletal muscle mass ($P = 0.013$) was statistically significantly higher for boys, and body fat ($P = 0.013$) for girls. Sarcopenic index changes correlated with height gain ($r = 0.483$, $P = 0.007$) and BMI changes ($r = 0.491$, $P = 0.006$), while angle phase correlated with changes in muscle mass ($r = 0.488$, $P = 0.006$), skeletal muscle mass ($r = 0.474$, $P = 0.008$) and mean rGH dose ($r = -0.390$, $P = 0.033$). In linear regression analysis with body composition parameters as dependent variables, puberty progression, age, age at treatment start, and duration of treatment were significant predictors for sarcopenic index change, with the model explaining 32,3% of the variation, albeit non-significant. There was no difference in body composition changes regardless of the indication for treatment.

Conclusions

Gender and pubertal status play a significant role in body composition changes while rGH seems to play a less significant role, regardless of the indication for treatment.

Keywords

short stature, bioimpedance, gender, pubertal status, rGH treatment.

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EP1155

JOINT2774

Impact of early menarche on adolescent health

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Aim

Patients who begin menarche between the ages of 9.5 and 11 do not initiate treatment. It is acknowledged that early menarche may adversely impact height. The onset of menarche at an early age affects the menstrual cycle, induces psychological repercussions in individuals, and leads to menstrual irregularities. Our study investigated the adverse impacts of early menarche on the menstrual cycle, psychological health, and final height.

Methods

This retrospective analysis involved children aged 9.5 to 11 years who consulted the pediatric endocrinology outpatient clinic for menarche from January 2012 to January 2018. The target height (TH) was determined from the patients' outpatient clinic assessment files, utilizing medical records at the beginning of treatment. The final height (FH) and weight of the patients were documented via a questionnaire. The TH and FAH of girls were compared across groups. We performed a paired t-test to assess the difference between TH and FAH. The study examined menstrual patterns, menstrual cycles, dysmenorrhea, duration of menstrual regularity, and a history of psychiatric disorders required pharmacological treatment.

Results

The patients' TH was 159.27 ± 4.52cm, FAH was 157.71 ± 5.19cm, target height SDS was 0.64 ± 0.76, and final height SDS was 0.81 ± 0.91. It was observed that 6 of the 11 patients who gained more than -1 SDS compared to the target height were accompanied by chronic disease, and those who gained more than $+1$ SDS compared to the target height were not accompanied by chronic disease($P = 0.014$). Ten patients (17.2%) used medication due to asthma, and 9 patients (15.5%)used medication due to menstrual irregularity. Painful menarche was found in 50% of the patients ($n = 26$). Early menarche was present in the families of 24.1% of the patients ($n = 14$). Psychiatric disorders were observed in 22.4% ($n = 13$) of early menarche cases. 15.5% ($n = 9$) of the patients were receiving

medication for psychiatric illness. The average duration of menstruation was 6.13 ± 2.11 days, the need for pads was 3.74 ± 0.82 pieces/day, and the time to regularization was 9.18 ± 9.95 months.
Conclusion
Though some studies assert that early menarche negatively impacts height, our research revealed no detrimental influence of early menarche on final height. The concurrent chronic disease negatively affected growth, leading to a -1 SDS deviation from the target height. The correlation between asthma and early menarche was significant. The requirement for psychiatric treatment increased far above population averages. We claim that the existence of a comorbid condition adversely impacts growth, regardless of whether early menarche has a definitive influence.

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EP1156

JOINT3691

Case report of ependymal pituicytoma

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Background
Pituitary pituicytoma is a rare, low-grade primary tumor originating from pituicytes in the neurohypophysis or infundibulum. Clinically, it presents with symptoms similar to other sellar region tumors, such as visual impairment, headache, and/or pituitary hormone deficiencies, depending on tumor size. Immunohistochemical examinations are crucial for diagnosis.
Case Presentation
A 63-year-old male patient with a history of basal cell carcinoma and squamous cell carcinoma, previously treated at another center, presented to our clinic due to visual disturbances. Pituitary MRI revealed a well-defined, lobulated, solid mass measuring 17 × 15 × 10 mm in the sella, extending to the optic chiasm and involving the infundibulum, consistent with a pituitary macroadenoma. Physical examination showed bitemporal hemianopsia without motor deficits or pathological reflexes. Preoperative laboratory tests, including liver, kidney, and thyroid function tests, as well as a complete blood count, were within normal limits. The patient had no history of regular medication use, Anterior pituitary hormone levels were appropriate for his age. The patient underwent surgery at our neurosurgery department, and histopathological examination demonstrated a diagnosis of WHO grade 1 pituicytoma, specifically an ependymal pituicytoma. Immunohistochemical staining showed positive TTF-1, Ki-67 of 1%, and negative staining for S-100, synaptophysin, GFAP, and anterior pituitary hormones. Postoperatively, the patient's visual symptoms improved, and follow-up evaluations displayed normal anterior pituitary hormone levels with no need for additional treatment.
Conclusion
According to the World Health Organization (WHO) classification, pituicytoma is a benign grade 1 tumor of the pituitary gland. It is challenging to diagnose due to its clinical and radiological similarities to other sellar region masses. The presence of a posterior pituitary lesion on MRI may suggest pituicytoma; however, immunohistochemical analysis is essential for a definitive diagnosis. To prevent recurrence, total surgical resection of the tumor is critical.

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EP1157

JOINT2528

Not just the skin rash: a case of coexistence of macroprolactinoma and metastatic neuroendocrine tumour

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Introduction
Hyperprolactinemia is a common finding in patients on antipsychotic medications. Markedly elevated prolactin levels warrant further investigation.
Case Presentation
A 57-year-old woman with schizophrenia on risperidone was referred to the endocrinology clinic after routine testing revealed asymptomatic hyperprolactinemia. She had no headaches, or visual disturbance and was 2-years post-menopause. Her main concern was a 3-year history of progressive large volume, watery diarrhoea associated with 12kg weight loss and a hyperpigmented rash. She denied flushing, wheezing, or symptoms of hypoglycaemia. She had been previously investigated with a normal colonoscopy and been diagnosed with irritable bowel syndrome. She had type 2 diabetes and had no family history of endocrinopathy. On examination, she had no clinical endocrinopathy. Skin examination revealed well-demarcated, hyperpigmented macules over her gluteal, inner thigh, feet and inframammary regions. The remainder of her clinical examination was normal, including normal visual acuity, eye movements and visual fields to confrontation with a red pin. Laboratory investigations showed a significantly elevated prolactin of 39,393 mU/l(normal range < 496 mU/l)with suppressed gonadotropins. The remainder of her anterior pituitary function and calcium were normal. The prolactin level was too high to be attributed to antipsychotic therapy. Pituitary MRI confirmed a 22 mm macroadenoma with right cavernous sinus invasion but no optic chiasm compression. After psychiatric consultation, risperidone was switched to aripiprazole, leading to an improvement in prolactin levels (9,315 mU/L). Further workup for her diarrhoea and rash revealed elevated 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) and chromogranins A and B, with normal fasting gut peptides and glucagon. Imaging, including 68Ga-DOTATATE PET-CT and triple-phase CT, identified a primary ileal neuro-endocrine tumour (NET) with mesenteric, liver, and lung metastases. Echocardiography showed no evidence of carcinoid heart disease and genetic testing for multiple endocrine neoplasia type 1 (MEN1) was negative. Histology confirmed a Grade 1 NET (Ki67 < 3%). She was initiated on 4 weekly Lanreotide injections and vitamin B complex, resulting in a significant reduction in diarrhoea and resolution of her rash, with normalisation of 24-hour urine 5HIAA.
Learning Points
1. While drug-induced hyperprolactinemia is common, significantly elevated prolactin levels necessitate further evaluation to exclude pituitary adenomas.
2. Aripiprazole is an atypical antipsychotic, which is effective at reducing serum prolactin and pituitary adenoma size when dopamine agonist therapy is contra-indicated. This is an off-license use.
3. The combination of diarrhoea and a rash should alert the physician to the possibility of an underlying neuro-endocrine tumour.

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EP1158

JOINT2559

A rare coexistence of acromegaly with metastatic adrenocortical carcinoma

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Background
Adrenocortical carcinoma (ACC) is a rare endocrine malignancy often with an unfavourable prognosis. The coexistence of acromegaly and ACC is quite rare. Here we describe a case of metastatic ACC in a patient who had Acromegaly treated with surgery, radiotherapy, and medical management.
Case
A male in his late 30s was referred to the endocrine department in 2018 to investigate for change in facial appearance. He was biochemically confirmed to have acromegaly, a 33 mm pituitary macroadenoma with bilateral cavernous invasion. He underwent transsphenoidal adenectomy and histology revealed somatotroph adenoma of partially granulated type with Ki-67 index of 3-5 %. Post-operatively, he had a biochemical recurrence of acromegaly along with panhypopituitarism and residual tumour in the left cavernous sinus. Hence, he was commenced on lanreotide 120 mg monthly injections. His IGF-1 failed to control on lanreotide and was then offered 25 sessions of pituitary radiotherapy in 2019. Subsequently, he was started on pegvisomant injections in 2021 due to suboptimal IGF-1 control following which IGF-1 levels were controlled. In 2023, while being continued on pegvisomant, he was noted to have progressive lower limb swelling, weight gain and deranged liver function tests. Therefore pegvisomant, lanreotide and hydrocortisone were discontinued. Detailed evaluation revealed non-suppressed plasma cortisol (1593 nmol/L), significantly raised urine cortisol (> 5000 nmol/l)and suppressed ACTH. Abdominal imaging revealed a right adrenocortical mass with metastasis, inferior vena cava thrombus, bilateral pleural effusion and ascites. He was initially planned for surgical excision followed by aggressive chemotherapy. However, a repeat CT scan of the adrenal showed rapid tumour progression, and his general condition deteriorated. He was initiated on Mitotane and Metyrapone with hydrocortisone. A multi-disciplinary team concluded that he was not for surgery and palliative care was

the best option. He was initiated on enoxaparin for IVC thrombus, unfortunately, the tumour bled resulting in further deterioration and death. Extensive evaluation for genetic studies revealed negative results for AIP, MEN1, CDC73, CDKN1B, PRKAR1A, RET, VHL genes.
Conclusion
Acromegaly is associated with greater morbidity and a high incidence of tumours, possibly due to the permissive role of elevated GH and IGF-I levels. Adrenal lesions seem more frequent in acromegaly than in the general population, however, no single factor (GH/IGF-I levels or disease duration) predicts them. Certain genetically inherited conditions are associated with aggressive pituitary tumours and ACC. Negative results of frequently mutated gene profiles open a path for more research on novel genetic associations.

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EP1159

JOINT3943

A diagnosis not to be missed

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New developments in targeted oncological treatment of craniopharyngioma provide innovative perspectives in the management of this challenging pathology. We report a clinical case demonstrating the fundamental role of pathological confirmation and molecular analyses for an optimal up to date treatment of craniopharyngioma. A 53-year-old male presented in August 2024vwith seven months history of visual failure and eventual visual deterioration. The ophthalmology assessment detected reduced visual acuity in both eyes, with OCT and visual field patterns in keeping with chiasmatic lesion. An MRI head demonstrated a suprasellar lesion involving the optic chiasm and the hypothalamus, and extending into the third ventricle, with features suggestive for an optic pathway/hypothalamic glioma. Hormonal testing demonstrated normal pituitary function with no diabetes insipidus. Initial steroid treatment with dexamethasone provided partial improvement of vision and interruption of deterioration. The case was reviewed by a Skull Base MDT and accordingly, the patient underwent a right sided pterional craniotomy in September 2024 and partial resection of suprasellar lesion with intraoperative neuro-monitoring including visual evoked potentials. The microsurgical procedure was recorded with a high-definition images, demonstrating the tumour appearances of a mixed density lesion and multiple fragments were collected for pathological analysis. The early postoperative visual function was overall stable compared to the vision prior to surgery. The integrated histopathology and molecular analyses confirmed a papillary craniopharyngioma WHO grade 1, B-RAF p.V600E mutated. The patient was initiated on a targeted monoclonal treatment combining vemurafenib and cobimetinib, BRAF/MEK inhibitors. The patient had an improvement in vision and the repeat MRI head from January 2025 demonstrated early response to treatment. In conclusion, the case presented demonstrate the relevance of the recent changes in the clinical management of suprasellar lesions, for which currently a pathological molecular confirmation is a cardinal step to guarantee the best oncological and functional outcomes.

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EP1160

JOINT2584

Peripheral precocious puberty leading to central precocious puberty due to ovarian sex cord stromal tumor with annular tubules (SCTAT)

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Objective
Sex cord tumor with annular tubules (SCTAT) is a rare type of sex cord stromal ovarian tumor. We report an 8-year-old female who presented with peripheral precocious puberty (PPP) evolving to central precocious puberty (CPP) after excision of right ovarian tumor due to SCTAT.
Method
Single case report.
Results
She was seen in the endocrine clinic at 6 years and 8 months. She developed thelarche at 5 years and 2 months, pubic hair at 6 years, and vaginal bleeding at 6 years and 7 months. Mid parental target height is 152.3 cm. Pertinent physical examination showed height 134.2 cm (99%), weight 32.7 kgs (98%), Skin: small 0.5 cm irregular café au lait macule on the right buttock, and GU: Tanner IV breast development, Tanner 3 pubic hair. Endocrine evaluation showed LH <0.005 mIU/ml, FSH $<$ 0.3 mIU/ml, estradiol level 121.7 pg/ml, DHEA-S sulfate 37 mg/dl, Anti-Mullerian Hormone 34.3 ng/ml (normal 0.256-6.34), β-HCG $<$ 2 Miu/ml, TSH 0.63 uU/ml, Free T4 1.16 ng/dl, inhibin B 1,250 pg/ml (normal $<$182 pg/ml). Bone age X-ray of the left hand was 10 years. Pelvic ultrasonography showed uterus 6.8 $\times$ 2.7 $\times$ 4 cm and endometrium 12 mm in thickness. The right ovary measured 6.2 $\times$ 3.3 $\times$ 3.5 cm with a 2 $\times$ 4.3 $\times$ 6 cm right ovarian cyst. The left ovary measured 2.6 $\times$ 1.4 $\times$ 1.7 cm. Bone scan was negative for fibrous dysplasia. CT of the abdomen and pelvis showed right ovarian complex cystic mass. CT of the chest was negative for metastasis. She underwent right oophorectomy at 6 years 11 months. Pathology was consistent with right ovarian SCTAT with focal areas with Sertoli cells and juvenile granulosa- like appearance with classification of FIGO 1A without need for adjuvant therapy. Repeat tumor markers were normal. At follow up at 7 1/2 years, she was Tanner 5 breasts and 4 pubic hair. She had CPP with serum LH 1.4 mIU/ml, FSH 6.5 mIU/ml, and estradiol level 12.7 pg/ml. Bone age X-ray of the left hand was 11 years. She was treated with a GnRH agonist.
Conclusion
Most children with SCTAT present with PPP. Our patient progressed to CPP after right oophorectomy necessitating treatment with a GnRH agonist. Close monitoring of pubertal status and hormonal evaluation after surgery is important to detect evolution of potential CPP and manage this appropriately.

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EP1161

JOINT2554

BMI impacts on quality of life and endocrine complications in patients with non-functioning pituitary adenomas – A prospective study in patients before and after transsphenoidal surgery

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Background
Whether Body mass index (BMI) impacts on surgical outcomes and complications in patients with non-functioning pituitary adenomas (NFPA) who undergo transsphenoidal surgery (TSS) has not been explored.
Objective
To assess the influence of BMI on quality of life (QoL) and surgical complications in patients with NFPA.
Methods
Before and 12 months after TSS, BMI, endocrine function, QoL (EQ-5D visual analogue scale (EQ-VAS)), peri- and postoperative complications were assessed in 122 consecutive patients with NFPA. A 5% body weight change was considered significant.
Results
The mean preoperative BMI was 27.9 $\pm$ 4.9, 42 (34%) patients had BMI <25, and 37 (30%) had BMI >30 kg/m^2. Preoperative hypogonadotropic hypogonadism (HH) was more common in patients with BMI >30 compared to those with BMI <25, 57% vs 33%; $P = 0.044$. High BMI was not associated with any perioperative complications. At 12 months after TSS the mean BMI was unchanged (27.9$\pm$5.3, $P = 0.53$), but 19 patients (16%) had lost weight and 17 (14%) had gained weight. A larger portion of patients with BMI >30 had growth hormone (GH) deficiency and HH compared to patients with BMI <25, 70% vs 45%; $P = 0.036$, and 57% vs 26%; $P = 0.01$, respectively. A larger portion of patients who gained weight had central hypothyroidism and adrenal insufficiency compared with those who had lost weight, 71% vs 26%; $P = 0.018$ and 53% vs 11%; $P = 0.010$, respectively. The median EQ-VAS score increased in patients

with BMI <25 from 70.0 (Interquartile range (IQR) 53-80) to 80 (65-93); $P = 0.008$, and in patients who lost weight, from 70 (40-80) to 85 (65-94); $P = 0.007$. In patients with BMI >30, EQ-VAS did not improve (70 [40-85] to 80 [63-90]; $P = 0.426$), nor in patients who gained weight (75 [60-90] to 80 [58-90], $P = 0.460$).
Conclusions
High BMI is common in patients with NFPA and is associated with preoperative HH and postoperative HH and GH deficiency. Adrenal insufficiency and central hypothyroidism occur more frequently in patients who gain weight after TSS. High BMI and increased body weight are associated with less improvement of QoL.

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EP1162

JOINT730

Recurrent primary pituitary abscesses in a young girl: a rare clinical challenge

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Recurrent primary pituitary abscesses are exceptionally rare in paediatric populations. They pose significant diagnostic and therapeutic challenges, often requiring a multidisciplinary approach for effective management. We report the case of a 14-year-old female who presented with vomiting and a year-long history of progressively severe headaches. This was associated with polyuria, polydipsia, and a five-month history of secondary amenorrhea. Neurological examination was unremarkable with no abnormalities in visual acuity, colour vision, or visual fields. There was a past medical history of autoimmune hypothyroidism, associated with raised TPO antibodies. Magnetic resonance imaging (MRI) of the head demonstrated a suprasellar lesion impinging on the optic chiasm with restricted diffusion. Investigations revealed normal prolactin (472 mIU/L), IGF-1 (23.7 nmol/L), cortisol (415 nmol/l)and gonadotrophins with undetectable oestradiol. She underwent transsphenoidal decompression, during which caseous yellow purulent material was encountered. Histopathology revealed non-neoplastic anterior pituitary tissue with acute inflammatory exudate, consistent with a pituitary abscess, and no evidence of adenoma. Postoperatively, she received a two-week course of intravenous antibiotics and six weeks of oral antibiotics. Further investigations excluded sarcoidosis and tuberculosis. Post-operatively, she developed diabetes insipidus (serum osmolality 296 mOsm/kg, urine osmolality 93 mOsm/kg), managed with sublingual desmopressin. Hydrocortisone was initially started but stopped after confirming normal adrenal axis on a short synacthen test (SST). Menstrual cycles resumed within a month. Three months postoperatively, she developed recurrent headaches. MRI showed a cystic sellar lesion with slight stalk deviation, suggesting recurrence. A second transsphenoidal surgery six months later revealed chronic inflammation consistent with a ruptured Rathke cleft cyst. No antibiotics were given postoperatively, and cortisol response to SST was satisfactory (peak cortisol of 618 nmol/L). Seven months later, severe headaches recurred. MRI demonstrated an enlarging sellar cystic lesion, necessitating a third surgery. Histology revealed a mixed inflammatory process. The lesion was treated as a pyogenic abscess with six weeks of intravenous Ceftriaxone and Meropenem. Recovery was favourable, with no further recurrences. Postoperative endocrine evaluations were satisfactory with normal cortisol on SST. She remains on levothyroxine for autoimmune hypothyroidism and desmopressin for diabetes insipidus. A nine-month follow-up MRI showed abscess regression, and she remains asymptomatic 13 months post-surgery. This case underscores the complexities of diagnosing and managing recurrent pituitary abscesses in adolescents. The literature suggests that infectious pituitary abscess usually requires prolonged broad-spectrum intravenous antibiotics. Early recognition, prolonged intravenous antibiotics and vigilant follow-up are essential to prevent recurrences and optimise outcomes.

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EP1163

JOINT1685

Germinoma of the suprasellar region: 2 cases report

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Introduction
Intracranial germinomas is a rare and hardly distinguishable malignancy, it presents 3% of brain tumours in children and adolescents. The clinical presentation primarily depends on the tumor's location, size, and the patient's age. This report presents a 2 cases of suprasellar germinomas.
Case presentation
Case 1: A 13-year-old patient with no significant medical history consulted at the emergency department for intracranial hypertension syndrome, ptosis, strabismus of the left eye by bilateral visual acuity decline, polyuria and polydipsia. Brain MRI revealed lesional formation in the sellar region extending suprasellarly, measuring 21×18×16 mm, in contact with the cavernous sinus and both internal carotid arteries, it infiltrates the optic chiasm and the terminal part of the right optic nerve. Additionally, there is a lesion in the mesencephalic tegmentum and pons, surrounded by edema, measuring 26×15 mm, along with a pineal gland formation measuring 14×11 mm, consistent with an extended germinoma with triple localization. Hormonal tests showed thyrotropic and corticotropic deficiencies (8 a.m. cortisol :1.54 µg/dl, FT4 :7.7 pmol/l(range: 9- 19 pmol)); FSH<0.1mIU/ml, LH: 0.1 mUI/ml. The study of tumor markers in the cerebrospinal fluid (CSF) and the biopsy of the tumor was indicative of a germinoma. **Case 2:** A 12-year-and-11-month-old patient complained of intermittent headaches for 1 year, associated with polydysptic polyuria, diplopia and recent weight loss, as well as intermittent constipation. Three months later, the clinical presentation worsened with signs of increased intracranial pressure. Brain MRI Imaging revealed a bifocal lesion measuring 53×34 mm, predominantly suprasellar, infiltrating the midbrain and extending to the pineal region. It had intimate contact with the optic chiasm, both middle cerebral arteries, and infiltrated the floor of the third ventricle, as well as the midbrain and pineal region posteriorly. Hormonal assessment revealed: FSH: 0.1 mIU/ml; LH: <0.1 mIU/ml; PRL: 100 ng/ml, FT4: 7.13 pmol/l(range: 9- 19 pmol), 8 a.m cortisol: 2,26µg/dl. The analysis of CSF supported the diagnosis of a germinoma.
Discussion/Conclusion
Suprasellar germinomas typically present with hypothalamic-pituitary dysfunction, most commonly manifesting as diabetes insipidus (DI). Endocrine disturbances appeared well before the onset of neurological symptoms and DI. Early diagnosis is essential and should be based on a rigorous evaluation of the patient's medical history, hormonal profile, laboratory results, and radiological findings. Early recognition is critical, as timely radiation and/or chemotherapy can significantly improve tumor outcomes.

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EP1164

JOINT2010

Ventriculoperitoneal shunting and diabetes insipidus

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Introduction
Hydrocephalus is a complication resulting from an obstruction in the cerebrospinal fluid pathway, and is frequently observed in encephalic tumors. Symptomatic treatment consists of cerebrospinal fluid bypass, either ventriculo-peritoneal or external. Diabetes insipidus is a rarely reported complication of ventriculoperitoneal shunting. We report a clinical observation of transient diabetes insipidus complicating the placement of a ventriculoperitoneal derivation (VPD).
Clinical Case
Sixteen years-old female patient, admitted for investigation of a 15-day history of cerebellar syndrome associated with intracarnal hypertension. A cerebral CT scan revealed a lesional process in the posterior cerebral fossa responsible for tri-ventricular hydrocephalus with incipient involvement of the cerebellar tonsils. This was confirmed on brain MRI, showing a process at the expense of the cerebellar vermis. Workup noted Na: 137 mmol/land K: 3,8 mmol/l. The patient initially benefited from a Ventriculo-Peritoneal shunt, then underwent psoter-omedian surgery with macroscopic subtotal excision of a friable hemorrhagic non-encapsulated mass with removal of VPD. The histological study is in progress. After surgery and during her stay in the intensive care unit, the patient

presented a polyuropolydipsic syndrome with 6.8 l in and 6.54 l out, with clear and hypotonic urine. Urinary osmolarity was at 188 mosm/land Na at 145 mmol/l. At this stage the diagnosis of diabetes insipidus was evoked. Monitoring of the water balance was intensified, with progressive and spontaneous regression of the input-output values, with urine concentration becoming normal at day 12 post-shunt.
Discussion
Treatment of hydrocephalus saves countless patients, but CSF bypass procedures are sometimes responsible for complications of varying severity. The most common complications reported in the literature are infection, hemorrhage and shunt valve migration. Diabetes insipidus was rarely described. The pathogenic mechanism behind this complication is that when the 3rd ventricle is dilated to a large extent, the shunt valve's position at its floor impinges on the hypothalamus and pituitary stem, exerting a mass effect on ADH neurons, when compression is reversible, diabetes insipidus would be transient, another mechanism is a distortion of the V3 wall with pituitary compression. This was the case in our patient, whose diabetes insipidus spontaneously regressed following removal of the VPD.
Conclusion
Transient diabetes insipidus is a rare complication of CSF shunts for the treatment of tumor-induced hydrocephalus. This fact should be borne in mind in order to detect this manifestation and institute any necessary therapeutic measures.
Key words
hydrocephaly, ventriculoperitonel derivation, insipidus diabetes.
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EP1165

JOINT1210
Clinical features of primary empty sella
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Introduction
Empty sella is a radiological finding characterized by herniation of the subarachnoid space into the sella turcica, leading to a reduction in pituitary gland thickness. It can be classified either as primary, if no preceding pituitary pathology is known or as secondary to pituitary disorders, treatment affecting the sellar region and brain injury. Primary empty sella may result from increased intracranial pressure or insufficiency of the sellar diaphragm. Factors contributing to this condition include obesity, hypertension, multiple pregnancies and female sex. The aim of this study was to characterize clinical features of primary empty sella.
Methods
We retrospectively analysed clinical data of 76 patients diagnosed with primary empty sella at the Department of Endocrinology, Metabolism and Internal Medicine in Poznan between 2011 and 2023.
Results
The majority of the cohort were women (58/76, 76%). Mean age of the diagnosis was 51 (SD 15.42) years. Partial empty sella (51/76, 67%) was more prevalent than complete empty sella (25/76, 33%). The symptoms leading to diagnosis included headaches (27/76, 35%), vertigo (6/76, 8%), irregular menstruation (4/76, 5%), recurrent syncope (3/76, 4%) and visual disturbances (2/76, 3%). Additionally, 9% (7/76) were diagnosed during evaluation of pituitary insufficiency, and 35% (27/76) were incidental findings. Obesity was present in 43% (33/76) of patients and overweight in 33% (25/76). Diabetes was diagnosed in 14% (11/76), while prediabetes was observed in 28% (21/76). A significant proportion of the cohort exhibited dyslipidaemia (43/76, 57%). Hypertension was also prevalent, affecting 53% (40/76) of patients. Hypopituitarism was diagnosed in 17% (13/76) of patients. The most common pituitary deficiency was hypogonadotropic hypogonadism, which was observed in 11 cases. Notably, two men had a history of anabolic steroid use, suggesting alternative potential cause for hypogonadism. Two or more pituitary hormone axes were affected in 77% (10/13), and among these, 90% (9/10) exhibited complete empty sella on MRI. Additionally, hyperprolactinemia was present in 5% (4/76) of patients.
Conclusions
Primary empty sella occurs predominantly in women with abnormal body weight and commonly presents with headaches. Hypertension, glucose intolerance and dyslipidaemia are frequently observed. A significant proportion of patients exhibit pituitary dysfunction, often with multiple axes involved, especially when complete empty sella is diagnosed. A substantial prevalence of metabolic comorbidities and hypopituitarism highlights the need for comprehensive evaluation and management in this patient population.
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EP1166

JOINT2344
Metabolic disorders and prolactin-secreting adenomas in men
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Introduction
Prolactinomas are the most common pituitary tumors. Beyond their well-documented endocrine effects, these tumors are also associated with metabolic complications that warrant careful evaluation and management.
Methods
We conducted a descriptive and analytical study involving men diagnosed with prolactin-secreting adenomas and followed at the Endocrinology and Diabetology Department of Hedi Chaker University Hospital in Sfax between January 1, 2000, and December 31, 2023. Our focus was to evaluate the metabolic effects of hyperprolactinemia in these patients.
Results
In a population of 36 men, metabolic syndrome was identified in 27.8% of cases, with overweight reported in 36.11% and obesity in 32.84% of patients. The mean waist circumference (WC) was 100.67 $\pm$ 19.21 cm. Body mass index (BMI) was positively correlated with prolactin levels, although this did not reach statistical significance in our study (rho $=$ 0.141, $P = 0.410$). However, no correlation was found between WC and prolactin levels. Regarding the metabolic effects of hyperprolactinemia, 7 patients (19.4%) were prediabetic, 3 patients (8.3%) were diabetic, and 20 patients (55.6%) presented with dyslipidemia, predominantly mixed dyslipidemia (25%). The mean total cholesterol (TC) level was 4.99 $\pm$ 1.61 mmol/l,with extremes ranging from 1.42 mmol/lto 8.8 mmol/L. Hypercholesterolemia was observed in 5 patients (13.9%). The mean LDL cholesterol level was 1.23 $\pm$ 0.49 g/l,with extremes ranging from 0.5 g/lto 2.49 g/l,and elevated LDL cholesterol was reported in 5 patients. The mean HDL cholesterol level was 1 $\pm$ 0.29 mmol/l,with extremes ranging from 0.41 mmol/lto 2.04 mmol/l,while low HDL cholesterol levels were observed in 2 patients. The mean triglyceride (TG) level was 1.90 $\pm$ 1.06 mmol/l,with extremes ranging from 0.5 mmol/lto 5.04 mmol/L. Hypertriglyceridemia was noted in 4 patients (11.1%). Our findings revealed positive correlations between prolactin levels and TC (rho $=$ 0.186, $P =$ 0.277), LDL cholesterol (rho $=$ 0.258, $P = 0.134$), and triglycerides (rho $=$ 0.022, $P = 0.901$). However, no relationship was identified between fasting blood glucose and prolactin levels in our cohort.
Conclusion
Metabolic syndrome represents a significant complication of prolactin-secreting adenomas in men. Its presence highlights the need for comprehensive evaluation and targeted management strategies to mitigate its impact on long-term health outcomes. Addressing these metabolic disturbances is essential for optimizing the overall care of patients with prolactinomas.
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EP1167

JOINT453
Pituitary macroadenoma in the menopause may be a prolactinoma?
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In women, prolactinomas are usually diagnosed between 20 and 40 years old, they are not frequently detected in postmenopausal women because they do not usually present symptoms of hyperprolactinemia as the ovarian function has stopped. There are scarce published data on their presentation and prognosis. The prevalent symptoms in this age are tumor mass effects. The exact incidence of prolactinomas in postmenopausal women is unknown.
Objective
Assess the clinical symptoms, biochemical and imaging findings at presentation, follow-up and the outcome in a cohort of postmenopausal women with prolactinomas.
Material and Methods
Retrospective, multicenter study in Argentina between 2014-2024. Nine patients with prolactinomas diagnosed in menopause were evaluated. The following

patients' data were recorded: age at last menstruation, age at prolactinoma diagnosis, adenoma size (mm), visual field, treatments performed, and biochemical determinations. For the statistical analysis, Infostat software was used. The results are expressed according to data distribution as median (Q1-Q3).
Results
The median age at diagnosis was 62 (60-68). The median age of the last menstruation was 47 (35-48); in 4 cases was reported before 40, 56% of patients had pregnancies before prolactinoma diagnosis. The most commonly symptoms at diagnosis were: headaches (2/9), and visual field defects (VFD) (5/9): 2 patients had bilateral hemianopsia, 1 had unilateral hemianopsia and 2 bilateral quadrantopsia; galactorrhea was present in 33%; 5/9 were incidental findings. Median serum prolactin was 1325 ng/ml (1000-2695), all patients had secondary hypogonadism (low levels LH, FSH and estradiol), 44% of the patients had other pituitary axes affected, the most frequent were thyroid and adrenal. Macroadenomas and cavernous sinus invasion macroadenomas were diagnosed in 56% and 44%, respectively. All the patients were treated with cabergoline, with doses between 1-4 mg/week, median treatment period was 60 (24-63) months. In the follow-up, 8/9 normalized prolactin levels, 7/9 women had reduction of the tumor size in more than 50 %, and tumor disappeared in the other 2. Most of these women (75%) normalized VFD.
Conclusions
In our series of patients with prolactinomas diagnosed in the postmenopausal period, the incidental finding at diagnosis of prolactinoma was more frequent compared to other publications. Almost half of the patients had the last menses in their fertile age, we can hypothesize that prolactinomas were present in that period but the diagnosis was made after menopause. All women treated with cabergoline had an excellent response in size reduction of adenomas, improved VFD and normalize prolactin levels.

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EP1168

JOINT1587

A hazard of transitional endocrine care

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A 25 year-old woman with childhood onset panhypopituitarism after surgery, cranial radiation and chemotherapy for a midline germinoma presented to a rural hospital in a low-middle income country with acute confusion and vomiting, which occurred during attendance at a party. Despite administration of appropriate parenteral stress dosing of glucocorticoids by her friend, improvement did not occur. Assessment suggested a presumptive diagnosis of gastroenteritis. She was initially managed with crystalloid intravenous fluid resuscitation, without recognition of her diabetes insipidus (DI). Serum sodium was reported as 114 mmol/L. Contact was made with an endocrinologist who advised cessation of intravenous fluids. With fluid restriction, hyponatraemia, confusion and vomiting resolved. Throughout her presentation she remained afebrile, had no diarrhoea, nor any other infective symptoms and recovered rapidly. On return home she subsequently stated that she thought her "drink may have been spiked". Although the evidence is presumptive that ingestion of 3,4-methylenedioxymethamphetamine (MDMA) is likely to have been involved, the case is important in that it demonstrates potential hazards that need to be navigated when negotiating transition to adult care for young adults who have complex disorders, and the need for awareness of drug and alcohol interactions that may have potentially catastrophic outcomes if not recognized. There have been multiple reports of hyponatraemia in MDMA users since it was first described in 1993, predominantly affecting females. To our knowledge, there are no reported cases of hyponatraemia following MDMA use in patients with DI. The mechanism for hyponatraemia following MDMA ingestion is thought to be multifactorial with proposed mechanisms including syndrome of inappropriate anti-diuretic hormone release; MDMA-induced polydipsia and dry mouth (with subsequent thirst and ingestion of hypotonic fluid); and recommendations to remain well-hydrated after MDMA use to counter-act the risk of dehydration from increased diaphoresis and hyperthermia all postulated as a possible contributors. In this case, the patient's DI excludes SIADH as an aetiology for her hyponatraemia and parenteral glucocorticoid administration was adequate. In conclusion, the case demonstrates an absolute need for meticulous transitional care and adequate advice for young adults with complex health issues for clinicians, both paediatric and adult.
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EP1169

JOINT3559

Validity of adult height prediction methods (bayley pinnaue charts and bonexpert) in indian children with idiopathic short stature

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Background
Adult height can be predicted using Bayley-Pinneau (BP) method and BoneXpert software. However, data comparing validity of these methods in Indian children is scarce.
Aim
To assess the accuracy of predicted adult height (PAH) in Indian children with idiopathic short stature (ISS) using BP method and BoneXpert software.
Methods
Children diagnosed with ISS and attending the Pediatrics OPD were identified from clinical records and contacted. Children with ISS and had achieved final adult height (FH) [closure of epiphyses/Bone Age (BA) $>$ 16 years (male)/$>$14 years (females)] were included, and those with non-availability of BA radiographs and birth weight $<$2kg were excluded. BA was calculated using GP atlas and BoneXpert software, and PAH was calculated using BP method and BoneXpert software. These PAHs were then compared with their actual FH to assess the accuracy of these prediction models.
Results
A total of 27 cases (12 males) (mean age: 13.7 $\pm$ 2.1 years in boys and 11.8 $\pm$ 2.2 years in girls) were enrolled for which BA was calculated using GP atlas and predicted adult height (PAH) using BP method. However, BoneXpert could be used for only 25 cases (11 males) as digital x rays were not available for 2 children. BA determination showed good correlation between GP method and BoneXpert (r = 0.85; P $<$0.001). BP method accurately predicted FH in 8 (6 girls) out of 27 cases with an accuracy of 29.6%. BoneXpert accurately predicted FH in 15 (8 females) out of 25 cases with accuracy of 60%. BoneXpert was more accurate than BP method in predicting adult height (P value = 0.027).
Conclusion
BoneXpert was more accurate than BP method in predicting adult height. Males had significantly greater difference in PAH using BP method compared to females.

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EP1170

JOINT871

Pre-treatment differentiation between non-functioning pituitary adenomas and prolactinomas based on serum prolactin levels

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Introduction
Non-functioning pituitary adenomas (NFPAs) can present with hyperprolactinemia, presumably due to the pituitary stalk effect. This makes it challenging to differentiate between NFPAs and prolactinomas. In turn, this negatively affects

the shared decision making process when choosing between primary dopaminergic treatment or transsphenoidal surgery. This shared decision making has increasing importance now that transsphenoidal surgery by an experienced surgeon is considered a valuable first line of treatment for prolactinomas. In the current position statement, elevated serum prolactin (PRL) levels above 250 µg/l(5.3 [IU]/L), around 11 times the upper limit of normal (ULN, set at 22 µg/l(0.47 [IU]/L)), are considered indicative of prolactinomas, whereas PRL levels of up to 150 µg/l(3.2 [IU]/l)in patients with NFPAs are attributed to the stalk effect.

Aim

To determine pretreatment cut-off values of PRL with the aim to differentiate between a prolactinoma and NFPA in patients with a radiological proven pituitary adenoma (PA) and elevated PRL.

Patients and Methods

Retrospective cohort study of patients who underwent transsphenoidal surgery between 2011 and July 2023. Inclusion criteria were 1) a histopathologically confirmed diagnosis of either a NFPA or a prolactinoma and 2) pretreatment elevated PRL levels and available pretreatment MRI. Peak PRL levels were converted to x times the local ULN to avoid standardisation differences between the used immunoassays. Diagnostic performance of peak PRL was analyzed using receiver-operating characteristics curves to calculate the area under the curve, and sensitivity and specificity. The reference standard was WHO 2017/2022 histopathological diagnosis of a (densely/sparsely granulated) lactotroph adenoma.

Pre-liminary results

Data of 80 patients (55 NFPAs and 25 prolactinomas) were analyzed. Median peak PRL levels in patients with a NFPA was 1.8 ULN (IQR 1.1, minimum 1.0, maximum 7.6). Median PRL levels in prolactinomas was 34.2 ULN (IQR 351.4, minimum 1.2, maximum 1140.0). Based on our pre-liminary results, not corrected for tumor volume, our suggested cut-off value of PRL to distinct between prolactinomas and NFPA with hyperprolactinemia ranges between 3.1 and 3.3 ULN (sensitivity range 88-92%, specificity range 80-84%).

Conclusion

Based on these preliminary results, a PRL level cut-off value of 3.1-3.3 ULN is suggested to distinct prolactinomas from NFPAs with hyperprolactinemia. This translates, based on a reference value of 22 µg/l(0.47 [IU]/L), to 68-73 µg/l(1.4-1.5 [IU]/L), substantially lower than the cutoff in the position statement. Additional analyses to evaluate the impact of tumor dimensions are ongoing.

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EP1171

JOINT2703

Radiological evaluation of central nervous system in children with gonadotropin-dependent precocious puberty

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Central precocious puberty (CPP) is caused by activation of hypothalamic-pituitary-ovarian axis. This leads to the appearance of secondary sexual characteristics in girls under 8 years of age, and in boys under 9 years of age. CPP must be determined on the basis of laboratory and imaging tests, and clinical examination.

The aim

of the study was to analyze the radiological changes of central nervous system (CNS) in MRI in CPP children treated with gonadotropin analogs (Triptorelin/Dipherelin) (aGnRH) in one endocrinology center.

The study group

consisted of 116 children with CPP: 96 girls (82.76%) and 20 boys (17.24%). Mean age of children was 6.77 ± 2.44 years. Significant changes in MRI were considered: pituitary enlargement, optic nerve glioma, hamartoma, pituitary malformation, hypoplasia of the corpus callosum, hydrocephalus, epileptic encephalopathy.

Results

CNS pathology was significantly more prevalent in boys (8/20; 40%) than girls (20/96, 20,8%). The most often diagnosed significantly important lesions of CNS were: enlargement of the pituitary gland/microadenoma (13), hydrocephalus (4), optic nerve glioma (3), hypothalamic hamartoma (3), pituitary deformity (2), gangliocytoma (1), corpus callosum hypoplasia (1), epileptic encephalopathy (1). Children with significant changes in MRI of the head were younger (girls 5.7 ± 2.5 and boys 4.86 ± 3.13) compared to children with a normal radiological image (girls 7.14 ± 2.24 and boys 7.41 ± 1.6). Clinically insignificant lesions included: pineal cyst (5), Rathke's pouch cyst (1), intermediate layer cyst (2), pituitary cyst (1), asymmetry of the sella turcica (1), mild downward displacement of cerebellar tonsils through the foramen magnum (1), and asymmetry of the left lateral ventricle (1). CNS significant pathology coexisted with the following diseases in our group: congenital adrenal hyperplasia (CAH, 2 boys), neurofibromatosis type I, (NF-1, 2 boys), epilepsy (1 girl), Silver-Russell syndrome during the rhGH therapy (1 girl), cerebral palsy (CP, 1 girl), McCune-Albright syndrome, (1 girl), panhypopituitarism (1 girl).

Conclusions

1. The frequency of significant abnormalities in the MRI of the head in our group of children with CPP is 24.1%.
2. Children with significant changes in MRI were younger at the time of diagnosis compared to children with a normal radiological image.
3. CPP is much more often diagnosed in girls in comparison to boys.

Keywords

gonadotropin-dependent precocious puberty, radiological imaging

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EP1172

JOINT479

Analysis of pituitary tumors in a single center in slovakia

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Background

Pituitary adenomas are the most common pituitary lesions. The prevalence of incidental pituitary adenomas ranges from 10% to 22%. In contrast, the prevalence of undiagnosed macroadenomas is very low, primarily due to their mass effects on nearby structures or their hormonal activity. Other, less common lesions are pituitary carcinoma, craniopharyngioma or Rathke's cleft cyst.

The objective

of this retrospective observational study was to evaluate the prevalence of pituitary tumors, as well as their demographic characteristics, treatment approaches, and clinical outcomes.

Methods and Results

In a single centre of the University Hospital, altogether 196 patients were diagnosed with pituitary tumors based on their laboratory and imaging results between 2009 and 2024 (106 women, 90 men, age 22–92 years). Of these, 125 patients were diagnosed with macroadenoma (63.8% vs. 68.7% in literature), 41 with microadenoma (20.9% vs. 10% in literature), 4 (2%) with picoadenoma, 5 (2.6%) craniopharyngiomas, 17 (8.6% vs. 13.1% in literature) Rathke's cleft cysts, and 4 (2%) other lesions, respectively. Surgical resection was performed in 103 patients (52.6%), and 11 (10.7%) of them required surgical revision. Additionally, 38 patients (19.4%) underwent radiation therapy. Histological analysis of resected macroadenomas revealed the following subtypes: 32 (38.6% vs. 22.8% in literature) nonfunctioning adenomas, 21 (25.3% vs. 21.8% in literature) gonadotroph adenomas, 18 (21.7% vs. 9.6% in literature) somatotroph adenomas, 5 (6% vs. 28.3% in literature) prolactinomas, 4 (4.8% vs. 9.4% in literature) corticotroph adenomas, and 3 patients (3.6%) with somatomammotroph adenomas. Based on hormonal secretion, 83 (66.4%) were non-functioning adenomas, growth hormone production was detected in 23 (18.4%), PRL secretion in 16 (12.8%), and ACTH secretion was demonstrated in 2 (1.6%) patients. One patient (0.8%) was diagnosed with concurrent PRL and GH secretion. Among microadenomas, 22 (53.6%) were non-functioning, 12 (29.2%) produced PRL, 5 (12.2%) GH, and 2 (4.8%) had ACTH, respectively. Overall, hypopituitarism developed in 77 patients (39.3% vs. 37–85% in literature). Gonadotropin deficiency was found in 26 (13.3% vs. 36–96% in literature), TSH deficiency in 55 (28.1% vs. 8–81% in literature), GH deficiency in 7 (5.6% vs. 61–100% in literature), and diabetes insipidus in 18 patients (9.2%). Hydrocortisone supplementation was required in 66 patients (33.7% vs. 17–62% in literature).

Conclusion

Among pituitary tumours, the most common are nonfunctioning adenomas. The prevalence of hypopituitarism was relatively high in our patients. Early diagnosis improves the clinical outcome of patients and may prevent irreversible pituitary destruction.

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EP1173

JOINT3540

Ectopic cushing's syndrome due to a pulmonary NET: diagnostic challenges and the need for a multidisciplinary approach

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Introduction
Cushing's syndrome (CS) is a rare disease, with 10–15% of cases caused by ectopic ACTH secretion. Clinical presentation ranges from mild to severe hypercortisolism with high mortality. The etiology includes well-differentiated neuroendocrine tumors (NETs) or undifferentiated tumors, complicating diagnosis and management. A multidisciplinary approach and advanced diagnostic techniques are essential. This case highlights the complexity of early diagnosis, comprehensive management, global support, and prolonged evaluation.
Objective
To describe a case of ACTH-dependent ectopic CS, emphasizing the integration of diagnostic methods and the importance of a multidisciplinary approach.
Case Report
A 34 year-old male with a history of anxiety-depressive disorder and progressive obesity was admitted for Fournier's gangrene requiring secondary intention wound closure. He developed severe hypokalemia (2.5mEq/l)resistant to treatment, new-onset Diabetes Mellitus (HbA1c 8.2%) requiring insulin therapy, and fluctuating psychiatric symptoms, including mutism and treatment refusal. PE revealed moon facies, dorsal fat pad, central obesity, violaceous abdominal striae, and significant proximal muscle weakness with generalized sarcopenia. CS was suspected and confirmed by endocrinological evaluation: - 24-hour urinary free cortisol: 3672.0µg/24h (normal 13-75µg/24h). - Serum cortisol: 22.80µg/dl (normal 5-25µg/dl). - Plasma ACTH: 89.95pg/ml (normal 10-50pg/ml). - Late-night salivary cortisol: 3.170µg/dl (normal $<$0.208µg/dl). Given the hypercortisolism severity, ectopic ACTH secretion was suspected.
Clinical Course
The patient was transferred to the ICU for hypokalemia management and psychiatric stabilization. Treatment with metyrapone and ketoconazole was initiated, rapidly escalating doses with a block-and-replace strategy using hydrocortisone. Spironolactone was added for hypokalemia and hypertension control. Thromboprophylaxis with heparin and antibiotic prophylaxis with TMP-SMX were implemented. Thoracoabdominopelvic CT revealed a 10$\times$15mm pulmonary nodule in the left lower lobe. 68Ga-DOTATOC PET/CT confirmed a high-uptake pulmonary nodule (SUVmax21.9), suggesting SSTR overexpression without metastases. A multidisciplinary team recommended surgery after hypercortisolism control. Nutritional support with high-protein supplements and rehabilitation were initiated. Following hypercortisolism control and clinical stabilization, left lower lobectomy was performed. Pathology confirmed a typical G1 pulmonary NET (WHO2021), 2cm in size, with clear surgical margins (Ki-67 1.7%). A supradiaphragmatic lymph node revealed metastatic typical carcinoid NET G1 with extracapsular extension (Ki-67 2.1%), pT1bN2. Immunohistochemistry was positive for TTF1, INSM1, chromogranin, synaptophysin, ACTH, and SSTR. Surgery allowed cessation of hypercortisolism treatment, where psychiatric symptoms corrected and Fournier's gangrene healed.
Conclusions
A multidisciplinary approach is essential for diagnosing and treating NET-associated CS. Advanced techniques such as 68Ga-DOTATOC PET/CT are crucial for early diagnosis. Management of complications are fundamental to successful treatment and patient recovery.

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EP1174

JOINT1499

A rare etiology of autoimmune hypophysitis

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Background
Chemotherapy is widely used to treat various cancers, but it can also result in a range of side effects, some of which are rare and underrecognized. Autoimmune hypophysitis, an inflammation of the pituitary gland, is an uncommon complication.
Case Report
A 47-year-old woman with a history of hypertension and breast cancer, treated with total mastectomy, adjuvant radiotherapy, and chemotherapy (cyclophosphamide, paclitaxel, and epirubicin), presented with palpitations. ECG showed a sinus tachycardia. A TSH test was ordered, revealing a low value of 0.06 µIU/ml, and she was referred to our endocrinology department. On examination, the patient was in a state of eucortisism, with a blood pressure of 14/10 cmHg, in an euthyroid state, without galactorrhea or exophthalmos. She has been menopausal for one year. Further tests showed a controlled TSH level of 1 µIU/ml, FT4 at 10 pmol/l(normal range: 7-16), morning cortisol at 44.5 µg/l,FSH at 72.1 mUI/ml, LH at 47.8 mUI/ml, and prolactin at 5.61 ng/ml. A Synacthen test confirmed adrenal insufficiency, and ACTH was measured at 13.5 pg/ml (normal range: 7-63), suggesting a central origin. The patient was started on hydrocortisone replacement. An MRI of the hypothalamo-pituitary region revealed a bulging aspect of the pituitary gland, with no focal lesions detectable, and a thin pituitary stalk, consistent with autoimmune hypophysitis.
Conclusion
This case report highlights a rare instance of chemotherapy-induced autoimmune hypophysitis, emphasizing the importance of early recognition and timely intervention.

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EP1175

JOINT2557

Calcitonin-secreting neoplasm of the lung: a case report

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Background
Calcitonin (CTN)-secreting neuroendocrine neoplasms of the lung are very rare tumors. Differentiating between medullary thyroid cancer and an ectopic source of calcitonin secretion is challenging. Abnormal calcitonin concentrations have been linked to extra-thyroidal sources in neuroendocrine neoplasms located in the pancreas, parathyroid glands, thymus, esophagus, lung, small intestine, adrenal glands, and bladder.
Case
A 54-year-old male patient presented with weight loss, nausea, vomiting, and back pain. He had no other disease and was not on any regular medications. Calcitonin was 1011 ng/l,and CEA was 3.8 ng/ml. Thyroid USG shows an iso-hypoechoic nodule measuring 21x23x24 mm in the right inferior posterior region, containing cystic degeneration areas and macrocalcifications. The nodule's fine needle aspiration cytology showed atypia of undetermined significance, and the CTN washout was negative. During chest and abdominal imaging, a mass measuring about 45x40 mm was found in the lower lobe of the right lung, and a 56x63 mm mass lesion that showed uneven enhancement was found in the right adrenal gland. Plasma metanephrine levels were normal. We referred him for an 18fluoro-deoxyglucose PET (18FDG-PET), which revealed normal metabolic activity throughout the thyroid. There was high uptake (SUVmax 14.39) within the 4.5 cm mass lesion located in the posterior lower lobe of the right lung and the 6.5 cm mass lesion in the right adrenal gland (SUVmax 10.77). A biopsy diagnosed the patient's lung mass as pulmonary neuroendocrine carcinoma. Malignant cells were positive for CD56, synaptophysin and calcitonin. Staining for chromogranin A and Napsin A was negative. The Ki-67 proliferation index was high at 70%. The medical oncology department initiated systemic chemotherapy. Follow-up imaging after chemotherapy showed progressive disease.
Conclusion
This case highlighted the complexity of the differential diagnosis of hypercalcitoninemia, more particularly the difficulty of distinguishing between medullary cancer and a tumor with ectopic calcitonin release. The different diagnoses are important since treatment and prognosis are different. The approach to hypercalcitoninemia requires a multidisciplinary one. It is important to perform a complete clinical evaluation of these patients so that ectopic calcitonin-secreting tumors are not overlooked.

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EP1176

JOINT4044

FIPA-AIP positive pituitary gigantism: post-surgical remission

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Introduction
Familial isolated pituitary adenomas (FIPA) are one of the most important inherited settings for pituitary adenomas and the most frequent genetic cause is a germline mutation in the aryl hydrocarbon receptor-interacting protein (AIP) gene. AIP mutations lead to young-onset macroadenomas that are di cult to treat. Most are growth hormone secreting tumors.
Clinical case
A 14-year-old male patient complained for insulin resistance and physiognomic changes throughout the last 2 years. His mother was diagnosed with acromegaly at the age of 16, cured after 2 surgeries and a short period of somatostatin analogues. On physical examination his height was 180,5 cm (+2.51 SDS), weight of 78 kg (+2,18 SDS), and Tanner stage IV. Target height was 172,25 cm -0.08 SDS (Δ H/TH: +2,6 SDS). The shoe size 42, and had acanthosis nigricans on the neck. Hormonal assessment revealed a basal GH of 21.5 ng/ml, a nadir post-glucose GH of 18.5 ng/ml, and IGF-1 of 556 ng/ml (Range age/sex: 211-512) (+ 3.97 SDS). Prolactin and testosterone levels were within the normal range, as well as the evaluation of the adrenal and thyroid axes. MRI showed a macroadenoma with mild suprasellar extension, and sphenoid sinus invasion, with no extension to cavernous sinuses. The patient was operated on by transsphenoidal approach without complications; the histopathology reported a sparsely granulated somatotropinoma, with Ki 67 of 10%. The AIP gene analysis performed using the MLPA technique, resulted positive for both the patient and his mother (Heterozygous missense pathogenic variant c.136G>T (p.Glu46*) Three months after surgery, IGF1 decreased to +0.31 SDS, with a random GH of 0.8 ng/ml; insulin levels normalized and the MRI did not show images of tumor remnant. Two years after surgery, the patient remained in remission, with a post-glucose GH nadir of 1 ng/ml and IGF1 < 1 UNL, and normal gonadal axis (IGF1: 399 ng/ml (+ 1,42 SDS) (57-426), Testosterone: 5 ng/ml). During follow-up there was a significant slowdown in growth velocity.
Discussion
This is a 16-year-old patient with familial acro-gigantism, AIP positive, operated on for a macroadenoma with histopathological markers of poor prognosis with a high chance of recurrence and aggressiveness. Two years after surgery, he presents biochemical remission markers, without tumor remnant and asymptomatic. Strict clinical, biochemical and imaging monitoring is necessary given the poor prognostic tumor markers and positive genetics.

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EP1177

JOINT3543

Transient arterial hypertension developed during therapy with triptorelin in a girl with central precocious puberty

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Introduction
Gonadotropin-releasing hormone analog (aGnRH) is used for the treatment of central precocious puberty (CPP) in childhood and has a good safety profile, with minimal side effects like menopause-like symptoms or local changes at the injection side. In the literature, there are a couple of case reports about the development of transient hypertension during aGnRH treatment.
Case report
We present a case of a girl with a fast progression of CPP with transient arterial hypertension developed during therapy with aGnRH. At the age of 8 years and 9 months, she was diagnosed in the Paediatric Endocrinology Department due to breast and pubic hair development before the age of 8 years. After LH-RH domination of LH was found, fast progression of breast development and advancement of bone age was observed, and bone age was 10 years. Her height was 135,8 cm (50-75pc), her weight was 32,5 kg (50-75pc), and her target height was 169 cm (50-75pc). Therapy with Diphereline SR was initiated. At the age of 8 years and 11 months, she started complaining of recurrent headaches and nose bleeding; BP was 135/85 mmHg at the beginning, with the progression to 155/104 mmHg six months later. In the abdomen ultrasound, double right kidney vessels were found. Hormonal profile with renin, aldosterone, and metoksycatecholamin were in the normal range. She was consulted with an ophthalmologist, and an eye fundus examination revealed no abnormalities. Heart image in echocardiography was proper, but LVMI was elevated at 39,46 (> 95pc for sex and age). In ambulatory blood pressure monitoring (ABPM), hypertension was diagnosed, and treatment with amlodipine was recommended; an initial dose was 2,5mg once a day. Although the treatment, BP was still above the normal range in home monitoring, and in ABPM, ACEI was added to the therapy. At the age of 10 years, due to the development of symptomatic hypertension with heart complications and due to mitigation of CPP progression, treatment with aGnRH was finished. After a month in ABPM, blood pressure was much below 50pc, and amlodipine was discontinued. After the following two months, due to BP values much below 50pc, ACEI was also discontinued. BP remains in the normal range.
Conclusions
Despite the good safety profile of aGnRH, hypertension could be a significant problem during therapy. Based on our case and other earlier reports, regular evaluation of BP should be a part of patient with CPP monitoring.

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EP1178

JOINT4043

Assessment of comorbidity resolution after long-term acromegaly remission

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Introduction
Acromegaly is a rare endocrine disorder associated with a wide range of comorbidities, including cardiovascular disease, metabolic disorders, and musculoskeletal complications. Surgical resection of the pituitary tumor is the primary treatment, and achieving long-term remission can significantly improve clinical outcomes. However, the impact of remission on pre-existing comorbidities and the development of new complications after surgery is variable.
Objective
This study aims to evaluate the resolution of comorbidities after achieving long-term acromegaly remission following surgical intervention.
Methods
Retrospective study of all surgically treated acromegaly patients followed at our center from 1992 to 2024. GH and IGF-1 levels were assessed to evaluate acromegaly remission. Resolution of each comorbidity was defined if it was controlled without requiring pharmacological treatment.
Results
Fifty-two patients with acromegaly were included, with 28 (54%) females. The mean age at diagnosis was 46 years, with a mean symptom duration of 6 years. The median follow-up was 7 years. Comorbidities were reported in most patients, including hypertension in 25 (48%), arthropathy in 16 (31%), type 2 diabetes (T2D) in 12 (23%), obstructive sleep apnea in 5 (10%) and colon polyps in 8 (15%). All patients underwent surgery and one-year postoperative biochemical remission was found in 21% of patients (8/39). Among patients who achieved remission, pre-surgery comorbidities included dyslipidemia in 38% (3/8), hypertension in 50% (4/8), T2D in 25% (2/8), and obstructive sleep apnea in 25% (2/8). Currently, with a mean follow-up of 10 years, resolution of comorbidities was observed in 33% (1/3) for dyslipidemia, 100% (2/2) for T2D, and 100% (2/2) for obstructive sleep apnea. No new comorbidities developed during follow-up.
Conclusions
Treating patients with acromegaly may improve associated comorbidities such as T2D, obstructive sleep apnea and dyslipidemia. Nevertheless, only a limited number of comorbidities can show full reversibility, emphasizing the need for early diagnosis and intervention to prevent long-term complications.

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EP1179

JOINT2449

Usefulness of serial prolactin measurement to confirm the presence of hyperprolactinemia

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Introduction
Hyperprolactinemia is a frequent cause of referral to endocrinology outpatient clinics, which is due to many causes (physiological, pharmacological, pathological). Once some have been excluded, many studies recommend performing a serial prolactin measurement to rule out stress hyperprolactinemia, although it isn't standardised. Objective: to evaluate the usefulness of serial prolactin measurement to confirm hyperprolactinemia diagnosis.
Materials and Methods
Descriptive study of 60 patients who underwent serial prolactin measurements between the years 2023-24 in follow-up in our clinics. Demographic (sex, age) and analytical (basal prolactin, at 20 and 40 minutes) variables were collected. Regarding the measurement, a peripheral intravenous line was inserted and a baseline, at 20 and at 40 minutes value was taken. It was established that prolactin was elevated above 20 (men) or 25 (women). The statistical analysis was performed with the IBM SPSS v.25 programme (Statistical significance $P < 0.05$).
Results
60 patients were analysed, 80% women with a mean age of 31.1 $\pm$ 14.7 years. 66.7% and 70% showed normal prolactin values at 20 and 40 minutes, respectively. Basal and 20-minute prolactin and basal and 40-minute prolactin means difference were 4 $\pm$ 7.1 and 6.5 $\pm$ 10.8, with a statistical significance of 0.01 in both.
Conclusions
In most patients, prolactin levels become normal after 20 and 40 minutes of sampling, after removing other confounding factors that may lead to stress hyperprolactinemia. A statistically significant difference is also observed between baseline, at 20 and at 40 minutes values. This demonstrates the usefulness of the measurement to rule out stress hyperprolactinemia, as well as to avoid redundant complementary tests and avoid unnecessary worries for the patient.

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EP1180

JOINT4016

Prevalence of sexual dysfunction in patients with pituitary disease: insights from the international DREAMS survey study

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Background
Sexual well-being is a complex process that involves both mental and physical aspects, influencing quality of life. Pituitary dysfunction is often associated with sexual dysfunction due to its critical role in regulating hormones involved in sexual health. In this patient group, sexual dysfunction may include impacts on sexual satisfaction, intimacy, function and fertility, significantly affecting quality of life. Despite its importance, there are limited systematic evaluations of sexual dysfunction across different subtypes of pituitary dysfunction. Therefore, this survey aimed to assess the prevalence and severity of sexual dysfunction in patients with pituitary disorders.
Methods
This cross-sectional, web-based, anonymous survey was designed by endocrinologists to evaluate sexual well-being, including aspects of sexual desire, behavior, and function, in adult patients with pituitary dysfunction. Participants were categorized into four groups: isolated anterior pituitary dysfunction (APD), isolated posterior pituitary dysfunction (arginine vasopressin deficiency, AVP-D), combined anterior and posterior pituitary dysfunction (Panhypopituitarism, PHP), and those with pituitary conditions without hormonal deficiency or excess (e.g., non-functioning pituitary adenomas). A Mean Global Index of Sexual Dysfunction (range: 0–3) was calculated using the Sexual Behavior Questionnaire. Sexual desire was assessed separately for dyadic (partnered) and solitary (individual) contexts using the Sexual Desire Inventory (SDI-2), with total scores ranging from 0 to 78, where higher scores reflect stronger desire. Total scores were compared between groups and adjusted for sex, age, and comorbidities.
Results
Between August and October 2024, 326 patients participated in the survey. The median age was 51 years [42–60], with 79% female participants, and the median duration of pituitary dysfunction was 8 years. Participants were categorized as follows: APD (44%), AVP-D (18%), PHP (26%), and non-hormonal pituitary disorders (12%). The most common etiologies were pituitary tumors or cysts (62%). 51% of patients were undergoing hormone replacement, while 28% had hormone excess. Sexual dysfunction and low sexual desire (median range: 20, [42–60]) were highly prevalent across all subgroups, with reference values of 38-42 in a healthy population. The highest severity was reported in patients with PHP. Sexual dysfunction was significantly correlated with sex, hormonal deficiencies, and comorbidities.
Conclusion
Sexual dysfunction is a prevalent and clinically significant issue in patients with pituitary dysfunction, affecting all subtypes. These findings highlight the importance for routine assessment and targeted treatment in this patient population. Further research is needed to better understand the underlying mechanisms and identify effective therapeutic approaches.

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EP1181

JOINT2753

A case of leydig cell tumor presenting with peripheral precocious puberty

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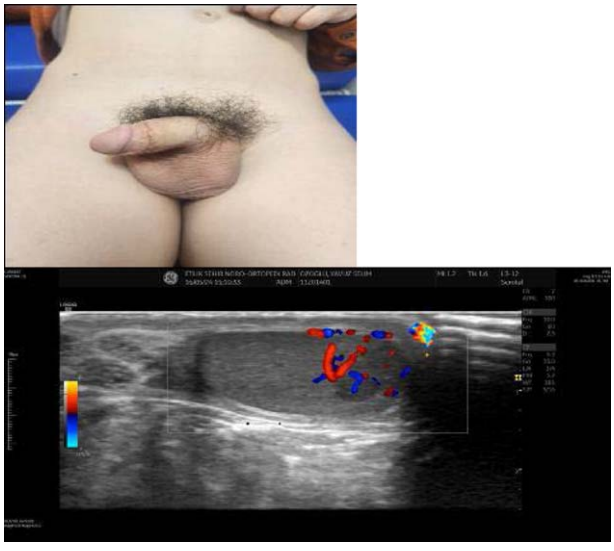
Introduction
Leydig cell tumors are sex cord-stromal gonadal tumors originating from Leydig cells. Although rare, accounting for 1-3% of all testicular tumors, they are the most common hormone-secreting testicular tumors. These tumors have been found to be associated with peripheral precocious puberty. In this study, we present a case of Leydig cell testicular tumor in a patient presenting with peripheral precocious puberty. **Case:**A 5-year-and-12-month-old male patient presented to our outpatient clinic with complaints of pubic hair growth. His medical history revealed that he had no known chronic illnesses, hospitalizations, or medication use. On physical examination, his height was 125.2 cm (2.64 SDS), body weight was 32.9 kg (3.22 SDS), body mass index was 20.99 kg/m^2 (2.66 SDS), and target height was 175 cm (-0.19 SDS). His genetic alignment was +2.83 SDS. The right testis measured 6 mL, the left testis measured 4 mL, and his stretched penile length was 7 cm. Pubic hair was noted at Tanner stage 3, and axillary hair was also present (Image 1). The patient's complete blood count, biochemistry, and thyroid function tests were normal. His FSH was <0.3 IU/l(0.2-2.1), LH was 0.36 IU/l(0.1-1.3), total testosterone was 301 ng/dl (2.5-32), and AFP and β-HCG were negative. His bone age was consistent with 11 years. Scrotal imaging showed the right testis measured 24$\times$14$\times$14 mm, the left testis measured 15$\times$10$\times$11 mm, and a lesion with increased vascularity was noted in the



right testis parenchyma, measuring 14x7x12 mm, presenting as a hypoechoic area resembling a mass (Image 2). An LH-RH stimulation test revealed a peak LH of 0.85 IU/land peak FSH of 1.21 IU/l,which was consistent with peripheral precocious puberty. The patient underwent a frozen-section guided right testis preserving mass excision, and the pathological diagnosis was Leydig cell tumor consisting of large, eosinophilic, and granular cytoplasm cells, measuring 1.2 cm in diameter. The surgical margins were reported as intact. Follow-up scrotal and abdominal ultrasonography performed one month later were normal, and subsequent gonadotropin tests showed FSH: 4.72 IU/l(0.2-2.1), LH: 3.89 IU/l(0.1-1.3), and total testosterone: 108 ng/dl (2.5-32). Considering the possibility of central precocious puberty, GnRH analog treatment was started.

Conclusion

Leydig cell tumors are a cause of peripheral precocious puberty, and these patients typically present with a testicular mass, pubic hair growth, elevated testosterone, and low gonadotropin levels. Scrotal imaging is essential in these cases. With testis-preserving surgery, the prognosis is generally favorable, but patients should be carefully monitored for the potential development of central precocious puberty.

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EP1182

JOINT3595

The association of neutrophil/HDL ratio, plasma atherogenic index and several cardiovascular risk scoring systems in acromegaly

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Acromegaly is associated with an increase in cardiovascular risk factors and cardiovascular disease mortality, and endothelial dysfunction. Acromegaly is also associated with subclinicasl inflammation. There is growing interest in indices derived from complete blood count due to the small cost and easy accessibility. Research has shown that Neutrophile-leucocyte ratio and platelet- leucocoyte ratio are higher in acromegalic patients compared to non-functioning pituitary adenomas. The neutrophil to HDL-cholesterol ratio (NHR) is a composite marker reflecting inflammation and lipid metabolism. NHR is a strong predictor of cardiovascular disease in many studies. To date, there are no studies of NHR in acromegaly. In this study, we aimed to determine hematological markers and the relationship between cardiovascular risk scores in acromegalic patients and healthy controls.

Methods

We retrospectively evaluated the hematological markers and lipid profiles of acromegaly patients and healthy controls. We calculated SCORE-2 and Framingham risk scoring systems and SCORE-DM system for diabetics. The patients with established cardiovascular disease were excluded.

Results

126 of the 204 patients were acromegaly and 78 were age and gender matched controls. There was no significant difference in Framingham and SCORE risk scores, neutrophile-leucocyte ratio(NLR), platelet-lymphocyte ratio (PLR) atherogenic index of plasma (AIP), neutrophile-HDL ratio(NHR) and platelet HDL ratio(PHR)between acromegaly and control groups. According to the remission status, the studied parameters did not show statistically significant difference. In the acromegaly group GH levels were positively correlated with SCORE risk (r^2:0.303, $P = 0.01$)IGF-1 levels showed a weak positive correlation with NHR(r^2:0.202, $P = 0.028$).

Discussion

We failed to demonstrate any significant difference in CBC derived indices of inflammation in acromegaly patients. Further studies indicating the effects of treatment modalities along with other indices of atherosclerosis are needed to determine the role of CBC derived parameters in acromegaly and atherosclerosis.

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EP1183

JOINT2634

Impact of somatostatin analogues on glycaemic control in patients with neuroendocrine tumours: a retrospective observational study

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Introduction

Long-acting somatostatin analogues (SSAs), such as Octreotide and Lanreotide remain the main stay of medical management of Neuroendocrine tumours (NETs). SSA use has been observed to impact glucose homeostasis based on results from randomised clinical trials. Although, there are only a limited number of studies which have appraised evidence from real-world clinical practice related to long term impact of SSA on glycaemic control.

Objective

The primary objective of our retrospective observational study was to evaluate impact of long acting SSA on glycosylated haemoglobin (HbA1c) which remains the most commonly used parameter to analyse glycaemic control.

Methodology

By using South Wales NET tertiary clinic electronic data base, we identified all the patients with confirmed diagnosis of NET who were initiated on SSA analogues from year 2014-2024. The NET patients were further sub-divided into 2 sub-groups: with or without Diabetes (prior to initiation of SSA therapy). The baseline clinical and biochemical parameters were recorded with focus on capturing data related to glycaemic control. Changes in body weight, medication dose and/or regimen and HbA1C levels were evaluated post initiation of SSA therapy.

Results

We identified 98 patients ($n = 98$) with confirmed diagnosis of NET who were initiated on SSA therapy from year 2014-2024. 80 of these NET patients were not known to have diabetes prior to initiation of SSA therapy. It was interesting to note that 12 (15%) out of these 80 NET patients, developed diabetes on long term follow up as evidenced by increase in HbA1C to $\geq$ 48 mmol/mol (mean HbA1c increase by 10.1 mmol/mol). The mean duration (post SSA initiation) for developing diabetes in this cohort was 27 months. In the other sub-group of 18 patients who were known to have diabetes prior to SSA initiation, 14 were observed to have an increase in HbA1c levels by an average 16.3 mmol/mol. Across the entire cohort, a mean HbA1C increase of 4.1 mmol/mol was documented post-SSA treatment.

Conclusion

Our retrospective observational study data suggests that long term SSA use in patients with NET has a modest detrimental impact on glycaemic control in patients with or without pre-existing diabetes. The sub-group of patients with pre-existing diabetes being initiated on SSA therapy need to be counselled about importance of self-monitoring of blood glucose (SMBG) levels. In case the SBMG readings reflects sub-optimal glycaemic control, a close liaison with primary and secondary care diabetes services can improve clinical outcomes.

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EP1184

JOINT2631

A case report on timely surgical intervention in pituitary apoplexy and cavernous sinus invasion

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Introduction

Pituitary apoplexy is a rare but potentially life-threatening emergency characterized by sudden haemorrhage or infarction of the pituitary gland requiring immediate medical attention. The urgency is heightened when cavernous sinus invasion is present as this significantly increases the risk of neurovascular compromise and other severe complications. Here we present a case of pituitary apoplexy complicated by cavernous sinus invasion which was successfully managed with transsphenoidal surgery. This highlights the critical importance of early surgical intervention in achieving favourable outcomes and preventing complications such as cranial nerve damage, carotid artery injury, and cavernous sinus thrombosis.

Case Presentation

A 50-year-old male presented with a 1-day history of severe headaches, vomiting, and right-sided ptosis. Initial investigations including blood tests and imaging were conducted to rule out other emergencies. Laboratory results showed IGF-1 of 113 ng/ml, prolactin of 86 ng/ml, cortisol of 41 nmol/l,TSH of 3.43 mIU/l,T4 of 5.8 µg/dl, LH of 12 IU/l,and FSH of 11 IU/L. An MRI revealed a well-circumscribed pituitary mass in the right paracentral region with invasion into the right cavernous sinus, measuring 3x2x1.5 cm. The patient's medical history included excess alcohol intake and type 2 diabetes mellitus. The patient underwent transsphenoidal surgery without complications leading to the resolution of right-sided ptosis. Postoperatively, he is on hormone replacement therapy with levothyroxine, testosterone and hydrocortisone.

Conclusion
Pituitary apoplexy complicated with cavernous sinus invasion warrants prompt surgical decompression to prevent neurovascular compromise of important structures as well as control bleeding within the cavernous sinus. Left untreated pituitary apoplexy with cavernous sinus invasion can lead to serious complications. The literature supports that immediate surgical decompression, coupled with hormone replacement therapy is essential for optimal patient recovery and long-term prognosis.
Questions for discussion
- Should surgical intervention be done as an emergency or electively?.
- If there is recurrence, would you advocate for further surgical intervention?.
- What is an appropriate timescale for follow-up for this patient?.

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EP1185

JOINT2651

Surgical management of pituitary adenoma: a single-centre experience

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Introduction
A pituitary adenoma is a tumour of the pituitary gland and is further classified by their size, cell type and hormone secretion. Microadenoma when the tumour is < 1cm and macroadenoma > 1cm. This is further classified if they are functioning (producing excess hormone) or non-functioning (no hormonal excess). Cell types include Prolactinoma, somatotroph, corticotroph, thyrotroph, and gonadotroph. In rare cases can also get malignant tumour. Around 1 in 10 people will develop pituitary adenoma in their lifetime. Treatment depends on the type of pituitary adenoma and includes medication, surgery and radiation therapy. Prolactinomas are the most common type of pituitary adenoma in the UK (40-60%) and then are non-functionating tumours.
Aim
of this study was to look at the diagnosis and surgical management of pituitary adenomas referred at Queen's Hospital, London, UK (BHRUT–Barking, Havering and Redbridge University Hospitals NHS Trust) in 2015-2022 (7 years).
Method
Retrospective single-centre study looking at patients referred for surgical management of pituitary adenoma between 2015-2025.
Results
55 patients were identified of which 42% female and 58% male. The age of presentation was more common in the age range of 71-80years (35%) and the least common was age range 31-40years (11%). Majority of the pituitary adenomas that underwent surgical intervention were functioning (65%), whereas 20% were non-functioning and rest compromised of malignancy or apoplexy. The most common functioning type of pituitary adenoma was gonadotroph (50%), then acromegaly 20% and least common in general was malignancy 5%. Corticotroph releasing were 15% and prolactinoma were 7.5%.
Conclusion
Our single-centre study showed that majority of pituitary adenoma referred for surgical intervention were functioning of which most common was gonadotroph and second most common was acromegaly. It is important that the hormone profile and imagining is done in a timely manner and if symptoms are worsening then to timely refer patient for surgical intervention when medical management is resolving the symptoms. This helps present complications and provides a better patient outcome. A Multidisciplinary (MDT) approach is vital and is individualised for each patient.

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EP1186

JOINT2595

A retrospective study of clinicopathological features of growth hormone and prolactin co-secreting pituitary tumors

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Co-secretion of growth hormone (GH) and prolactin occurs in approximately 25% of GH-secreting tumors. Monomorphic expression of a single cell type producing both GH and prolactin occurs in the mammosomatotroph adenoma (MSA), while dimorphic expression of two cell types separately secreting GH and prolactin occurs in the mixed somatotroph-lactotroph adenoma (MSLA). Compared to pure GH-secreting adenomas, co-secreting adenomas are associated with younger age, larger tumor size, greater tumor invasion, and more frequent presurgical hypopituitarism. We retrospectively reviewed the medical records of patients at our medical center with a histopathological diagnosis of MSA ($n = 19$) or MSLA ($n = 3$) following surgical resection from 2021 to 2024. The mean age at surgery was 48 years and 64% were female. Preoperative symptoms included headache (68%), irregular menses (60%), acromegalic features (59%), arthralgias (45%), and visual disturbances (36%). Comorbidities included hyperlipidemia (59%), glucose intolerance (45%), colon polyps (45%), thyroid nodules (41%), hypertension (36%), obstructive sleep apnea (36%), and carpal tunnel syndrome (27%). Preoperatively, the average prolactin level was 53 ng/ml, GH level 17 ng/ml, and IGF-1 level 856 ng/ml. Radiographically, the majority were macroadenomas (91%) with cavernous sinus invasion in 45%, suprasellar extension in 41%, and optic chiasm compression in 23%. T2-hypointensity was noted in 27%. Tumor size did not correlate with IGF-1 levels. All tumors stained positive for GH, prolactin, and PIT-1. Somatic mutations in GNAS were detected in 32%. Resection was subtotal in 7 cases (32%). The postsurgical remission rate was 50%. The frequencies of postoperative hypogonadism, hypothyroidism, and adrenal insufficiency were 27%, 18%, and 45%, respectively, with recovery in 17% and 25% for hypogonadism and adrenal insufficiency, respectively. There was one case of postoperative total anterior hypopituitarism and no cases of permanent AVP deficiency. With regards to methylation data, the identified pituitary adenoma classes were pituitary adenoma, STH densely granulated, group B ($n = 14$), pituitary adenoma, STH sparsely granulated ($n = 5$), pituitary adenoma, TSH ($n = 2$), and pituitary adenoma, STH densely granulated, group A ($n = 1$) with a positive calibrated score (>0.9) in 82%. Both cases of pituitary adenoma, TSH class were associated with a score below threshold. To our knowledge, this is the first study examining the different methylation classes in GH and prolactin co-secreting tumors. Further investigation is needed to better characterize these co-secreting adenomas and how they differ both from their pure GH-secreting counterparts as well as amongst themselves to guide prognosis and management with consideration for tumor methylation data as a potential tool.

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EP1187

JOINT877

Clinical results in an aggressive coricotroph adenoma with a unique molecular expression profile expressing high levels of different oncogenic splicing variants (SSTR5TMD4, In1-ghrelin and GHRH-R)

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Silent corticotrope pituitary adenomas (SCPAs) comprise approximately 20% of all corticotrope adenomas and 3-19% of non-functioning pituitary adenomas (NFPAs), and are considered high-risk pathologies. Therefore, appropriate treatment decisions and a close follow-up should be tailored to improve patient outcomes. A 43-year-old male patient with fatigue, decreased libido, frontal headaches, right eye strabismus and ptosis was referred to our Endocrinology Department due to an invasive giant pituitary tumor in November 2022. MRI revealed a large sellar-mass with invasion of both cavernous sinus with right dominance and progression towards the sphenoid sinus, and ethmoidal cells on the right and clivus [diameter: 70 mm anterior-posterior, 73 mm cranio-caudal, and 57 mm transversal; pituitary stalk presented slight displacement to the left]. Transcranial surgery was conducted to decompress the optical nerve of the right eye, with improvement in visual acuity, ptosis and headaches. Post-surgery lab tests revealed normal TSH, FT4, cortisol, prolactin, IGF-I levels, but low LH, FSH and total free and bioavailable testosterone levels. A second surgery (transsphenoidal) was performed and pathological report showed a neoplastic

proliferation that infiltrated the stroma below the pavement cells with some intraluminal tumor emboli, increase in the mitotic number and absence of necrosis. Immunostaining and molecular studies showed: CK++, SYN+++, CK8.18++ with perinuclear rings, P53++, KI 67<1%, ACTH isolated positivity and negative prolactin/GH/TSH/LH/FSH/TSH/FSH and PIT 1, but T-PIT positive ++ nuclear and GATA 3 positive +++ in all cells. Moreover, tumor sample expresses high POMC levels (ACTH-precursor), DR1 (only dopamine-receptor subtype significantly expressed) and GHRH-R. Interestingly, oncogenic splicing events of key genes were significantly expressed in tumor sample, including high expression of the splicing-variant of the SSTR5 with 4 transmembrane-domains (SSTR5TMD4; no expression of other SSTRs was found), and of In1-ghrelin and GHRH-R spliced-variants. Due to the extensive tumor persistence, we decided to begin Temozolomide in a multidisciplinary-session, but no response was found after receiving 4-cycles. PD-L1 expression and Microsatellite instability were negative. Then, Stereotactic Fractionated radiotherapy was performed. MRI showed slight decrease of the tumor size. Current treatment: cabergoline 2 mg/week, hydrocortisone and testosterone, being tumor stable and the patient is being closely followed-up. The treatment of aggressive NFPAs is a challenge because patients usually need combined therapies such as multiple surgeries, radiotherapy and oncologic drugs. Molecular studies are necessary to identify tumors' features to select adequate treatments. Oncogenic splicing variants expressed in this tumor might be associated to the aggressive-features found in this patient.

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EP1188

JOINT21

A fifteen-year-old boy with GH/PRL-secreting pituitary neuroendocrine tumor without excessive height growth

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We have experienced a case of a fifteen-year-old boy with a past history of congenital hydrocephalus and past surgeries for spina bifida and myelomeningocele, who was referred to our department for the assessment of elevated IGF-1. The patient had been receiving a regular check-up at the neurosurgery department at our hospital, and a swelling of the pituitary gland was detected during a routine brain MRI but was considered a physiological change. At the age of fifteen, he developed chest pain, and upon examination at the local hospital, anterior mediastinum tumor and elevated IGF-1 level were found. After undergoing surgery for the tumor, further investigation was conducted for elevated IGF-1 at our department. He showed no excessive height, but he had enlarged hands and feet, and protruding brow bone and lower jaw. Brain MRI identified a nodular lesion in the pituitary with a low signal on T2-weighted imaging, and endocrinological evaluation was performed with several loading tests. Oral glucose tolerance test (OGTT) showed lack of growth hormone (GH) suppression. Thyrotropin-releasing hormone (TRH) stimulation test revealed elevated serum GH concentrations, and bromocriptine stimulation test resulted in a reduction of serum GH concentrations. Additionally, LHRH stimulation test showed an exaggerated LH/FSH response. We diagnosed him with acromegaly caused by an excessive GH production from the pituitary tumor, and transsphenoidal adenomectomy was performed. Pathological examination revealed PIT1-positive tumor cells, while TPIT and SF-1 were negative. Densely granulated GH secreting cells and sparsely granulated prolactin (PRL) secreting cells were detected, leading to the diagnosis of GH/PRL secreting pituitary neuroendocrine tumor (PitNET). Three months after surgery, a follow-up OGTT was conducted, and serum GH concentration was suppressed to normal range. Although elevated GH levels in childhood often leads to gigantism, our patient had no excessive height. We presume that this was because GH elevation occurred during adolescence when his bone maturation was nearly complete. Despite the exaggerated LH/FSH response, no secretion of LH/FSH was pathologically proved in the tumor cells. High LH and FSH levels may have been due to hydrocephalus, which can cause compression of the third ventricle, leading to GnIH suppression. While there are few reports on the coexistence of PitNET with other tumors, we found no cases of PitNET occurring with mediastinum tumor. This could be a rare case, and we plan on conducting further investigations.

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EP1189

JOINT1733

Late onset isolated corticotrope deficiency induced by pembrolizumab

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Introduction
Pembrolizumab is a monoclonal anti-programmed death receptor-1 (PD-1) antibody that suppresses T-cell function. While it has gained approval for the treatment of numerous cancers, it is crucial to recognize the potential for serious immune-related adverse events, particularly concerning the endocrine system. Few cases of pembrolizumab-induced isolated corticotrope deficiency were reported in the literature. Herein, we report a new case of a late isolated corticotrope deficiency induced by pembrolizumab.
Observation
A 74-year-old woman was referred to the Department of Endocrinology for secondary adrenal deficiency. Her medical history was notable for hypertension, hypertrophic cardiomyopathy, cervical surgery for primary hyperparathyroidism, and lobectomy for non-small-cell lung carcinoma. Following a recurrence of her lung cancer, she underwent three chemotherapy regimens, including Carboplatin, Alimta, and pembrolizumab. Nine months post-initiation of chemotherapy, she presented with asthenia, weight loss, nausea, and vomiting. On physical examination, the patient had a weight of 69 kg, a height of 1.63 m, corresponding to a body mass index of 25.97 kg/m^2, an orthostatic hypotension, and a diffuse abdominal tenderness. The rest of examination was normal. The diagnosis of corticotrope deficiency was established based on a significantly low cortisol level of 28 nmol/lwith a low ACTH level of 4.9 ng/L. Other pituitary hormone levels were normal, confirming the diagnosis of isolated corticotrope deficiency. Magnetic resonance imaging (MRI) of the pituitary gland appeared normal, showing no tumors. The posterior lobe bright spot was intact, and the pituitary stalk was median and thin. The patient was treated with hydrocortisone and responded positively to the therapy.
Discussion
Corticotrope deficiency represents a potentially life-threatening complication of pembrolizumab treatment. Its clinical presentation can often be non-specific, as reported in this case. Previous reports indicate that the median onset of corticotrope deficiency following pembrolizumab administration is approximately 12 weeks. However, late-onset cases, including those occurring after the discontinuation of the drug, have also been documented. Regular monitoring of adrenal function is therefore essential during treatment and following the last dose of pembrolizumab.

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EP1190

JOINT68

The pituitary stone: a rare prolactinoma find

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Introduction
Pituitary calcifications, though rare, pose diagnostic and therapeutic challenges. These lesions, frequently associated with prolactin-secreting adenomas, can present with varied clinical manifestations and often require multimodal management. This report highlights the clinical, biochemical, and imaging findings in a young female patient with a pituitary calcification, along with a review of therapeutic approaches.
Case Presentation
A 26-year-old woman, heterozygous for sickle cell disease, presented with bilateral milky galactorrhea persisting for three months. Her menstrual cycles were regular. Clinical examination confirmed provoked galactorrhea. Biochemical evaluation showed hyperprolactinemia at 38 ng/ml, confirmed on two subsequent measurements, and decreased free thyroxine (FT4) at 0.74 ng/dl, while the remaining pituitary hormonal panel was normal. MRI of the hypothalamic-pituitary region revealed a calcified anterior pituitary lesion measuring 3.7 × 3 mm, consistent with pituitary lithiasis. The patient was started on cabergoline (Dostinex) and levothyroxine replacement therapy, with plans for reevaluation after three months.
Discussion
Calcifications within the pituitary gland are rare, often linked to prolactinomas or other adenomas. They can impede tumor shrinkage despite appropriate medical

management. Cabergoline remains the first-line therapy for hyperprolactinemia, effectively reducing prolactin levels and ameliorating symptoms. Imaging plays a pivotal role in distinguishing calcified adenomas from other entities such as Rathke's cleft cysts or craniopharyngiomas. Histopathological analyses frequently reveal amyloid and calcium deposits, suggesting chronicity or degenerative processes.
Conclusion
The case underscores the importance of integrating clinical, biochemical, and imaging findings for accurate diagnosis and management of pituitary calcifications. Dopamine agonist therapy, complemented by hormonal replacement where necessary, remains the cornerstone of treatment. Longitudinal follow-up with imaging and biochemical monitoring is essential to assess therapeutic response and guide management in such rare cases.

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EP1191

JOINT838

Meningeal syndrome revealing craniopharyngioma of the sellar region: a case report

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Introduction
The most frequent clinical manifestations of sellar craniopharyngiomas are endocrinological disturbances or symptoms from masse effect such as visual impairment, headache, and rarely signs of intracranial hypertension. However, rare cases in the literature have been described mimicking a febrile meningeal syndrome, often in the context of an infected meningeal breche but rarely amicrobial due to meningeal irritation.
Case presentation
Patient aged 34, admitted to emergency initially for a febrile meningeal syndrome with intracranial hypertension consisting of vomiting, headache, fever between 39-40°C, with meningeal stiffness evident on clinical examination. As part of the emergency management following a lumbar puncture following a normal cerebral CT scan, the patient was immediately put on antibiotics while awaiting the results of additional tests which confirmed the biological infectious syndrome through an increase in CRP and white blood cells with a predominance of neutrophils. After transfer to the infectious diseases department, these tests were supplemented by cerebral MRI angiography, which revealed a sellar and supra-sellar lesional process measuring 22*20*35.8 mm, initially suggesting a cystic craniopharyngioma. Antibiotic therapy was discontinued in view of the normal results of the puncture and a progressive and spontaneous improvement in the paraclinical parameters. A posteriori and after stabilisation of the patient, we reconstructed her medical history revealing a tumour syndrome evolving for 4 months with amenorrhoea for 2 years, supported by the hypopysogram which had revealed panhypopituitarism with corticotropic insufficiency substituted first, thyreotropic insufficiency subsituted 72 hours later and gonadotropic insufficiency.
Discussion
It is commonly accepted that they are either diagnosed based on the presence of abnormal endocrinological secretion or by the compression of a surrounding structure. However, enlargement of a sellar craniopharyngioma can reach the meningeal structures, causing breaches with rinorrhea that can become infected and lead to true meningitis, or more rarely, simple irritation mimicking aseptic meningitis with meningeal syndrome, as in our patient in whom the pituitary adenoma had caused febrile meningeal syndrome.

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EP1192

JOINT343

Treatment of acromegaly patients with resistance to first-generation somatostatin receptor ligands (fg-SRLs)

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Among monohormonal densely&sparsely granulated somatotrophic tumors (DGSTs&SGSTs), SGSTs are more difficult to treat, as they are marked by invasive growth, recurrent course and refractoriness to drug therapy (DT) with fg-SRLs. Prioritized and undifferentiated use of fg-SRLs without considering ST receptor status inevitably leads to low efficacy of DT and negative life prognosis of patients with SGSTs.
Aim of this study
To investigate the reasons for low efficacy of fg-SRLs monotherapy and efficacy of combined administration of fg-SRLs&pegvisomant (PEG) for achieving acromegaly control.
Materials and methods
We retrospectively analyzed the efficacy of secondary DT of fg-SRLs in 62 acromegaly patients with a verified morphologic diagnosis who received prolonged forms of octreotide (20-30mg/28days) and lanreotide (120mg/28-56days). Based on final IGF-1 index (II) value, all patients were divided into 2 groups with II ≤ 1 [group 1(30 patients)] and >1 [group 2(32 patients)].
Results
In both groups patients did not differ in age of diagnosis [42.2 $\pm$ 12.2 vs. 41.0 $\pm$ 11.2 years($P = 0.68$)] and duration of treatment [31.1 $\pm$ 20.1 vs. 31.5 $\pm$ 19.0 months($P = 0.9$)]. In group 2 (resistant) patients had larger baseline II [3.1 $\pm$ 0.9 vs. 2.4 $\pm$ 0.8($P = 0.0025$)], larger residual tumor volume [1.9 $\pm$ 3.4 vs. 0.5 $\pm$ 1.3cm^3($P = 0.0391$)] and higher final II [1.7 $\pm$ 0.6 vs. 0.8 $\pm$ 0.2($P < 0.0001$)] compared to group 1. Low percentage of IGF-1 level reduction after 3-6 months of treatment in patients of group 2 [28.2 $\pm$ 22.0&26.6 $\pm$ 23.0% vs. 57.0 $\pm$ 22.6&61.3 $\pm$ 20.7%($P < 0.0001$)] is also different compared to patients of group 1, which indicates key importance of STs selective receptor sensitivity factor to fg-SRLs. In group 2 immunohistochemical analysis revealed high presence of patients with SGSTs [72%(23) vs. 37%(11); $P = 0.0075$], lower SSTR2 expression [7.1 $\pm$ 4.0 vs. 9.1 $\pm$ 3.7 scores(IRS); $P = 0.0479$], lower SSTR2/SSTR5 ratio [1.5 $\pm$ 1.2 vs. 3.4 $\pm$ 3.1($P = 0.0025$)] and higher proportion of cells with fibrous bodies [2.6 $\pm$ 0.8 vs. 2.1 $\pm$ 0.9 scores($P = 0.024$)] compared to group 1. Regarding cellular composition of STs, tumors from chromophobic cells were predominant in group 2 [69%(22) vs. 23%(7); $P = 0.0006$], tumors from intermediate-type cells were observed less frequently [25%(8) vs. 50%(15); $P = 0.046$] and tumors from eosinophilic cells were even less frequent [6%(2) vs. 27%(8); $P = 0.0285$] compared to group 1. To control acromegaly, patients in the resistant group were treated with combined therapy of fg-SRLs&PEG (18.4 $\pm$ 8.8mg/day) for 6-55 months, as a result of which 73% of patients achieved biochemical remission in the absence of significant adverse events. The final II value decreased from 1.7 $\pm$ 0.6 to 0.97 $\pm$ 0.4($P < 0.0001$).
Conclusions
1. Among the reasons for insufficient efficacy of fg-SRLs monotherapy high secretory activity, specificity of cellular composition of STs and low SSTR2 expression should be emphasized. 2. Combined use of fg-SRLs&PEG in refractoriness to fg-SRLs monotherapy contributes to achievement of biochemical remission in 73% of cases.

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EP1193

JOINT982

Indexes of liver steatosis and fibrosis in metabolically associated fatty liver in hypopituitarism

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Aim
To investigate relationship between insulin resistance, hepatic steatosis and fibrosis in hypopituitarism.
Patients and Methods
Study included 282 hypopituitary patients (136 women and 146 men) aged 49.2 $\pm$ 15.1 years, body mass index 27.9 $\pm$ 5.8 kg/m^2, $n = 140$ (49.6%) due to non-functioning pituitary adenoma.
Results
Fatty liver on ultrasound was obesrved in 20.6% ($n = 58$). The metabolic syndrome (MetS), defined by IDF criteria, was present in 57.1% ($n = 161$) and 48.6% ($n = 137$) using NCEP ATP III. The LAP (171.8 $\pm$ 150.1 vs 54.6 $\pm$ 39.4, $P < 0.001$) and FLI (15.7 $\pm$ 15.5 vs 4.9 $\pm$ 9.8, $P < 0.001$) were significantly higher in patients with hypopituitarism and fatty liver, compared to those with

		Fatty liver						*P* value
		N	Mean	SD	Median	Perc. 25	Perc. 75	
FIB4	No	111	1.24	.87	1.10	.70	1.50	0.327
	Yes	41	1.25	.56	1.20	.90	1.60	
BARD score	No	109	2.28	.89	2.00	2.00	3.00	0.732
	Yes	37	2.35	1.06	2.00	2.00	3.00	
LAP	No	79	54.58	39.41	46.50	25.40	71.40	<0.001
	Yes	32	171.78	150.17	122.55	87.57	203.05	
FLI	No	64	4.87	9.85	1.17	.60	4.05	<0.001
	Yes	29	15.71	15.46	10.05	2.70	24.70	

hypopituitarism alone., while fibrosis scores FIB4 and BARD were not significiantly different between the two groups. Signifficant corellations were found between fatty liver disease, MetS and steatosis indexes LAP and FLI ($P <$ 0.001), but not with fibrosis indexes BARD and FIB4. HOMA IR and Matsuda index were siginificantly higher in patients with fatty liver compared to those with hypopituitarism alone and highly correlated with fatty liver findings on ultra sound, and steatosis indexes LAP and FLI ($P <0.001$), but not with indexes of liver fibrosis BARD i FIB4.

Conclusion

Indexes of fatty liver correlated with insulin resistance and ultrasound finding of fatty liver in patients with hypopituitarism, while no such correlation was observed with indexes of liver fibrosis. Liver steatosis but not fibrosis is fueled by insulin resistance and metabolic syndrome in patients with hypopituitarism.

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EP1194

JOINT2384

Therapeutic challenges in male patients with prolactin-secreting pituitary adenomas

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Introduction

The management of prolactin-secreting pituitary adenomas in men presents unique challenges due to their frequent late diagnosis and aggressive presentation, especially in cases of macroprolactinomas or giant prolactinomas. This study aimed to evaluate therapeutic approaches and their outcomes in male patients with prolactinomas.

Methods

We conducted a retrospective, descriptive, and analytical study of 36 men treated for prolactin-secreting adenomas at the Endocrinology and Diabetology Department of Hedi Chaker University Hospital, Sfax. Treatment modalities included dopamine agonists, surgery, and radiotherapy, with assessments of their clinical, biological, and radiological responses.

Results

From a therapeutic perspective, 20 patients (62.5%) were treated with dopamine agonists alone, 12 patients (37.5%) underwent surgical excision combined with dopamine agonists, and 4 patients (11.1%) had undergone surgical excision at the time of diagnosis without any association with medical treatment, either before or after the surgical procedure. However, radiotherapy was not indicated for any patient in our study cohort. Regarding disease progression, 17 patients (47.22%) had regular follow-up with good therapeutic adherence, with an average follow-up duration of 49.27 $\pm$ 59.17 months, ranging from 1 to 180 months. Among them, 11 patients (30.56%) achieved remission, and 6 patients (16.67%) had a favorable outcome. Of those who achieved remission, 3 patients (27.27%) experienced a late relapse. However, no patient had an early recurrence. Treatment resistance was only observed in 3 patients. We investigated the effectiveness of dopamine agonists (DA) in reducing prolactin levels and controlling tumor volume. We demonstrated that, regardless of tumor size, Cabergoline is more effective in achieving normal prolactin levels at lower to medium doses when compared to Bromocriptine. However, we could not identify any statistically significant correlation between the different therapeutic approaches and their effect on tumor volume ($P = 0.440$). For patients who achieved clinical remission, they had a significantly smaller average tumor volume ($P = 0.008$) and a lower initial prolactin level ($P = 0.031$) compared to those with a favorable progression or post-treatment resistance.

Conclusion

The management of prolactin-secreting adenomas in men remains challenging due to frequent resistance to medical therapy, tumor aggressiveness, and treatment-related complications. While dopamine agonists are highly effective in most cases, surgery is indispensable for resistant or complicated tumors. Long-term follow-up is crucial to monitor recurrence and manage persistent complications.

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EP1195

JOINT1558

Endocrine-related adverse events in patient receiving combined immune checkpoint inhibition – a case report

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Introduction

In recent years, immune checkpoint inhibitors (ICI) have emerged as a powerful innovative therapeutic strategy in the treatment of various types of cancer. They exert their effect by targeting the immune response towards malignant cells, blocking the usual inhibitory pathways of T-cell regulation, thereby allowing T-cell mediated destruction of cancer cells. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or its associated ligand (PD-L1) are major immune checkpoints that serve as targets for inhibition.

Case report

A male with known type 2 diabetes mellitus on treatment with metformin, SGLT-2 inhibitors, and GLP-1 receptor agonists, was diagnosed with poorly differentiated non-small cell lung carcinoma (T2N3M0) at 45 years of age. After chemotherapy and radiotherapy, immunotherapy with Ipilimumab (CTLA-4 inhibitor) and Nivolumab (PD-L1 inhibitor) was initiated. After the 5th cycle of immunotherapy, laboratory and imaging findings indicated autoimmune thyroiditis with hormonal constellation suggestive of secondary hypothyroidism (TSH 0.818 mIU/L; FT4 6.7 pmol/L; anti-TPO 68.97 IU/ml (<12)). Levothyroxine treatment was started with gradual dose titration up to 100 mg. After the 6th cycle of immunotherapy, the patient reported general fatigue, easy tiring with minimal physical effort, and dizziness. Laboratory tests revealed evidence of immune-mediated hepatitis and hypoglycemia, and hormonal analysis showed uncontrolled hypothyroidism and secondary hypocorticism, but with no data of hypogonadism and hyposomatotropism (ACTH <5.00 pg/ml, Cortisol 08:00h: 22.22 nmol/L; TSH 61.05 uIU/ml, FT4 5.69 pmol/L; LH 8.38 mIU/ml; FSH 6.48 mIU/ml; Total testosterone 12.5 nmol/L; Growth hormone 0.27 ng/ml (0.05 - 3.0); IGF-I 154.0 ng/ml (48 - 209)). MRI of the pituitary shows mild general non-homogeneity of the gland, suggestive of hypophysitis. Treatment with intravenous methylprednisolone at a dose of 20 mg daily was initiated until clinical stabilization, followed by oral hydrocortisone with gradual dose reduction to 20 mg daily. Additionally, after initiating corticosteroid replacement therapy, the dose of Levothyroxine was increased to 150 mg and switched to liquid form.

Conclusions

Immune checkpoint inhibitors have rapidly become an integral part of many cancer treatment regimens. These new drugs can significantly improve survival rates for several forms of cancer. However, these benefits come with the cost of autoimmune side-effects (especially when immunotherapy is combined) that affect a number of tissues, including the endocrine glands. Keywords: cancer, checkpoint inhibitors, autoimmune side-effects, endocrine glands.

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EP1196

JOINT2524

Anterior pituitary deficiencies: a descriptive study in a pediatric hospital in cameroon

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Background

Anterior pituitary deficiencies can be isolated or combined, affecting single or multiple hormonal axes, often congenital. The clinical description varies based on the deficient hormones, and prevalence in Cameroon is not well-known.

Methodology
We conducted a retrospective descriptive study by examining 27 patient records followed at the Mother and Child Center of the Chantal Biya Foundation in Yaoundé, Cameroon. We analyzed the circumstances of discovery, anthropometric parameters during the first endocrinology consultation, the affected axes, and hormonal results when they were available. The data were recorded and analyzed using Microsoft Excel 2010.
Results
The median age of our participants was 16 [12.5–21] years, with a male predominance of 74%. In 59.3% of cases, children were brought to consultation by parents after an average symptom evolution duration of 3 [5–13] years. The reasons for consultation included short stature (78%), hypoglycemia (7.4%), and convulsions. The median age at diagnosis was 9 [1–4] years. Severe stunted growth was observed in 74% of cases, with a mean parental target height of 171 cm. Underweight was noted in 35% of cases, and severe malnutrition in 18.5% of cases. Hormonal assays were not always completed, with 37% of cases showing isolated GH deficiency and 63% showing multiple combined anterior pituitary deficiencies. The deficient axes included somatotropic (66.6%), corticotropic (22.2%), thyrotropic (25.9%), and gonadotropic (22.2%). No genetic diagnosis was made in any of the cases. Among the patients, only 33% had their cortisol levels measured, 40.7% had their FT4 levels measured, 37% had their IGF-1 levels measured, and 18.52% had their growth hormone levels measured. FSH/LH levels were measured at 18.5%, and bone age was assessed in 37%. The average bone age was 8.2 $\pm$ 3.19 years.
Conclusion
Anterior pituitary deficiencies are diagnosed late in our context. Parents raise the alarm when stunted growth is severe. In a context where hormonal assays are costly, emphasis should be placed on clinical surveillance and early warning. There is an interest in the genetic diagnosis of anterior pituitary deficiencies in our country.
Keywords
Hypopituitarism, growth delay, clinical diagnosis delay, Cameroon.
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EP1197

JOINT1922

Adrenal crisis after missed diagnosis of pituitary sarcoidosis: a case report

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Sarcoidosis is a disease characterized histologically by multiple non-caseating granulomata without a clear infectious or toxic trigger, with an unclear aetiology. The prevalence of sarcoidosis in the Middle East population is not well known. The clinical features of patients with sarcoidosis in the Middle East appear to be like that reported in the world with female predominance than males. In many cases, the diagnosis of sarcoidosis was made based on intrathoracic biopsy. Neurosarcoidosis (NS) is a rare form of sarcoidosis, with hypothalamic-pituitary involvement being uncommon. We report a 27-year-old man presenting with nausea, vomiting, diarrhoea, abdominal pain, weight loss, bilateral neck swellings and generalized fatigue. The patient was admitted to the hospital for suspected acute gastroenteritis. He further developed mental confusion, arterial hypotension (90/60 mmHg), and hypokalaemia (2.6 mmol/L). Initial assessment revealed adrenal crisis, and the patient received parenteral hydrocortisone. Further hormonal evaluation revealed hypopituitarism with secondary hypothyroidism, adrenal insufficiency and diabetes insipidus Table 1. Magnetic resonance imaging demonstrated pituitary stalk thickening, initially suggestive of hypophysitis. CT chest reported enlarged bilateral hilar lymph nodes with noted bilateral lower lung lobes few sub-pleural consolidative patches suggestive of sarcoidosis. Biopsy was performed from the suspected cervical lesions showed granuloma confirming the diagnosis sarcoidosis. The patient started prednisolone 60 mg daily, tapered to 7.5 mg daily and he was maintained on replacement therapy with levothyroxine and desmopressin. The condition of the patient improved during follow up.

Table 1. Results of the basal laboratory investigations of the patient.

Variables (units)	Results	Normal range
Thyroid stimulating hormone, TSH (μIU/ml)	0.42	0.27–4.2
Serum free thyroxine, fT4 (ng/dl)	0.76	0.89-1.76
Serum free T3(pg/ml)	1.9	2.3-4.2
Serum cortisol 8:00 am (ug/dl)	0.5	3-25
Adrenocorticotroph hormone, ACTH (pmol/L)	1.4	1.5-14.7
Prolactin (ng/ml)	14	3.8-23
Potassium (mmol/L)	2.6	3.5-5
Sodium (mmol/L)	143	136-145
Calcium (mg/dl)	10	8-11
Phosphorus (mg/dl)	2.9	2.5-4.9
Albumin (g/dl)	4.2	3.4-5
Total Bilirubin (mg/dl)	0.59	Up to 1
Protein (g/dl)	6.5	5.7-8.2
ALT (U/L)	26	10-49
Creatinine (mg/dl)	0.9	0.5-1.3
BUN (mg/dl)	9	9-23
Blood Urea (mg/dl)	19	15-45
Uric acid (mg/dl)	4.6	3.5-7.2

Conclusion
We report a case of undiagnosed hypopituitarism initially presenting as a case of adrenal crisis with hypotension and gastrointestinal symptoms. The patient also displayed clinical diagnosis of pulmonary and pituitary sarcoidosis with secondary hypothyroidism and diabetes insipidus. The case highlights the importance of endocrine sequelae of sarcoidosis.
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EP1198

JOINT2212

Is partial empty sella or empty sella a risk factor for visual field defects?

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Background
Parasellar lesions may affect the optic chiasm leading to visual symptoms, such as a constricted visual field. However, partial empty sella and empty sella—despite involving subarachnoid space herniation into the sella turcica—may not produce vision abnormalities. The purpose of this study was to assess if empty sella and partial empty sella are risk factors for visual field defects.
Material and Methods
Out of 594 patients who had undergone pituitary magnetic resonance imaging (MRI), we selected 43 patients diagnosed with empty sella or partial empty sella syndrome, who subsequently underwent ophthalmological examination (86 eyes) with visual field assessment via full-field 120-point screening test, MRI of the pituitary and optic nerves, and hormone profile.
Results
The evaluated eyes were divided into two groups: Group 1: the eyes of patients with empty sella and the pituitary measuring $<$ 3 mm craniocaudally (n = 46), Group 2: the eyes of patients with partial empty sella and the pituitary measuring $\geq$ 3 mm craniocaudally (n = 40). Patients from the study groups did not differ in terms of the extent of visual field defects (%) in the entire visual field (5.33 $\pm$ 9.00 vs. 4.27 $\pm$ 8.75, P = 0.455). Logistic regression analysis showed none of the following parameters: the pituitary craniocaudal diameter (OR 1.092; 95%CI [0.451–2.642], P = 0.846), pituitary volume (OR 0.995; 95%CI [0.987–1.003], P = 0.258), sellar volume (OR 1.00; 95%CI [0.999–1.001], P = 0.976), or MRI-measured optic nerve area (OR 1.002; 95%CI [0.996–1.008], P = 0.441) to be independent risk factors for defects in the entire visual field.
Conclusions
Neither the volume nor craniocaudal diameter of the pituitary is a risk factor for visual field defects.
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EP1199

JOINT615

GnRH analogs in pediatric practice: efficacy, safety, and side effects—a comprehensive review

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Introduction
Gonadotropin-releasing hormone (GnRH) analogs are critical in managing central precocious puberty (CPP) in pediatrics, effectively halting pubertal progression and improving predicted adult height. Despite their clinical benefits, potential risks such as bone mineral density reduction, metabolic disturbances, and menstrual irregularities require careful evaluation, especially in long-term use. This review synthesizes recent literature to provide a detailed understanding of GnRH analogs' efficacy, safety, and potential side effects in pediatric applications.
Objectives
To evaluate the efficacy and safety of long-acting (3-month) vs short-acting (1-month) GnRH analogs in managing CPP in children, with a focus on growth outcomes, metabolic impacts, and side effects.
Methods
A literature review from 2009 to 2023 identified peer-reviewed studies assessing GnRH analog treatments in pediatrics. Key inclusion criteria included studies reporting clinical outcomes such as pubertal suppression, height outcomes, and metabolic effects. Table 1 provides an overview of the main findings from selected studies.
Results
• Efficacy: Long-acting GnRH analogs effectively suppressed pubertal progression and improved predicted adult height, comparable to monthly formulations. Ramos *et al*. (2021) reported an increase in height SDS and a reduction in BMI in 22 CPP patients treated with a 3-month formulation. Klein *et al*. (2020) showed effective pubertal suppression with 6-month leuprolide acetate. (Ramos *et al*., 2021), (Klein *et al*., 2020).
• Safety:.
• Bone health: Both 1-month and 3-month formulations had minimal impacts on bone density (Vatopoulou *et al*., 2020).
• Glucose metabolism: No significant alterations were reported (Yuan *et al*., 2015).
• Side effects: Some studies noted minor BMI increases and transient menstrual irregularities during initiation.
• Risks: Long-term suppression with depot preparations raised concerns about delayed recovery of the hypothalamic-pituitary-gonadal axis upon cessation, though these effects were largely reversible (Silverman *et al*., 2015).
Discussion
Both long-acting and short-acting GnRH analogs provide effective CPP management in pediatrics. Long-acting formulations offer enhanced compliance due to reduced injection frequency, which is particularly beneficial in children. However, they may pose challenges for quick dose adjustments and recovery post-treatment. Short-acting formulations allow for greater flexibility but require more frequent clinic visits, potentially affecting compliance.
Conclusions
GnRH analogs are highly effective and safe in managing CPP in pediatric populations. Long-acting formulations improve compliance and are well-tolerated, making them preferable in many cases. Monitoring for rare side effects, such as bone density loss or delayed recovery post-treatment, remains essential. Future research should explore long-term outcomes to optimize treatment strategies.

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EP1200

JOINT1902

Cushing's disease and severe resistant hypertension: surgical challenges due to rare kissing carotids

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Background
A 44-year-old male (BM) was referred for severe, resistant hypertension managed with quadritherapy since age 41. Clinical evaluation revealed hypokalemia, facial plethora, adiposity with a rounded facial appearance, and lower limb muscle atrophy, raising suspicion of hypercortisolism.
Case Presentation
Biochemical investigations confirmed ACTH-dependent Cushing's disease with elevated ACTH levels (>20 pg/ml) and cortisol non-suppression on the dexamethasone suppression test. Pituitary MRI identified a microadenoma associated with "kissing carotids," a rare vascular anomaly characterized by the medialization of the internal carotid arteries. This malformation significantly increased the risk of vascular injury during transsphenoidal surgery, the standard treatment for Cushing's disease.
Management Challenges
The rare association of a pituitary microadenoma with "kissing carotids" complicated the surgical approach, necessitating multidisciplinary planning. Alternative therapies considered included medical management with steroidogenesis inhibitors, stereotactic radiosurgery, or bilateral adrenalectomy to control hypercortisolism.
Conclusion
This case illustrates the complexities of managing Cushing's disease in the presence of "kissing carotids," a rare but clinically significant vascular anomaly. Multidisciplinary collaboration and individualized treatment planning are essential to optimize safety and outcomes in such challenging scenarios.

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EP1201

JOINT2085

Evaluation of alexithymia and quality of life in patients with acromegaly

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Introduction
Alexithymia, defined as emotional 'blindness', is a personality structure characterized by difficulties in understanding one's own emotions, distinguishing them from physical arousal signals, and verbally expressing one's emotions to others. Alexithymia, which is a transdiagnostic risk factor for depression, anxiety and post-traumatic stress disorder, may be a psychological risk factor for quality of life in patients with. In this study, we aimed to assess psychopathological conditions such as alexithymia in patients with acromegaly and determine their impact on quality of life.
Materials and Methods
The study included a total of 120 consecutive patients with acromegaly who were followed at the Endocrinology and Metabolism Outpatient Clinic of the Cerrahpasa Faculty of Medicine. Sociodemographic and disease-related clinical follow-up data were obtained from the medical records of all patients. In addition, the Toronto Alexithymia Scale-20, consisting of 20 items, and the Acromegaly Quality of Life Questionnaire (AcroQoL), consisting of 22 questions, were used for quantitative scale assessment.
Results
A total of 120 patients with acromegaly (71 females and 49 males) were included in this study. The mean age of all participants was 47 $\pm$ 10 years and the median disease duration was 90 $\pm$ 68 months. When the remission status of the patients was evaluated, there was no significant difference between the groups in terms of disease duration (90 $\pm$ 66 vs. 85$\pm$36 months, $P = 0.153$). The total scores of alexithymia and subscales (difficulty identifying feelings, difficulty describing feelings, and externally-oriented thinking) scores were similar in patients with and without remission (51 $\pm$ 11.3 vs. 51.5 $\pm$ 12.7; 17 $\pm$ 5.5 vs. 16 $\pm$ 5.5; 12 $\pm$ 3.8 vs. 14 $\pm$ 4.1; 22 $\pm$ 4 vs. 22 $\pm$ 5; respectively, $P > 0.05$ for all). Since there was no control group in our study, we compared the alexithymia scores in a population-based other Turkish study with 503 healthy participants from the literature; we found that our patients had similar alexithymia scores (49.6$\pm$11.1 in the literature vs. 50.7$\pm$11.5 in our study). Finally, when classifying patients according to remission status and disease duration, we found no significant difference between the groups in terms of AcroQoL scores.
Conclusion
In the present study, we demonstrated that alexithymia and quality of life in patients with acromegaly do not change depending to remission status and disease duration and that this was comparable to population-based studies.

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EP1202

JOINT2151

Aggressive prolactinoma with failed temozolomide therapy: management strategies & literature review

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A 55-year-old male was diagnosed with aggressive macroprolactinoma (APRL) in 2001. He underwent transsphenoidal surgery (TSS) in 2002 and 2005, followed by radiotherapy and further craniotomy in 2009. Temozolomide, an oral alkylating chemotherapeutic agent, was initiated in 2009, achieving biochemical control for over a decade. Patient was panhypopituitarism, requiring hormone replacement (levothyroxine, hydrocortisone, & testosterone) & severe sight impairment due to bilateral optic atrophy. In 2024, he presented with tumour relapse evidenced by rising prolactin levels. MRI confirmed subsellar and left cavernous sinus recurrence. Clinically, he had severe stabbing pain in the left V1 region along with left cranial nerve VI palsy. A cycle of Temozolomide was given but failed to control prolactin levels or alleviate pain. TSS was then undertaken which resulted in temporary prolactin reduction, but levels soon rebounded. Multidisciplinary discussion was undertaken, and tumour histology was analysed. Immunohistochemistry for DNA mismatch repair proteins (MSH2, MSH6, MLH1, PMS2) revealed absent MSH6 staining but others positive. Ki-67 proliferation index was 12%, and bone invasion confirmed aggressive behaviour. The findings were consistent with an aggressive prolactinoma/PITNET (WHO 2022). The patient is now undergoing radiotherapy, with further chemotherapy options being explored. Whole genome methylation and next-generation sequencing are underway to guide future treatment.

Conclusion

Aggressive prolactinomas are a rare subset of pituitary tumours. Effective management requires a multidisciplinary approach incorporating surgery, radiotherapy, and systemic therapy. We present a case of an aggressive prolactinoma successfully controlled with Temozolomide, from 2009 until 2022. However, in 2024, tumour recurrence demonstrated resistance to Temozolomide therapy. Immunohistochemical analysis of tumour tissue revealed absent MSH6 staining, suggesting a potential mutation in the *MSH6* gene. Loss of MSH6 expression has been associated with poor response to temozolomide therapy, as highlighted in a study where intact MSH6 correlated with a favourable treatment response. [1] This case underscores the importance of molecular profiling in guiding therapeutic decisions for aggressive pituitary tumours. The observed MSH6 loss may provide an explanation for acquired resistance to Temozolomide and suggests the need for alternative treatment strategies, such as immune checkpoint inhibitors or other targeted therapies. Multidisciplinary management remains essential in optimizing outcomes for these challenging cases.

Reference

Hirohata T, etal. DNA Mismatch Repair Protein (MSH6) correlated with the responses of atypical pituitary adenomas and pituitary carcinomas to temozolomide: the national cooperative study by the Japan society for hypothalamic and pituitary tumors. Journal of Clinical Endocrinology and Metabolism 2013 98 1130–1136. (https://doi.org/10.1210/jc.2012-2924).

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EP1203

JOINT2323

Systematic review of cardiometabolic outcomes in young people with gender dysphoria and the impact of puberty blockers

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Background

There is evidence of an increased risk of cardiovascular disease in transgender adults compared to the cisgender population. It is unclear whether this is secondary to hormonal treatment, or if individuals with gender dysphoria inherently have a higher baseline risk for cardiometabolic complications. Data on the safety and efficacy of gonadotrophin-releasing hormone analogues (GnRHa) is limited in adolescents with gender dysphoria.

Aim

This systematic review aims to assess the cardiometabolic status in treatment-naive adolescents with gender dysphoria and evaluate the impact of GnRHa on these outcomes.

Methods

Three databases (Embase, Medline and Cochrane Library) were searched to April 2024 for studies which evaluated cardiometabolic outcomes in adolescents with gender dysphoria <18 years and/or those who had had been treated with GnRHa. Quality assessment was performed by two independent reviewers using an adapted version of the Newcastle-Ottawa Scale for cohort studies in gender dysphoria. The Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guidelines were used.

Results

Ten pre-post studies and five cross-sectional studies published between 2014 and 2023 fulfilled eligibility criteria. A narrative synthesis was performed. Quality assessment identified one high quality, twelve moderate quality and two low quality studies. Seven studies (47%) provided data on baseline characteristics and ten studies (67%) provided data on the impact of GnRHa. There was a total of 3772 adolescents with gender dysphoria along with 78792 age-matched cisgender controls. Multiple studies reported an increased prevalence of overweight and/or obesity or an increased BMI z-score in adolescents with gender dysphoria at baseline. There was no evidence of significant change in BMI following treatment for approximately one year. Limited and/or conflicting evidence was available in relation to body composition, blood pressure and metabolic markers at baseline and following GnRHa treatment.

Conclusion

This systematic review found an increased risk of excess weight in young people with gender dysphoria. There was no evidence of an increase in BMI with GnRHa treatment. Due to limited data, no definitive conclusions can be drawn about other cardiometabolic outcomes in adolescents with gender dysphoria, either at baseline or following pubertal suppression. Longitudinal prospective studies with standardized designs and key outcome measures are essential for advancing knowledge in this area.

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EP1204

JOINT3797

Obstructive sleep apnea in patients with acromegaly

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Introduction

Acromegaly is a severe neuroendocrine disorder caused by chronic excessive secretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) in individuals who have completed their physiological growth. The most common causes of mortality in acromegaly are cardiovascular and cerebrovascular diseases, as well as respiratory system pathologies. Sleep-disordered breathing worsens the quality of life and increases the risk of various cardiovascular complications. It is essential to emphasize the importance of timely diagnosis of the disease and the development of optimal treatment pathways to prevent the progression of complications.

Objective

To analyze the referral process for patients with acromegaly to a sleep specialist and the possibilities for conducting diagnostic assessments.

Materials and Methods

A survey of specialists from various fields using a questionnaire.

Results

A total of 171 specialists participated in the survey, with the majority being endocrinologists (81.9%), followed by dentists (7.6%), pediatric endocrinologists (4.7%), maxillofacial surgeons (1.75%), and physicians from other specialties (4.1%). Among the respondents, 71.9% of specialists had experience working with patients suffering from acromegaly. However, among them, 68.4% did not refer patients to a somnologist due to the paid nature of the process, while 29.2% encountered a lack of specialists who could assess sleep, diagnose sleep apnea, and recommend treatment methods such as CPAP. According to the survey data, 81.9% of physicians believe that somnological assistance for such patients is inadequate, highlighting the need for improved access to specialized care and referrals in the field of somnology for patients with acromegaly.

Conclusions

This study demonstrates the inadequacy of the diagnosis and treatment provided to patients with acromegaly suffering from apnea. According to the results obtained, this is related to the inaccessibility of free consultations and the conduct of cardiorespiratory monitoring. The analyzed data will serve as a foundation for

improving the pathway for patients with acromegaly, which could significantly enhance the quality of medical care and improve the quality of life for patients.

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EP1205

JOINT3374

Case report: infectious hypophysitis as a complication of sphenoiditis

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Introduction
Hypophysitis, an inflammation of the pituitary gland, is a rare condition that can be caused by infections, autoimmune disorders, or tumors. When complicated by sphenoiditis, it poses diagnostic and therapeutic challenges. This case report describes a 51-year-old male patient diagnosed with sphenoiditis complicated by infectious hypophysitis.
Case Presentation
A 51-year-old man, with no significant past medical history, presented with a complaint of persistent headaches, fatigue, somnolence, and rhinorrhea. These symptoms prompted him to seek consultation with the ear, nose, and throat(ENT) department. Upon examination, imaging was performed, including facial MRI and pituitary sections. The MRI revealed bilateral sphenoiditis. Additionally, there wasan evidence of hypophysitis with pituitary enlargement and an 18mm intrasellar collection. These findings were indicative of an infectious process affecting both the sphenoid sinus and the pituitary gland. The patient was immediately started on intravenous antibiotic therapy for 15 days. Biological assessments revealed anterior pituitary dysfunction: Specifically, the cortisol level was markedly low (2ug/dl), consistent with corticotropic insufficiency, and low FT4 levels (0,67 ng/dl) and a normal TSH level (1,3 mUI/l), consistent with thyrotropic insufficiency. The patient was placed on corticosteroid and thyroid hormone replacement therapy. There were no complaints of erectile dysfunction or libido reduction. Prolactin and testosterone levels were within normal limits The patient showed marked improvement, with complete resolution of headaches, asthenia, and somnolence. A follow-up MRI at three months confirmed the resolution of sphenoid sinusitis and the disappearance of the intrasellar mucocele. No additional complications were observed.
Conclusion
This case highlights the rare and complex link between infectious sphenoiditis and hypophysitis, leading to anterior pituitary insufficiency. Early diagnosis and prompt management, including targeted antimicrobial therapy and hormone replacement, are crucial for optimal outcomes. Clinicians should remain vigilant for pituitary involvement in patients with sinusitis and hormonal imbalances, especially when other causes of pituitary dysfunction are absent.

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EP1206

JOINT3494

A rare case of TSH-oma in a frail patient: diagnostic and therapeutic challenges

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Introduction
Thyrotropin-secreting pituitary adenomas (TSH-omas) are rare causes of hyperthyroidism, accounting for 0.5% to 2% of all pituitary adenomas, with an estimated incidence of 1 to 2 cases per million. These tumors autonomously secrete TSH, leading to inappropriate stimulation of the thyroid gland and subsequent hypersecretion of thyroxine and triiodothyronine. Unlike other thyroid disorders, TSH-omas exhibit equal gender distribution and are typically diagnosed around the age of 46 $\pm$ 6 years. This report presents a rare case of a TSH-oma in a frail patient with multiple comorbidities, highlighting diagnostic and therapeutic challenges.
Case Presentation
A 74-year-old Tunisian male with a history of well-controlled type 2 diabetes of 8 years, hypertension, stage 3 chronic kidney disease, iron deficiency anemia, global heart failure with preserved ejection fraction, and stage 4 peripheral artery disease presented with a 3-month history of asthenia and hand tremors. Biochemical analysis revealed severe hypocalcemia and hyperphosphatemia. Hormonal assays confirmed central hyperthyroidism with elevated TSH and FT4. There was no anterior pituitary deficiency. Pituitary MRI revealed a macroadenoma measuring 29x26 mm, with extension to sphenoid and cavernous sinuses, especially on the left, with filling of the suprasellar cisterns leading to a slight dilation of the lateral ventricles. Fundus examination revealed minimal diabetic retinopathy and dense bilateral cataract.
Discussion
The first line treatment for TSH-omas is transsphenoidal pituitary surgery, aimed at reducing thyroid hormone levels to prevent thyrotoxicosis and thyroid storm. However, due to the patient's multiple comorbidities and potential contra-indications to general anesthesia, medical management with somatostatin analogs was considered as an alternative. Early diagnosis and appropriate treatment are crucial to preventing complications.

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EP1207

JOINT3515

Comparison of normetanephrine and metanephrine secretion in pheochromocytoma: clinical and radiological features

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Introduction
Pheochromocytoma are neuroendocrine tumors originating from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia. The aim of this study was to compare clinical and radiological characteristics of normetanephrine- and metanephrine secreting pheochromocytomas.
Subjects and Methods
This retrospective single-center study included 12 patients with confirmed pheochromocytoma followed up at the outpatient clinic of the endocrinology department in Tunis Military Hospital. Clinical and paraclinical data were extracted from patients' medical records. Patients were divided into two groups: Group 1 ($n = 6$) with normetanephrine-secreting tumors, defined as normetanephrine level more than 3 times the normal limit and Group 2 ($n = 4$) with metanephrine-secreting tumors, defined as metanephrine level more than 3 times the normal limit. Two mixed-secretion cases were excluded.
Results
The median age (IQR) at diagnosis was 45 (29 – 65) years in the first group and 58 (37 – 74) years in the second group ($P = 0.257$). Clinical presentation included paroxysmal hypertension (2 cases in each group), permanent hypertension (G1: 4 vs G2: 1), resistant hypertension (G1: 2 vs G2: 1) and Menard triade (G1: 4 vs G2: 3). No significant difference was noted in the two groups. Adrenal incidentaloma was the circumstance of discovery in all cases in group 1 and 3 cases in group 2. Median heart rate was 82 bpm (IQR:74 – 105) in group 1 and 76 (IQR:68 – 106) in group 2 ($P = 0.476$). Median blood pressure during crisis was 190/105 mmHg in group 1 ($P = 0.393$) and 180/100 in group 2 ($P = 0.629$). Complications were present in 3 cases in the first group and 2 cases in the second group. They included albuminuria (1 vs 2, $P = 0.524$), ventricular hypertrophy (1 case in each group), hypertensive retinopathy (2 vs 1, $P = 1.000$), haemorrhagic stroke and myocardial infarction in 1 case in group 2. Radiological findings showed a median size of 57 mm (IQR:48 – 68) in group 1 vs 50 mm (43 – 68) in group 2 ($P = 0.762$). Median washout was 28% (IQR:21 – 39) in group 1 and 45% in group 2 ($P = 0.610$). All normetanephrine tumors were heterogeneous, vs 3 (75%) of the other group. Left location of the tumor was more frequent in both groups. All patients had adrenalectomy. One patient had persistent hypertension postoperatively. However, the number of antihypertensive drugs decreased from 3 to 1.
Conclusion
This study found no significant differences between normetanephrine- and metanephrine-secreting pheochromocytomas. Due to the rarity of these tumors, further large-scale studies are needed to validate these findings.

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EP1208

JOINT3416

A comparative analysis of three positron emission tomography tracers in a patient with residual acromegaly

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Background
Molecular imaging is gaining importance in the localisation diagnostics of pituitary disease. However, the availability of tracers varies between different centres. The currently best evidence exists for the amino acid tracer ^{11}C-methionine (MET).^{18}F-fluoroethyl-tyrosine (FET) has been reported as a potential alternative to MET with broader availability. While ^{68}Ga-DOTATOC (DOTATOC) shows high uptake in the normal pituitary gland, data is limited regarding uptake in adenomas.
Methods
Here we report a 35-year-old patient with residual acromegaly after two endoscopic transsphenoidal surgeries who had intolerable side effects under medical therapy and underwent DOTATOC-PET, FET-PET and MET-PET. All scans were undertaken in line with published PET acquisition references for each tracer.
Results
MET-PET and DOTATOC-PET identified two distinct foci of increased tracer uptake. In the context of the anatomical imaging (pre- and post-op), the most intense left-sided focus was suspected to represent physiological uptake within normal gland and the right-sided focus to represent residual somatotroph tumour. In contrast, FET-PET did not clearly identify a discrete focus of intrasellar uptake and only showed physiological uptake in the cavernous sinuses. Four months after CyberKnife therapy targeting the suspected tumour in the right cavernous sinus – and limiting the radiation dose to the physiological pituitary gland to $\leq$20% of the maximum – the insulin-like growth factor I declined from 1.55 to 1.18 times the upper limit of normal. No new pituitary deficits were observed.
Conclusion
This case confirms a role for MET-PET in accurate localisation of residual tumour in acromegaly and is consistent with previously published studies. Although not matching the higher resolution of MET-PET, DOTATOC-PET facilitated similar clinical decision-making. In contrast, FET-PET did not offer any diagnostic benefit in this case.

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EP1209

JOINT2472

Associations between central diabetes insipidus and brain mri findings: a comprehensive analysis in a large cohort with extensive clinical experience

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Background
The causes of central diabetes insipidus (CDI) are often unclear at the time of diagnosis. The clinical presentation and typical brain MRI findings in CDI are not always specific to a particular cause.
Aims
This study aims to assess the prevalence of distinct brain MRI abnormalities in CDI patients and explore potential associations between these findings and the underlying etiology of CDI.
Methods
Data from 131 patients were analyzed, including 109 with CDI of various causes and 22 with Langerhans cell histiocytosis (LCH) without CDI, with disease onset between 0 and 17.99 years and a follow-up period of at least two years. A total of 1,355 brain MRIs were reviewed to identify specific MRI changes. The thickness of the proximal, middle, and distal segments of the pituitary stalk was measured at onset and six months later. Hormone deficiencies were also evaluated and correlated with MRI abnormalities.
Results
Extrasellar lesions were found in 16 of the 109 CDI patients (14.7%), with a significantly higher prevalence in LCH patients compared to those with neuro-oncological causes ($P = 0.004$) and genetic, malformative, or post-infectious causes ($P = 0.012$). However, the prevalence of extrasellar lesions did not significantly differ between LCH and idiopathic CDI. In LCH patients, extrasellar lesions were more common in those with CDI ($P = 0.024$). FLAIR hyperintensity of the tuber cinereum was noted in 8 CDI patients (7.3%), and this was more frequent in CDI patients with LCH than those with other etiologies ($P < 0.0001$), being absent in LCH patients without CDI. Hypothalamic involvement was significantly more common in CDI patients with neuro-oncological causes. A mismatch pattern was observed in 21 CDI patients (19.3%), more commonly seen in idiopathic CDI and CDI with LCH ($P < 0.0001$). No significant change in pituitary stalk thickness was observed between the initial and six-month follow-up assessments in any patient group.
Conclusions
FLAIR hyperintensity of the tuber cinereum was more frequently seen in patients with LCH, suggesting it could be a specific marker for LCH. Extrasellar lesions were more common in LCH patients compared to those with other CDI causes and were more frequent than in idiopathic CDI, highlighting their potential as an early indicator of LCH.

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EP1210

JOINT3439

A rare association between pituicytoma and cushing's syndrome

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Pituicytoma is a rare, low-grade spindle-cell astrocytic tumor of the posterior pituitary or its stalk, classified as a WHO grade I central nervous system tumor. It's typically located in the sellar or suprasellar region and is often misdiagnosed as other sellar lesions such as pituitary adenoma or craniopharyngioma. Clinically, a pituicytoma presents with signs of mass effect and hypopituitarism due to compression of the pituitary gland. It's also common to have hyperprolactinemia because of stalk effect. Additionally, diabetes insipidus was described. While less than 200 cases of pituicytoma have been reported in the literature, endocrine hyperfunction, particularly Cushing's disease and acromegaly, is a rare occurrence. Here, we report two cases of pituicytoma associated with Cushing's syndrome. **Case 1** A 38-year-old woman presented with hirsutism mostly on the face and the abdomen. Eleven years earlier, she had undergone endocrinological evaluation for hirsutism, acne, and a 10-kg weight gain. In 2023 tests showed hypercortisolism: urinary free cortisol (UFC) 1.12 ULN, ACTH 56 pg/ml, cortisol after 1 mg dexamethasone suppression test (F-1mgDST) 6.58 µg/dl. 8-mg overnight dexamethasone suppression test and desmopressin stimulation test were suggestive for Cushing's disease. MRI identified a 3-mm hypointense lesion on T1-weighted sequences in the right anterolateral pituitary, suggestive for pituitary microadenoma. She underwent surgery, achieved disease remission and developed secondary adrenal insufficiency. Histology revealed that the lesion was a pituicytoma. **Case 2** A 40-year-old woman complained of with

symptoms including hirsutism, buffalo hump, easy bruising, hypertension, and weight gain over the past two years. Laboratory tests confirmed a diagnosis of overt Cushing's disease (UFC 5.47 ULN, ACTH 53 pg/ml, F-1mgDST 17.4 μg/dl,) and MRI showed a 4-mm microadenoma in the left pituitary. The desmopressin test result was consistent with Cushing's disease (ACTH increase of 115% over baseline). She underwent transsphenoidal surgery, achieved clinical remission and developed adrenal insufficiency. Histological features were indicative of pituicytoma.

Discussion

About 15 cases of pituitary tumors associated with Cushing's syndrome have been documented so far. Since pituicytomas are classified as gliomas, hormone secretion is considered unusual. The observed ACTH production could potentially result from an undetected microadenoma, such as a Crooke's cell adenoma, or from paracrine signaling that stimulates the proliferation of anterior pituitary cells. This coexistence might not be coincidental but could suggest an unknown pathophysiological connection or a shared progenitor cell origin. Performing histological analysis with ACTH immunostaining could help to identify hidden lesions and provide insight into the underlying mechanisms.

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EP1211

JOINT3589

Adverse hepato-biliary-pancreatic events in acromegaly patients treated with first generation somatostatin analogues: an italian multicenter study

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Introduction

First-generation somatostatin analogues (SSa) are first-line medical therapy for acromegaly. They are generally well-tolerated but during long-term therapy, cholelithiasis, which may require cholecystectomy (CH-Tx), and other hepato-biliary-pancreatic adverse events can occur. This study aimed at evaluating the prevalence of hepato-biliary/pancreatic adverse events during SSa treatment, and at identifying factors influencing their development.

Methods

371 acromegaly patients (223F, age 63 ± 0.77yrs) were evaluated retrospectively, collecting clinical/biochemical/instrumental data at diagnosis (T0), at SSa therapy start (T1) and at last follow-up visit (120 ± 6.54 months). The occurrence of CH-Tx, cholecystitis (CH), mild hypertransaminasemia (<5xULN) or severe hypertransaminasemia (>5xULN) (HT), mild (<5xULN) or severe (>5xULN) hyperlipaemia/hyperamylasemia (HH) during SSa treatment, and their relationship with clinical and biochemical features at T0/T1 have been investigated.

Results

61 patients (16.4%)(40F) underwent CH-Tx, 14 (3.8%) developed CH, 8 (2.2%) severe HH and 19 (5.12%) mild HH, 4 (1.1%) severe HT and 24 (6.47%) mild HT, without significant differences in terms of gender or after patients' stratification by age >/< 50yrs. Chi-square test revealed that patients undergoing CH-TX or CH had a higher prevalence of biliary lithiasis at T1 ($P = 0.002$, $P = 0.005$, respectively), while mild hypertransaminasemia was associated with higher frequency of diabetes mellitus at T1 ($P = 0.019$). Cholecystectomy was associated to higher age and biliary sand at T1 ($P = 0.018$; $P = 0.016$, respectively), according to multivariate analysis, and with ursodeoxycholic acid (UDA) treatment at T1 in univariate analysis ($P = 0.035$). Cholecystitis was associated with UDA treatment ($P = 0.003$) and elevated GH-levels at T1 ($P = 0.044$) in univariate and multivariate analyses, respectively. Severe HH was associated with UDA treatment in both univariate ($P = 0.003$) and multivariate analyses ($P = 0.026$). The occurrence of mild or severe HT was associated, in univariate analysis, with UDA treatment ($P = 0.056$) and biliary lithiasis at T1 ($P = 0.055$), respectively. When considering hepato-biliary-pancreatic adverse events overall, they were found to be significantly associated to age, biliary lithiasis, and biliary sand at T1 in both univariate ($P = 0.013$, $P = 0.006$, $P = 0.010$, respectively) and multivariate analyses ($P = 0.044$, $P = 0.029$, $P = 0.028$, respectively).

ConclusionS

Hepato-biliary/pancreatic adverse events during long-term treatment with SSa are not infrequent, and overall influenced by age, cholelithiasis and biliary sand. The relevance of preexisting hepato-biliary issues in their occurrence is also demonstrated by the evidence of the association with UDA treatment.

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EP1212

JOINT2598

Clinico-radiological correlation analysis of a cohort of 50 children with pituitary stalk interruption syndrome

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Pituitary stalk interruption syndrome (PSIS) is diagnosed on the basis of clinical manifestation and the characteristic picture of pituitary gland on MRI. PSIS may represent an isolated morphological abnormality or may be accompanied by other structural defects of the midline of the brain. In terms of endocrine evaluation, it is characterised by a wide spectrum ranging from the absence of significant endocrine abnormalities to combined pituitary hormone deficiency (CPHD). In patients with PSIS, it is difficult to predict when hypopituitarism (isolated or CPHD) will become apparent.

The aim of this study was to characterize the correlation between the pituitary hormonal pattern and the MRI features in 50 children with PSIS.

Results

Out of 50 subjects, 30 (60%) were diagnosed with CPHD, while 18 (36%) with isolated GHD. In 1 boy with vasopressin deficiency, endocrine function of the anterior pituitary was normal (2%), while in 1 girl (2%) who remains under the neurological care due to cerebellar vermis dysplasia, no endocrine abnormalities were found. Five patients out of 50 (10%) were diagnosed with arginine vasopressin deficiency. GHD was diagnosed in 47 children (94%). It should be noted that one patient presenting with IGF-1 and GH below normal (0.05 ng/ml) has achieved age-appropriate growth (90-97c) was not classified as a child with GHD. MRI examination showed anterior pituitary hypoplasia in 45/50 children (90%), none of them presented with aplasia. Agenesis of the pituitary stalk was observed in 13/50 patients (26%) and hypoplastic pituitary stalk in 36/50 patients (72%). The ectopic posterior pituitary lobe was diagnosed in 45/50 subjects (90%), while in 5 patients the posterior lobe was not visible. Septo-optic dysplasia was diagnosed in 21/50 patients (42%): 3/3 criteria – 9 children, 2/3 criteria -12 children. In the group with pituitary stalk agenesis, isolated GHD was diagnosed in 15.4% patients, whereas CPHD was presented in 84.6% cases. In the group with pituitary stalk hypoplasia isolated GHD or no abnormalities in anterior pituitary were diagnosed in 47% patients whereas CPHD was observed in 53% cases. In 15/16 children (94%) with optic nerve hypoplasia were found to have CPHD. Diabetes insipidius was diagnosed exclusively in the 5 patients in whom the posterior pituitary lobe was not visualised 1. Picture of pituitary stalk agenesis and optic nerve hypoplasia in MRI may determine the severity of endocrine disorders of the anterior pituitary. 2. The absence of the posterior pituitary correlates with the development of diabetes insipidus.

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EP1213

JOINT2140

Cabergoline therapy in adolescent cushing's disease: hypercortisolism improvement with persistent tumor

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Background
Cushing's disease is the most common etiological agent of endogenous hypercorticism. Furthermore, 90% of corticotropic adenomas are microadenomas. While surgery is typically the go-to treatment, there are situations where medication can play a key role in managing the condition.
Case report
We present the case of a 17-year-old patient referred for evaluation of hypercortisolism. The clinical examination revealed overt signs of Cushing's syndrome, with a predominance of catabolic manifestations: extensive, horizontal, purple stretch marks on the abdomen, axillae, and proximal limbs, as well as muscle atrophy in the girdle regions. The 24-hour urinary free cortisol (UFC) level was 7 times the upper limit of normal. A 2-day low-dose dexamethasone suppression test and an elevated ACTH level of 11.32 pmol/l(> 4.4 pmol/l)confirmed the diagnosis of ACTH-dependent Cushing's syndrome. A high-dose suppression test further supported the diagnosis of Cushing's disease. A pituitary MRI identified a 1.8 mm microadenoma. Since ketoconazole was not available, we started him on Cabergoline, 0.5 mg once a week, and referred him to neurosurgery for further evaluation. After 18 months, the patient had not undergone surgical intervention. Remarkably, clinical follow-up demonstrated significant regression of hypercortisolism symptoms, with normalization of 24-hour UFC levels. Repeat hypothalamic-pituitary MRI showed no change in the size of the microadenoma.
Conclusion
Depending on the series, the efficacy of cabergoline ranges from 25 to 40%. In certain cases of Cushing's disease, particularly when accompanied by a pituitary picoadenoma, it may still be a useful treatment option.

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EP1214

JOINT2170
Bilateral achilles tendon rupture: a rare presentation of cushing's disease

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Introduction
Cushing's disease, an endocrine disorder caused by ACTH-secreting pituitary adenomas, encompasses a wide spectrum of systemic complications. While metabolic, cardiovascular, and musculoskeletal alterations are common manifestations, tendon ruptures are exceptionally rare as an initial presentation. These ruptures reflect the profound impact of chronic hypercortisolism on connective tissue integrity, highlighting the need for vigilance in diagnosing atypical presentations of this condition.
Case Report
A 40-year-old woman presented to the endocrinology consultation with a two-year history of amenorrhea and infertility following the discontinuation of oral contraceptives, accompanied by progressive hirsutism, weight gain, easy bruising, and proximal muscle weakness. Additionally, she had a bilateral Achilles tendon rupture, with no preceding trauma or excessive physical exertion. Her medical history was relevant for hypertension and prediabetes, with no medication. On presentation to our clinic, she reported proximal myopathy and had a BMI of 21.1kg/m^2 with no evident signs of Cushing's disease. Biochemical evaluation revealed elevated 24-hour urinary free cortisol (138 nmol/L; reference: 11.5–102), a lack of suppression on a low-dose dexamethasone suppression test (post-dexamethasone cortisol: 7.2 µg/dl), and elevated salivary cortisol (0.4 µg/dl; reference: <0.27). ACTH levels were elevated at 40 pg/ml, suggesting an ACTH-dependent cause. Magnetic resonance imaging identified an 11 mm right-sided pituitary macroadenoma. The patient was started on metyrapone 500mg/day while awaiting surgery. She was submitted to an uneventful endoscopic transsphenoidal resection, which confirmed a corticotroph pituitary neuroendocrine tumor with positive ACTH immunostaining. Postoperatively, the patient demonstrated significant clinical improvement, with resolution of muscle weakness and normalization of cortisol levels on follow-up.
Discussion
This case highlights the broad and atypical spectrum of presentations in Cushing's disease. Bilateral Achilles tendon rupture is an uncommon yet severe complication attributed to the detrimental effects of chronic hypercortisolism on connective tissue. In fact, cortisol excess disrupts collagen synthesis by impairing fibroblast function and increasing matrix metalloproteinase activity, which degrades the extracellular matrix. These effects weaken tendons and predispose them to rupture, even in the absence of significant trauma. Proximal myopathy further exacerbates tendon vulnerability by altering biomechanical stress patterns. This case underscores the importance of recognizing atypical manifestations of Cushing's disease, such as bilateral tendon rupture, and highlights the need for multidisciplinary management to optimize patient outcomes. A high index of suspicion and thorough clinical evaluation are essential for early diagnosis and treatment of this condition.

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EP1215

JOINT2367
Giant prolactinoma in adult males

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Introduction
Pituitary adenomas represent 15% of brain tumors, with prolactinomas accounting for 40% of these. Prolactinomas are classified into micro, macro, and giant prolactinomas based on size. Macroprolactinomas and giant prolactinomas are more common in men, often without specific clinical signs, leading to delayed diagnosis.
Methods
We conducted a descriptive and analytical study of 36 men followed at the Endocrinology and Diabetology Department of Hedi Chaker University Hospital in Sfax for prolactin-secreting adenomas. We specifically investigated the characteristics of giant prolactinomas, defined as those with a size greater than 4 cm.
Results
Giant prolactinomas were observed in 11 patients (30.6%). The mean age at diagnosis was 43.6 $\pm$ 15.1 years, with extremes ranging from 19 to 75 years. The primary clinical presentations included headaches (86.1%), visual disturbances (69.4%), and sexual dysfunction (47.2%). Hypopituitarism was common, with gonadotropic insufficiency in 63.9% of cases. Imaging revealed significant tumor extensions into suprasellar and lateral regions. The mean prolactin level was 18,662 $\pm$ 52,817 ng/ml. Dopamine agonists were the first-line treatment, with surgery reserved for resistant or complicated cases. A positive correlation was observed between tumor size and prolactin levels (rho $=$ 0.658, $P < 0.001$). Additionally, tumor size was associated with increased risk of hypopituitarism, particularly gonadotropic and thyrotropic insufficiencies. However, no significant correlation was found between tumor size and metabolic parameters such as BMI or waist circumference.
Conclusion
Giant prolactinomas in men present challenges due to their size and nonspecific symptoms, often resulting in delayed diagnosis. Early identification and multidisciplinary management are essential to prevent complications related to vision, endocrine dysfunction, and quality of life.

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EP1216

JOINT2280
When hormones disagree: a case of elevated ACTH with normal cortisol and suspected macro-ACTH

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Background
Pituitary adenomas are common intracranial neoplasms, often presenting with symptoms related to hormone overproduction or mass effect. Cushing's disease results from adrenocorticotropic hormone (ACTH) secreting pituitary adenomas, typically leading to cortisol overproduction. However, some patients exhibit elevated ACTH levels with normal cortisol and an atypical clinical presentation, complicating the diagnosis. In rare cases, this discrepancy may be due to macro-

ACTH, a condition in which pituitary corticotroph cells produce large, biologically inactive ACTH molecules. These molecules have prolonged circulation, leading to falsely elevated ACTH readings without cortisol excess. We present a case of a 34-year-old male with elevated ACTH and normal cortisol levels, raising suspicion for macro-ACTH or a similar rare condition.
Case report
A 34-year-old male was referred by a neurologist with complaints of fatigue, lightheadedness, and mental fog. Neurological examination revealed no meningeal or focal neurological signs. Physical examination was unremarkable, with no signs of hypercortisolism or hypocortisolism. Contrast-enhanced MRI revealed a 15×26×18 mm pituitary macroadenoma with intrasellar, infrasellar, and laterosellar extension, sparing the optic chiasm. Hormonal tests showed elevated ACTH- 215.1 pg/ml (7.2–63.6 pg/ml) but normal morning cortisol levels - 417.3 nmol/l(133–537 nmol/L). Salivary cortisol and 24-hour urinary free cortisol were normal (18.2 nmol/land 42 mg/day, respectively). Levels of the remaining pituitary hormones were within normal limits. Following the low-dose dexamethasone suppression test, cortisol levels were appropriately suppressed, but ACTH remained persistently elevated. The discordance between elevated ACTH and normal cortisol, without clinical signs of cortisol excess, raised suspicion for macro-ACTH secreting adenoma, which releases large, biologically inactive ACTH molecules. However, due to the unavailability of specialized laboratory tests, a definitive diagnosis could not be confirmed. The patient was referred for neurosurgical assessment and management is ongoing.
Discussion
This case highlights the diagnostic challenges in ACTH-secreting pituitary adenomas with atypical presentations. Macro-ACTH, though rare, should be considered when ACTH is elevated despite normal cortisol levels and the absence of clinical signs of cortisol dysregulation.
Conclusions
When laboratory and clinical findings are inconsistent, macrohormone-related interference, such as macro-ACTH, should be considered. Although confirmatory testing was unavailable in this case, recognizing this possibility helped avoid unnecessary treatments. In cases where specialized laboratory tests are unavailable, clinicians should rely on a combination of clinical judgment, biochemical patterns, and response to treatment to guide management. While routine testing for macrohormones is not recommended, awareness of their impact can prevent unnecessary interventions and improve patient outcomes.

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EP1217

JOINT1911

Thyrotropin deficiency and transient central adrenal insufficiency with anterior pituitary hypoplasia in an infant with neurofibromatosis–noonan syndrome

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Neurofibromatosis–Noonan syndrome (NFNS) is a rare genetic entity associated with the clinical phenotype of two conditions: neurofibromatosis type 1 syndrome (NF1) and Noonan syndrome (NS). Sellar and suprasellar disorders with or without pituitary hormone deficiencies are not commonly associated with both NF1 and NS. However, there are reported cases of such presentations in both adults and children with NF1 or NS. To-date, there is only a case of 13-year-old girl with NFNS reported to have isolated growth hormone deficiency with pituitary hypoplasia. We describe the case of an 1-year-old boy with clinical NFNS, anterior pituitary hypoplasia, transient central adrenal insufficiency (CAI) and thyrotropin deficiency (TSHD) presented at 9 months old with failure to thrive (both height and weight < 3rd centile), severe airway obstruction required tracheostomy secondary to right neck plexiform neurofibroma and recurrent hypoglycaemia. The diagnosis of TSHD was established with inappropriate low normal TSH and low FT4. CAI was diagnosed with a hypoglycaemic (glucose 2.9 mmol/l)critical sampling showing an inappropriate low cortisol level of 155 nmol/land an undetectable early morning ACTH levels. He was treated with hydrocortisone and levo-thyroxine replacement at that time. A Synacthen test off hydrocortisone showed normal cortisol response (Peak cortisol 590.6 nmol/l)and normal ACTH of 6.78pmol/lat 11-month-old followed by a normal 16 hours diagnostic fasting test profile. His other pituitary profile revealed normal IGF-1, prolactin and pre-pubertal levels of gonadotropins. The diagnosis of NFNS was made as he fulfilled the diagnostic criteria of NF1 (> 6 café-au-lait spots (>5 mm) with one plexiform neurofibroma) and the Van der Burgt criteria of NS. Clinically, he has short stature, frontal bossing, café-au-lait spots and pectus excavatum. His pituitary MRI findings revealed a small anterior pituitary gland. In summary, we presented a 1-year-old boy with NFNS and anterior pituitary hypoplasia. The case is the youngest NFNS patient to have pituitary hormone deficiencies with abnormal pituitary imaging in the literature. The findings in this patient show that seller or suprasellar anomalies with pituitary hormone deficiency can be a feature of NFNS as early as infancy. Therefore, there should be a high index of suspicion of pituitary hormone deficiency in children with NFNS.

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EP1218

JOINT3098

Case Report: SIAD caused by LGI-1 antibody encephalitis

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Antibodies against LGI-1 (Leucine-rich glioma-inactivated 1) were first described in 2010[1]. LGI-1 antibody encephalitis is rare with an incidence of 0.83 per million persons per year[2]. It is more common in men and has a median age of onset of 65 years. It is characterised by features of limbic encephalitis with frequent focal seizures and associated hyponatraemia is common. We present the case of a 73yo man who presented to the emergency department with a transient episode of expressive aphasia and numbness of his right hand that lasted approximately 15 minutes. Background medical history included diverticular disease, hiatus hernia, hypercholesterolaemia and benign prostatic hypertrophy. He was not taking any regular medications at the time of admission. He had a good functional baseline and was independent in all activities of daily living. Examination was unremarkable and he was noted to be clinically euvolaemic. CT brain and subsequent MRI brain did not show any acute abnormalities. Serum sodium on admission was 126mmol/lwith serum osmolality 257mmol/kg and urine sodium 71mmol/lwith urine osmolality 552mmol/kg, in keeping with syndrome of inappropriate antidiuresis (SIAD). Thyroid function tests were normal and random cortisol was 263nmol/lso he underwent a short synacthen test which had a 30 minute cortisol value of 752nmol/L. CT thorax, abdomen and pelvis did not show any evidence of malignancy. Sodium improved following fluid restriction and he was discharged home. He represented 2 weeks later with a generalised tonic clonic seizure. On further questioning his wife recounted fluctuating memory over the last few months, sleep disturbance and a change in mood. He was commenced on levetiracetam and had investigations for autoimmune encephalitis. A serum sample detected the presence of LGI-1 antibodies. He completed a course of intravenous immunoglobulin followed by plasma exchange. Sodium increased to 135mmol/land he has not had any further seizure events. The diagnosis of LGI-1 antibody encephalitis provided a unifying diagnosis in this case. In cases of SIAD it is important to consider alternative aetiologies where a cause is not immediately obvious and LGI-1 antibody encephalitis is an important diagnosis to consider in older adults presenting with SIAD, neurological and cognitive symptoms.
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EP1219

JOINT159

Sheehan's syndrome revealed by profound hypothyoidism: a case report

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Introduction
Sheehan's syndrome is a rare but potentially serious complication of the post-partum period. It involves ischaemic necrosis of the anterior pituitary gland secondary to a sudden and/or prolonged state of shock during a delivery haemorrhage.
Case report
A 59-year-old patient with a history of iron deficiency anemia and dyslipidemia over the past 2 years. She was consulted for major asthenia associated with chilliness and chronic constipation. Examination revealed bradycardia and a thyroid work-up showed TSH at 0.7 U/lwith low FT4 <0.42 ng/dl. Questioning revealed a history of haemorrhagic childbirth 15 years ago with absence of lactation and seondary amenorrhoea. An 8-hour cortisol test showed 23 ng/ml and hypogonadotropic hypogonadism. The MRI showed an arachnoidocele. The

patient was substituted.
Discussion
The incidence of this condition is underestimated because diagnosis is often late, made more than ten years after the obstetric event in 50% of cases. Furthermore, it is estimated that around 25% of women who die within the first 30 days post-partum have developed clinical signs of pituitary necrosis. There is an abundance of literature concerning the discovery of Sheehan's syndrome at a distance from childbirth. However, there have been very few reports of this syndrome being diagnosed in the immediate post-partum period.
Conclusion
Postpartum pituitary necrosis is a difficult diagnosis in the acute phase, often unrecognised. Careful questioning can contribute enormously to the diagnosis and early management of our patients.
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EP1220

JOINT3679
Rheumatological manifestations of acromegaly: a report of 78 cases
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Introduction
Acromegaly can manifest itself through very frequent degenerative rheumatological complications responsible for long-term after-effects.
The objective
To describe the rheumatological manifestations of acromegaly.
Patients and Methods
This is an retrospective study of 78 cases of acromegaly followed up in the endocrinology department of Ibn Rochd University Hospital from 2005 to 2024. Rheumatological complications were noted at diagnosis or during follow-up.
Results
The mean age was 45 years (18–72), the sex ratio: 0.33, the mean duration of the disease was 8 and a half years. The mean IGF-1 level was 582 ng/ml or 2.62 times the normal. The rheumatological manifestations like peripheral articular manifestations were dominated by knee pain in 55 patients (42.9%). Diffuse arthralgia was present in 5 acromegalic patients (3.9%), elbow pain in 7 patients (5.46%) and shoulder arthralgia in 3 patients (2.34%). Dorso-lumbar back pain, was present in 36 patients (28.08%) associated with unilateral sciatica in two patients. Carpal tunnel syndrome, were reported in 5 patients (3.9%). The phosphocalcic profile was without abnormality. The mean vitamin D level was 14.3 ng/dl. Bone densitometry showed osteopenia in 5 patients, osteoporosis in one patient and was normal in the rest of the patients.
Conclusion
The rheumatological manifestations linked to acromegaly include peripheral, axial and canal joint involvement, hence the importance of looking for them at the time of diagnosis and during follow-up in order to limit their impact on the functional prognosis of patients.
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EP1221

JOINT1828
Genotype-negative MEN 1 - limitations of genetic testing
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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant disorder caused by germline mutations of the tumor suppressor MEN1 gene. The most common manifestations include: primary hyperparathyroidism (PHPT), pituitary adenomas (PA) and gastroenteropancreatic neuroendocrine tumors (GEP-NET). The classical Sanger monogenic sequencing of the MEN1 gene is the gold standard for the genetic diagnosis. In 10-30 % of MEN1 patients, no mutation is identified through this technique and those are defined as genotype-negative (GN)-MEN1. GN-MEN1 typically has a more favorable clinical course than the genotype-positive MEN1. We herein report two cases of genotype-negative MEN1.
Case Presentation
The first patient, a 60-years-old woman with no family history of MEN1, presented with classic features of MEN1: primary hyperparathyroidism caused by double parathyroid adenomas, for which she underwent surgical excision of the left parathyroid glands, a non-functional pituitary microadenoma and a well-differentiated NET of the ileum, with hepatic and lymph node metastases, for which she was admitted to surgery. She is currently undergoing treatment with lanreotide. She associates non-functional left adrenal hyperplasia and a history of papillary thyroid carcinoma for which she underwent total thyroidectomy and radioactive iodine therapy. The Sanger sequencing of the MEN1 gene revealed no pathogenic variant. The second patient is a 33-years-old woman with two manifestations suggestive for MEN1: double pituitary microadenomas with prolactin secretion and primary hyperparathyroidism with no ecographic localisation, for which she will undergo parathyroid scintigraphy. There is no family history of MEN1. She associates non-functional bilateral andrenal hyperplasia. No MEN1 gene mutations have been identified by the Sanger sequencing.
Conclusion
Sanger sequencing of the MEN1 gene is the gold standard method for accurate detection of single nucleotide variants and small deletions/insertions, but it cannot identify gross gene deletions/insertions. Multiple ligation-dependent probe amplification (MLPA), a multiplex PCR technique that is able to detect large MEN1 coding region deletions/duplications should be considered in MEN1 index cases with negative MEN1 sequencing test. In addition, germline mutations in other genes that may cause a MEN1-like disorder, such as the AIP gene and the cyclin-dependent kinase inhibitor genes CDKN1A, CDKN2C, CDKN2B and CDKN1B, should be considered for further investigations. In conclusion, all methods of genetic testing have their limits, but a high clinical suspicion should be reason enough for more thorough research.
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EP1222

JOINT2707
A clinical case of infective endocarditis in a patient with acromegaly: impact on biochemical markers
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Introduction
Acromegaly is a neuroendocrine disorder characterized by excessive growth hormone (GH) secretion, which exerts anabolic effects on various organs and tissues. Through direct action or indirectly via insulin-like growth factor-1 (IGF-1), GH can contribute to endothelial dysfunction, which is closely linked to cardiovascular complications, including cardiac pathology.
Clinical Case
A 54-year-old patient with acromegaly, who had undergone transnasal transsphenoidal pituitary adenoma resection on October 2019, was admitted to the Endocrinology Research Centre for remission assessment. Notably, two months prior to hospitalization, the patient was diagnosed with infectious spondylodiscitis of unspecified etiology, presenting with persistent fever and back pain. Spinal MRI confirmed spondylodiscitis at the Th6-7, Th9-11, and L3-5 levels. Despite antibacterial therapy, fever persisted. Rheumatological evaluation ruled out HLA-B27-associated spondylodiscitis, and NSAID therapy yielded no improvement. In the neuroendocrinology department, laboratory tests revealed elevated inflammatory markers: ESR 62 mm/h, ferritin 316.1 ng/ml, and CRP 272 mg/l,while procalcitonin remained within normal limits. Given the suspicion of hematogenous infection, transthoracic echocardiography suggested vegetations on the anterior mitral valve leaflet. Transesophageal echocardiography confirmed the presence of vegetations and severe mitral regurgitation. Blood cultures identified *Enterococcus faecalis*, and targeted antibiotic therapy with linezolid was initiated for two months, resulting in clinical improvement and subsequent mitral valve replacement. To assess acromegaly activity, IGF-1 levels were measured at 179.2 ng/ml (reference range: 104–230), while GH was slightly elevated at 6.79 ng/ml (0.4–3.6). However, the presence of an active infection complicated result interpretation. An oral glucose tolerance test (OGTT) for GH suppression was deemed unreliable due to the high likelihood of false-positive results. Brain MRI with contrast enhancement revealed residual adenomatous tissue, no ophthalmological signs of optic-chiasmal syndrome were noted at perimetry. Upon resolution of the inflammatory process, IGF-1 levels increased to 276 ng/ml, with persistent GH elevation and lack of suppression during OGTT. Consequently, octreotide therapy was initiated.

Conclusions
Acute inflammatory processes can significantly impact the interpretation of biochemical markers in acromegaly. Therefore, dynamic monitoring is essential to ensure accurate assessment and timely treatment adjustments.

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EP1223

JOINT3795

Home capillary monitoring of sodium in a patient with adipsic diabetes insipidus

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Introduction
Adipsic diabetes insipidus (ADI) is a rare variant of central diabetes insipidus, characterized by hypotonic polyuria due to arginine-vasopressin deficiency and failure to generate the sensation of thirst in response to hypernatremia secondary to hypothalamic osmoreceptors damage. This predisposes to the development of significant hypernatremia, so its management is complex and requires strict water balance control and treatment with desmopressin.
Clinical case
23-year-old male with neurofibromatosis type 1 and suprachiasmatic pilocytic astrocytoma treated with surgery, chemotherapy and proton therapy. After his last surgery in January 2021, he was diagnosed with ADI, panhypopituitarism and hypothalamic syndrome. For the treatment of ADI, he required high doses of desmopressin (minimum 600 mg/24 hours orally) and instructions were given to family members for its adjustment, as well as for the fluid intake control (minimum 2 liters/24 hours). He had basal natremias between 142 and 150 mmol/l,with frequent episodes of hypernatremia (around 1 to 4 per month) without trigger, up to >160 mmol/l,which were very difficult to control due to multiple factors (adipsia, neurological deterioration, refusal to eat, inability to record diuresis, …). For a period of less than 2 years, he required regular analytical measurements (at least 1 to 2 per month), several Home Hospitalization Unit visits for the administration of intravenous hypotonic solution, and as a last option, visits to the Emergency Department. In addition, he had 2 hospital admissions for this reason. In May 2023, a portable home blood analyzer (EPOC blood analysis system) was provided, properly validated for the determination of capillary sodium, and already used in pediatric ADI patients. Family members began to perform 1 or 2 capillary sodium measurements per week or when symptoms suggested hypernatremia, and instructions for adjusting desmopressin and water intake were reviewed. Given the earlier detection of elevated natremia, to date the patient has not required Home Hospitalization Unit assistance nor has he gone to the Emergency Department again for this sole reason, and switched to having lab tests only every 3 months. In addition, and also importantly, the quality of life of the patient and their relatives improved significantly.
Conclusion
Home capillary monitoring of natremia is an appropriate and cost-effective therapeutic measure for the treatment of ADI in both children and adults. For its proper use, it requires structured education for the patient and/or family members to adjust the treatment based on the results of capillary natremia.

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EP1224

JOINT3928

Is the coexistence of acromegaly with primary empty sella syndrome rare?

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Objective
The association between growth hormone (GH)- secreting pituitary adenomas and primary empty sella (ES) has been reported mostly in case reports and is thought to be rare. In this study aimed to evaluate the coexistence of primary ES in newly diagnosed acromegaly and to investigate the effect of the presence of ES on the clinical and laboratory parameters of acromegaly.
Methods
Fifty-two patients with GH-producing pituitary adenomas who were followed up in our clinic between February 2017 and June 2024 and whose pituitary magnetic resonance imaging (MRI) was available at the time of diagnosis were analyzed retrospectively. Pituitary magnetic resonance imaging (MRI), computed tomography (CT) imaging, and pituitary function tests were evaluated. ES was defined as the pituitary gland and adenoma occupying less than 50% of the sella turcica on midsagittal magnetic resonance (MR) imaging. Demographic data, pituitary adenoma size, hormonal profile and postoperative pathologies of the patients were examined.
Results
Of 52 patients with acromegaly due to GH-producing pituitary adenomas, 27 (51.9%) were female and 25 (48.1%) were male (age range 21-73 years). Empty sella was detected in 8 (15.4%) patients and 2 had complete and 6 had partial empty sella. No ectopic adenoma cases were found in acromegaly patients with empty sella. No significant difference was found in preoperative pituitary hormone levels in patients with and without ES. Postoperative GH and insulin-like growth factor 1 (IGF-1) levels decreased in all patients.
Conclusion
This study showed that newly diagnosed acromegaly and primary ES coexisted in 15.4%. Acromegaly and ES coexisted more frequently than expected. The pathophysiology of this coexistence may be due to soft and hard tissue changes and serebrospinal fluid pressure changes that develop with the paracrine effect of GH during abundant GH production. The association between GH-producing adenomas and ES is not rare, but the underlying mechanism is not yet clear and requires further study.

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EP1225

JOINT1746

A case of hypophysitis successfully treated by corticotherapy: a diagnostic challenge with germinoma in a 5-year-old chil

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Background
Hypophysitis is a rare inflammatory disease of the pituitary gland that can closely mimic neoplastic tumors such as histiocytosis or germinoma. In pediatric patients, it's challenging to distinguish between these conditions because of their overlapping clinical, endocrinological, and radiological features.
Case Presentation
We report the case of a 5-year-old child who initially presented with polyuria, and polydipsia. A hormonal evaluation confirmed central diabetes insipidus, and the patient was started on desmopressin therapy. Brain magnetic resonance imaging (MRI) revealed an enlarged of pituitary gland and thickened stalk, Tumor markers commonly associated with germinoma, including beta-human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP), were negative. Autoimmune evaluation was negative. The patient was started on oral steroid therapy at a dose of 1 mg/kg per day for one month. The initial response was significant, with regression of pituitary stalk thickening on follow-up MRI. However, new anterior pituitary deficiencies (GH, TSH, and ACTH deficiencies) developed. A Follow-up MRIs showed a progressive disappearance of pituitary stalk thickening, while the pituitary gland became hypoplastic. Considering the persistent endocrine abnormalities and the possibility of an underlying neoplastic process, Regular clinical monitoring was maintained through serial imaging and endocrine evaluations.
Conclusion
Autoimmune (lymphocytic) hypophysitis is a rare disease that should be considered in the differential diagnosis of any nonsecreting pituitary mass. An accurate diagnosis is crucial in guiding appropriate treatment and preventing long-term complications.

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EP1226

JOINT2683

A complex case of growth hormone deficiency and pituitary mass in an adolescent girl

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Introduction
Growth hormone (GH) deficiency and pituitary stalk diseases are rare but significant conditions in pediatric endocrinology. However, distinguishing between infundibulohypophysitis and germinoma is crucial, as their management differs significantly—infundibulohypophysitis requires glucocorticoid pulse therapy, whereas germinoma necessitates alternative oncological treatment. In this case, a biopsy is necessary to determine the nature of the lesion.
Objective
This case highlights the importance of accurate differential diagnosis and a multidisciplinary approach in managing patients with GH deficiency.
Case
A 13-year-old girl was referred to the endocrinology department for evaluation of growth retardation, polydipsia, and polyuria, first noted at age 9. During examination height SDS was -3.43, BMI SDS was -2.49, and the bone age was 9–10 years. Karyotyping confirmed a 46XX genotype. Initial evaluations raised a suspicion of diabetes insipidus. Brain magnetic resonance imaging suspected lymphocytic infundibulohypophysitis. Laboratory investigations showed slightly elevated prolactin levels: 39.45 ng/ml (N <23.3 ng/ml), reduced IGF-1: 73.6ng/ml (IGF-1 SDS= -3). Other autoimmune diseases, including celiac disease, were ruled out. A comprehensive immunological panel yielded no abnormalities. Neuroendocrinological assessments included alpha-fetoprotein and beta-human chorionic gonadotropin (β-hCG), both of which were normal. Considering the possible autoimmune nature of the underlying disease, the IgG4 level was assessed and found to be normal. Growth hormone (GH) deficiency was confirmed following two stimulation tests. The arginine stimulation test revealed a peak GH level of 1.57 ng/ml, while the insulin test showed a maximum GH level of 1.03 ng/ml, both below the normal range. Cortisol levels were within normal limits during the initial testing; however, during hypoglycemia, cortisol did not appropriately increase, leading to a diagnosis of subclinical hypocorticism. With water deprivation test urine specific gravity was 1015, which ruled out diabetes insipidus. But one month later she was readmitted with persistent polyuria, polydipsia, and weight loss. To address these symptoms, desmopressin treatment was initiated to evaluate its effectiveness. A lumbar puncture was also performed, AFP and HCG were determined in the lumbar exudate to rule out germinoma, and no abnormalities were found. She started treatment with GH. A follow-up MRI is planned three months later to evaluate the size of the suspected mass.
Conclusions
This case underscores the importance of a thorough and systematic approach in the diagnosis of growth retardation and suspected hypopituitarism. As we were unable to perform a biopsy, a repeat MRI is necessary to further evaluate the pituitary mass.

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EP1227

JOINT1532

TSH-secreting pituitary macroadenoma: a case report and therapeutic considerations

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Background
TSHomas are rare pituitary tumors with an incidence of approximately 1 per million, accounting for 0.5% to 3% of pituitary adenomas. They present significant diagnostic and management challenges.
Case Presentation
A 51-year-old woman with a history of pulmonary embolism, hypertension and hypothyroidism on levothyroxine (LT4) with no regular follow-up, on her preoperative evaluation for an ovarian cyst removal had elevated TSH and free T4 (fT4) levels and was referred to our center for further evaluation. LT4 was discontinued and six weeks later the patient was clinically hyperthyroid with a TSH: 8.3 (0.27-4.20) mU/l,fT4: 5.3 (0.93-1.70) ng/dI, fT3: 11.2 (2.0-4.4) pg/mI. Her sex hormone-binding globulin was raised (SHBG >19 µg/mlæ upper normal limit 10.5) and the rest of her pituitary function was within normal range. Thyroid ultrasound revealed no goiter and there was no family history of thyroid disease. Due to technical and financial constraints, serum alpha subunit measurements were not performed. After assay interference was excluded, dynamic endocrine testing was conducted. The TSH response to TRH stimulation (200 µg TRH intravenously, with TSH measured at baseline, 20, 30, and 60 minutes) was blunted: baseline TSH 12.9 mU/l,peak TSH 17.9 mU/lan increase of 1.4-fold. A T3 suppression test (100 µg of liothyronine daily divided into four doses over 10 days; 25 µgX4) showed no suppression of TSH (TSH 8.4 mU/lafter T3-test.) SHBG levels remained elevated. The findings of these tests were indicative of a TSHoma and therefore the patient had a pituitary MRI which revealed a 17 mm× 11 mm×10 mm suprasellar pituitary macroadenoma. A long-acting somatostatin analog therapy (octreotide LAR 20 mg every 28 days) was initiated and her TSH and fT4 levels dropped within the normal ranges (2.4 mU/land 1.3 pmol/lrespectively).
Conclusion
TSHomas typically present with elevated free thyroid hormone levels and inadequate TSH suppression or are incidentally discovered as sellar masses. The diagnostic approach involves biochemical evaluation (including SHBG, and serum alpha subunit), dynamic testing (TRH stimulation and T3 suppression tests), and often a short course of long-acting somatostatin analog therapy. Pituitary MRI typically reveals findings consistent with an adenoma. While transsphenoidal resection remains the treatment of choice, pharmacotherapy with long-acting somatostatin analog treatment may also be appropriate in selected cases. Factors such as patient preference, absence of chiasm compression, and cavernous sinus invasion (Knosp grade 3B-4) with a low likelihood of gross total resection influence the final decision for treatment.

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EP1228

JOINT2942

Pituitary stalk interruption syndrome as a cause of central hypothyroidism, growth hormone deficiency and hypogonadotropic hypogonadism: a case report

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Background
Pituitary stalk interruption syndrome (PSIS) is a congenital disorder characterised by the triad of an absent or exceedingly thyn pituitary stalk, an ectopic or absent one of pituitary part. PSIS is a common cause of congenital hypopituitarism, and causes a growth hormone deficiency. PSIS features in later childhood may inculde: short stature and delayed puberty. The prevalence of PSIS is unknown. The diagnosis is confirmed through MRI. Treatment should commence as soon as a diagnosis is established to avoid complications, and consists of hormone replacement.
Case report
The 10- year- old boy was diagnosed with short stature. He was born from a normal pregnancy, delivery in 40hbd, in good general condition, weight 4800g, length 63cm. According to anthropometric data, from early childhood, height was below the 3rd percentile. Due to decreased fT4 levels with normal TSH levels, l-thyroxine was included in the therapy. When the patient became euthyroid, he was diagnosed with growth hormone deficiency. Magnetic resonance imaging visualized pituitary stalk interruption syndrome. Actually during therapy with recombinant growth hormone we observed increasing velocity of growth. At puberty, the boy was diagnosed with hypogonadotropic hypogonadism and started therapy with gonadotropins. Genetic testing excluded a mutation within the complex pituitary hormone deficiency genes.
Results
1. PSIS is a rare disease with various clinical characteristics. 2. Diagnosis of PSIS is often delayed, because signs and symptoms are often not evident during the neonatal period. 3. Early diagnosis of hypothyroidism, growth hormone deficiency, hypogonadtropic hypogonadism and appropriate treatment gives a chance for normal development of the child.

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EP1229

JOINT1362

Autoimmunity in a patient with prolactinoma: coincidence or consequence?

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Objectives
Prolactinomas are pituitary adenomas that usually respond well to treatment with dopamine agonists with reduction in both prolactin levels and tumor size. Additionally, patients with autoimmune diseases, such as systemic lupus erythematosus (SLE), have been shown to have elevated prolactin levels. We describe an interesting patient with a prolactinoma who responded biochemically to dopamine agonists, but the tumor size remained resistant to treatment. The course was complicated by evolution of an autoimmune presentation questioning the cross talk between prolactin and autoimmunity.
Case Presentation
A 17-year-old female was referred to pediatric endocrinology for primary amenorrhea and headaches. Biochemical investigation identified hyperprolactinemia with prolactin levels of 1234 ng/ml with undetectable gonadotropin levels and pituitary imaging suggested a macroprolactinoma measuring 1.2 x1.3 x1.5 cm, with a cystic component. Treatment was initiated with cabergoline, leading to a reduction in prolactin levels to 24.8 ng/ml after 6 weeks and onset of menses after 3 months. Over the subsequent 3 years, even though prolactin levels significantly reduced, the reduction in the size of the tumor was not significant with the latest measurements of 1 x 1 x 1.2 cm with persisting cystic component with serum prolactin levels of 112 ng/ml. At the age 19 years, 2 years into treatment with cabergoline, the patient developed arthralgia with positive ANA levels with a working diagnosis of SLE. The patient also tested positive for thyroglobulin and thyroid peroxidase antibodies, indicative of Hashimoto's thyroiditis.
Discussion
A cystic prolactinoma, a less common variant, may present with discrepancy between the degree of hyperprolactinemia and tumor size. Some prolactinomas may also be resistant to treatment with dopamine agonists questioning the presence of a nonfunctioning adenomatous tissue. Hyperprolactinemia has been linked to the pathogenesis of several autoimmune disorders. Although there is some evidence of interaction between hyperprolactinemia and autoimmunity, the exact mechanisms and directionality remain unclear. Patients with SLE, in particular, have been shown to have concurrent hyperprolactinemia, with some cases showing a positive correlation between serum prolactin levels and severity of autoimmune disease. Rare patients have been described with SLE and prolactinoma.
Conclusions
This is a patient with cystic prolactinoma that responded poorly to tumor size reduction despite significant improvement in prolactin levels. The clinical course was complicated by onset of arthralgia with a working diagnosis of SLE. There appears to be a complex interplay between hyperprolactinemia and autoimmunity. Future research should aim to unravel the mechanisms underlying this interaction.

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EP1230

JOINT1250

Clinical features and metabolic risk in girls with premature adrenarche

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Aim
To evaluate the signs of premature adrenarche (PA) in girls and its relationship with clinical signs.
Material and Methods
The study included 148 girls who had clinical signs of PA, and in 85 the corresponding pathology was confirmed. The control group consisted of 30 healthy girls. Serum levels of dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS) and androstenedione (Δ4A) were analyzed. The prevalence of childhood metabolic syndrome (CMS) was assessed using modified WHO criteria.
Results
Based on these results, girls with PA and pubic/axillary hair growth (PAHG; $n = 77$) had higher levels of DHEA, DHEAS, and Δ4A than girls without PAHG ($n = 8$). Increased levels of adrenal androgens were also observed in the PA group without PAHG compared with the control group. The frequency of pMS among girls with PA was 18.5% (63/85), which was higher than the control group (10%, 3/30). The most common component of pMS among girls with PA was overweight (59% vs. 41% in the control group, $P < 0.05$). Girls with PA and PAHG were more likely to have elevated fasting insulin levels (28% vs. 10% in the control group, $P < 0.05$).
Conclusion
An increased concentration of adrenal androgens in serum is associated with the presence of pubic and axillary hair in girls with premature adrenarche (PA). Girls with PA have an elevated risk of developing metabolic syndrome, with excess weight being the most significant risk factor. The obtained data highlight the need for early monitoring of body weight and metabolic parameters in girls with PA to prevent metabolic disorders.

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EP1231

JOINT426

Development of empty sella in neurosarcoidosis; a case report

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Introduction
Sarcoidosis is a multisystem disorder marked by noncaseating granulomatous lesions. Central nervous system involvement, estimated in 5–15% of sarcoidosis patients, localized most commonly to the leptomeninges, cranial nerves or the pituitary gland and hypothalamus, Sellar sarcoidosis comprising less than 1%, presenting with neuroendocrine related features such as diabetes insipidus, hypothyroidism, hypoadrelinism or hyperprolactineamia.
Case report
A 70-year-old woman with a medical history of hypothyroidism on levothyroxine 100 µg/day The patient was diagnosed as pulmonary sarcoidosis four years ago Multi slice CT showed mild diffuse pulmonary interstitial changes with right upper lateral area of subsegmental atelectasis and scattered atelectatic bands likely postinflammatory, focal liver lesions 2x2 cm FDG-PET/CT showed multiple uptakes in lung, liver, pitutary gland bronchoscpony revealed non caseating granuloma. The patient was diagnosed systemic sarcoidosis with propable pitutary neurosarcoidosis she was treated with prednisone(1mg/kg/day) and methotrexate 10mg once a week Follow up multislice CT abdomen showed only mildly enlarged fatty liver with no focal lesions & right renal cortical cyst. Prednisone was tapered after 1 year The dose of eltroxin decreased a couple of years later into 50mg due to constant decrease of TSH which was explained as overcorrection. A year later, She presented to outpatient clinic with weakness, fatigue, anorexia for 3 weeks Examination revealed Bp 110/80 but with orthostatic hypotension, pulse 70/minute, weight 59 kg Labs showed TSH 0.20(0.5-5mIu/l), FT4 0.52 (5-12ug/dl), Serum cortisol AM. 2.6 (5-25 mg/dl), consistent with hypopituitarism MRI pituitary showed partial empty sella with accentuated CSF in the suprasellar cistern compressing the gland against the sellar floor Her eltroxin dose was adjusted to be 75mg/day & she was given hydrocortisone 15 mg.
Conclusions
This case report demonstrates the evolution of a pituitary hyperplasia in a patient with neurosarcoidosis into an empty sella this condition is rarely mentioned among the causes of empty sella.

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EP1232

JOINT1153

A case of spontaneous remission of active pituitary macroadenoma

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A 39-year-old female patient with history of type 2 diabetes mellitus (DM 2) and pituitary macroadenoma was referred to endocrinologist for the follow-up examination. She had regular menstrual cycle on combined oral contraceptive pills (COCPs). Her physical, ophtalmological and neurological examinations were unremarkable except for BMI of 34 kg/m^2. Further testing demonstrated CBC, liver function tests fasting blood glucose, glycated hemoglobin, creatinine, serum electrolytes, TSH levels within the normal range, but decreased GH <0,05 (reference range 0,126-9,88) ng/ml, IGF-1–34,9 (135-449) ng/ml, PRL – 2,5 (6,0-29,9) ng/ml levels and signs of pituitary macroadenoma on MRI about the same size compared to previous examination. After the first delivery (at the age of 24

years) she had irregular menstrual cycle. During the second pregnancy (at the age of 28 years) gestational diabetes was diagnosed. After the second delivery she has received COCPs. At the age of 35 years DM 2 was established. Metformin and DPP-4 inhibitors were administered. At about the same time arterial hypertension and complaints of episodic headaches have appeared. Two years later (at the age of 37 years) pituitary macroadenoma with infra-laterocellar growth with maximal size of 16 mm was detected on MRI, and she was referred to endocrinologist. Patient denied any significant changes in her appearance. Laboratory testing showed normal PRL – 17,15 (6,0-29,9) ng/ml and TSH – 1,6 mIU/ml, but elevated GH–11,7 (0,126-9,88) ng/ml and IGF-1–678,7 (135-449) ng/ml. Somatotropinoma was diagnosed, but patient refused recommended surgery. 3 months later she was admitted to the neurology department with severe headache, resistant to NSAIDs, and vomiting. No visual impairment was detected. Stroke was ruled out on CT scan. Subsequent examination showed normal GH – 0,5 (0,126-9,88) ng/ml, IGF-1 – 154 (135-449) ng/ml, TSH – 2,0 mIU/ml, fT4 – 12 pmol/l,ACTH – 9,0 (6,3-46) pg/ml and depressed PRL – 0,79 (6,0-29,9) ng/ml. The diagnosis of non-active pituitary macroadenoma was established. At the follow-up examination, presented at the beginning of the abstract, further declines in GH and IFG-1 levels were observed. This case demonstrates spontaneous remission of somatotropinoma, gradually resulted in GH deficiency, most likely caused by pituitary adenoma apoplexy. It is remarkable to note that somatotropinoma was initially revealed in the absence of obvious typical features of acromegaly. Further monitoring is needed. Medical specialists should refine their knowledge about pituitary adenoma apoplexy.

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EP1233

JOINT1488

Aggressive somatotropinoma: collaborative management by endocrinologists and oncologists

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Introduction
Acromegaly is a neuroendocrine disorder caused by chronic hypersecretion of growth hormone (GH). The primary treatment goals include achieving biochemical remission, reducing or stabilizing pituitary adenoma size, and alleviating clinical manifestations. While remission is not achieved in approximately 50% of patients, aggressive adenoma growth occurs in only 1-5% of cases.
Clinical Case Description
A 36-year-old patient was diagnosed with acromegaly after presenting with facial features enlargement and an elevated insulin-like growth factor 1 (IGF-1) level of 1000 ng/ml (reference range: 82.0–283.0 ng/ml). Brain MRI revealed a pituitary macroadenoma measuring 24×37×28 mm. Ophthalmological evaluation showed partial atrophy of the right optic nerve and strabismus. The patient underwent transnasal adenomectomy. However, five months post-surgery, the tumor measured 16×22×17 mm, with an IGF-1 level of 1549.5 ng/ml, indicating persistent disease activity. Medical therapy was initiated with 30 mg of long-acting octreotide every 28 days, later replaced with 120 mg of lanreotide every 28 days, followed by the addition of 20 mg of pegvisomant daily. One year later, MRI revealed continued tumor growth (28×29×20 mm), prompting a second adenomectomy. Despite this, the tumor further enlarged within six months (30×35×30 mm), with an IGF-1 level of 1277.6 ng/ml, necessitating radiosurgery. Two years after radiosurgery, MRI showed negative dynamics (tumor size: 32×32×24 mm) with optic chiasm compression. Given the challenging adenoma location and lack of response to conventional therapies, an oncologist was consulted. The patient underwent four courses of chemotherapy with temozolomide, and the pegvisomant dose was increased to 30 mg. However, one month after chemotherapy, tumor progression continued (32×32×38.7 mm), accompanied by worsening vision and right-sided ptosis. To assess the tumor's sensitivity to checkpoint inhibitors, an immunohistochemical study was performed. PDL-1 and VEGF expression was detected in 70–80% of tumor cells, with a Ki-67 index of 17%. Weak expression of somatostatin receptor subtype 5 (IRS-1) was also noted. Based on a multidisciplinary consensus, considering resistance to standard acromegaly treatments and positive PDL-1 and VEGF expression, a combined regimen of nivolumab and bevacizumab was initiated.
Conclusion
This case highlights the importance of extended immunohistochemical analysis and interdisciplinary collaboration between endocrinologists and oncologists in the management of aggressive somatotropinomas. Personalized treatment strategies, including immunotherapy, may be crucial for patients unresponsive to conventional therapeutic approaches.

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EP1234

JOINT1860

A case of nonfunctioning pituitary macroadenoma – 7 year follow-up after transsphenoidal surgery and radiation therapy

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Introduction
Pituitary macroadenomas, particularly nonfunctioning types, are benign tumors that can cause significant endocrine dysfunction due to their mass effects on surrounding structures, including the pituitary gland and optic chiasm. These tumors often present with symptoms related to hormonal deficiencies, visual disturbances, or neurological findings. Diagnosis typically involves a combination of hormonal assessments: ACTH, Cortisol, TSH, FT4, FSH, LH, Testosterone, Prolactin, IGF-1 and imaging, primarily MRI, while management often requires surgical resection. However, complete resection can be challenging, especially in larger tumors with suprasellar extension, where residual tissue may persist, potentially leading to tumor regrowth.
Case Report
A 62-year-old patient initially presented in 2018 with severe fatigue, weakness, weight loss, visual disturbance, headache and episodes of syncope, leading to the diagnosis of adrenal insufficiency. Further evaluation revealed secondary adrenal insufficiency, central hypothyroidism, and secondary hypogonadism, prompting suspicion of a pituitary disorder. MRI imaging identified a 2.7 cm pituitary macroadenoma with suprasellar extension and compression of the optic chiasm. In November 2018, the patient underwent transsphenoidal resection of the pituitary adenoma, which led to significant clinical improvement. Despite initial surgical resection, residual tumor tissue remained, with evidence of gradual growth. Radiation therapy was considered but could not be pursued at that time. In 2022 and 2023, the patient underwent two additional transsphenoidal resections of the residual adenoma. In October 2023, Gamma Knife radiation therapy was performed. The patient is currently well-managed, with no complaints, continues appropriate replacement therapy including levothyroxine, hydrocortisone, and testosterone. Subsequent imaging demonstrates gradual decrease of residual tumor.
Conclusion
This case highlights the challenges of managing large pituitary macroadenomas, particularly those with suprasellar extension and residual tissue post-surgery. It also underscores the importance of a multidisciplinary approach, including surgery and radiation, to address persistent tumor growth and prevent further endocrine dysfunction. Ongoing hormone replacement therapy and careful monitoring of pituitary function remain critical in managing the patient's long-term care.

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EP1235

JOINT924

Clinical and therapeutic management of hypopituitarism during pregnancy in a patient with PROP1-related combined pituitary hormone deficiency

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Introduction
Mutations in the *PROP1* gene lead to combined pituitary hormone deficiency. The clinical and therapeutic management of hypopituitarism and particularly of adrenal insufficiency (AI) during pregnancy is influenced by lack of standard protocols, different cortisol and ACTH threshold values, a higher risk of complications (including adrenal crisis), and non-specific symptoms. We present the case of a pregnant patient with hypopituitarism due to a *PROP1* mutation.

Case presentation
A young Caucasian woman was on regular follow-up for hypopituitarism (GH deficiency, hypothyroidism, AI, and hypogonadism) due to a *PROP1* mutation (homozygous pathogenic variant c.150del(p.Arg53AspfsTer112)), receiving hormonal replacement for all deficiencies since childhood. At 28 years old, she achieved pregnancy after ovarian stimulation treatment and *in vitro* fertilization. Before pregnancy, she was treated with levothyroxine (LT4), modified-release hydrocortisone, and GH replacement therapy (GHRT). The corticotropic and somatotropic axes were adequately replaced, while LT4 dosage had been increased in preparation for assisted reproduction. Once pregnancy was confirmed, GHRT was discontinued and modified-release hydrocortisone was replaced with the standard formulation. Throughout the pregnancy, biochemical monitoring included thyroid function (fT3, fT4) blood glucose and electrolytes, while clinical monitoring focused on symptoms, blood pressure, and weight measurements every 2-3 weeks. As suggested in the literature, during the late second and third trimesters, both hydrocortisone (up to 30 mg/day) and LT4 (up to 3 μg/kg/day) dosages were increased. The patient remained clinically stable and fetal growth was normal for gestational age. At 26 weeks, a glucose tolerance test was performed with normal results. Delivery was planned at a third-level Neonatal Intensive Care and Gynecology center to enable a multidisciplinary approach. The patient delivered a healthy male newborn by C-section at 39 weeks. For adrenal crisis prevention, intravenous hydrocortisone was given at the onset of active labor, followed by a continuous infusion for 24 hours, and additional boluses in the 2 days after delivery due to moderate hyponatremia. After that, oral hydrocortisone was restarted at twice the dose used during pregnancy due to general malaise. LT4 dosage remained also increased in the postpartum period.
Conclusions
The management of AI during pregnancy is hindered by the lack of dedicated guidelines. Hydrocortisone is the glucocorticoid of choice, and a 20-40% dose increase is often needed during the last trimester. Clinical monitoring for signs and symptoms of under- or over-replacement is recommended. Gestation in patients with congenital hypopituitarism is a clinical challenge, but it can be safely managed in specialized centers.

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EP1236

JOINT1826

Anthropometric or biochemical markers to predict the onset of menarche

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Purpose
The potential of height growth is decreased to about 2-2.5cm after menarche and many children and their parents worry about the early menarche. This study is to find out the markers to predict the onset of menarche.
Method
We collected the anthropometric data (height, weight, and growth velocity), chronologic and bone age, Tanner stage, biochemical data (serum LH, FSH, estradiol, and progesterone levels) at 12 months and 6 months before the onset of menarche in 28 girls who visited the growth clinic of a university hospital from Jan 1, 2020 to Jul 31, 2024. The data of 12 months and 6 months were compared with the paired T-test using SPSS ver.28.
Result
The comparison of the data between the 12 months and 6 months before menarche were as follows. The mean growth velocities of height were 2.94cm and 2.92cm, and weight were 1.48kg and 2.03kg ($P=NS$). The bone ages were 12.5 and 12.79 years old ($P=NS$). The Tanner stages were almost 4 in both. The serum levels of LH were 2.34 ± 1.38 and 4.06 ± 2.53 mIU/ml ($P<0.01$). The serum levels of FSH were 4.37 ± 1.69 and 5.86 ± 2.07 mIU/ml ($P<0.05$). The serum levels of estradiol were 24.52 ± 13.39 and 45.61 ± 19.7 pg/ml ($P<0.01$). The serum levels of progesterone were 0.12 ± 0.1 and 0.18 ± 0.16 ng/ml ($P=NS$).
Conclusion
The periodic measurements of baseline serum levels of LH, FSH, and estradiol are more valuable than anthropometric data to predict the onset of menarche in girls.

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EP1237

JOINT2389

"Whispering" cushing syndrome: presentation of three cases

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Introduction
'Whispering' pituitary adenomas (WPA) are a rare subtype of pituitary neuroendocrine tumors (PitNETs), characterized by immunohistochemical evidence of pituitary hormone production or specific transcription factors, along with biochemical activity, but minimal or no clinical symptoms. These adenomas represent 1.1–6% of surgically resected pituitary tumors and 17–22% of adrenocorticotropic hormone ACTH-positive tumors.
Aim
To describe three cases of pituitary adenomas later identified as WPAs. **Case 1**: A 36-year-old female with menstrual disturbances, headaches, and galactorrhea was diagnosed with a pituitary macroadenoma ($1.4\times1.2\times1.15$ cm). She was treated with cabergoline due to mild hyperprolactinemia, which improved her symptoms. Hormonal evaluations showed a morning cortisol of 21 μg/dl (10-20), ACTH of 37 pg/ml (7.2-63), and a normal overnight dexamethasone suppression test (ODST). After worsening headaches, she underwent transsphenoidal surgery. Histology revealed ACTH staining and a Ki-67 index of 3%. Two years post-surgery, the patient remains asymptomatic with no signs of Cushing's disease. **Case 2** A 76-year-old female was referred after pituitary macroadenoma apoplexy (adenoma size 1.9×1.6 cm), managed conservatively. The tumor had been discovered incidentally seven years earlier ($1.3\times1.1\times0.8$ cm), but no functional evaluations were conducted. The patient showed no clinical signs of hypercortisolism but had mild metabolic disturbances (overweight and osteopenia.). Biochemical tests indicated ACTH-dependent Cushing's syndrome (ACTH = 91.7 pmol/l,ODST = 11.1 μg/dl, urine cortisol = 126.8 μg/gCR). Given tumor progression, surgery was performed, and histopathology confirmed an ACTH-positive pituitary adenoma with a Ki-67 index of $<1\%$. Postoperative follow-up showed normalized biochemistry and no residual disease. **Case 3:** A 60-year-old male presented with a history of transsphenoidal pituitary adenomatectomy 17 years before. Postoperatively, he had developed deficiencies in the gonadotropic and thyrotropic pituitary axes and was placed on replacement therapy. Histological examination confirmed the diagnosis of a pituitary adenoma. Three years before, a follow-up pituitary MRI showed tumor relapse measuring 3.2×2.1 cm. The patient displayed no clinical signs of hypercortisolism, and hormonal evaluation revealed a morning cortisol level of 8.53 μg/dl, ACTH at 10.9 pg/ml. Surgery was repeated, histopathological findings were consistent with pituitary adenoma, with a Ki-67/MIB1 index of 2-3% and limited positivity for ACTH.
Conclusions
Corticotropic adenomas present with varied clinical manifestations, from subtle symptoms to no signs at all. Diagnosis relies on biochemical profiles and immunohistochemistry. Close monitoring post-surgery, including regular imaging and biochemical follow-up, is critical for managing these tumors effectively.

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EP1238

JOINT3814

Acromegaly and metabolic complications: a report of 78 cases

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Introduction
Metabolic disorders caused by acromegaly are responsible for morbidity three times higher than that of the general population.
The objective
To analyze the different metabolic complications in acromegalic patients.
Patients and methods
This is a retrospective study of 78 cases of acromegaly followed at the endocrinology department of Ibn Rochd University Hospital from 2005 to 2024. All our patients underwent a metabolic assessment: fasting blood sugar, HbA1c, total cholesterol, HDLc, LDLc, triglycerides with uric acid measurement.
Results
The mean age was 45 years, sex ratio: F/M of: 0.45. The mean BMI rate was 28 kg/m^2 with overweight in 14 patients (10.9%), and obesity in 26 patients

(20.28%). On metabolic assessment: prediabetes in 18 patients (14.04%) and diabetes in 32 patients (24.96%). Dyslipidemia was observed in 41 patients (31.98%) with a mean cholesterol level of 2 g/l,mean triglyceride of 1.69 g/l,mean HDL of 0.41 g/land mean LDL level of 0.99 g/L. Hyperuricemia in 5 patients (6.25%) with a mean uric acid level of 46 mg/L. Treatment of diabetes was based on life style management associated with oral antidiabetics (88%), and insulin therapy + ADO (12%). Patients with dyslipidemia were put on life style management with statins in 58.5%.

Conclusion

Systematic screening of metabolic complications in acromegalic patients and their early and adequate management is of major interest in order to prevent the resulting morbidity and mortality.

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EP1239

JOINT3307

Pituitary apoplexy complicated by subarachnoid hemorrhage: the role of stress and cabergoline therapy

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Introduction

Giant prolactinomas, due to their size and invasive nature, can lead to serious complications. While cabergoline is effective in reducing the tumor and normalizing prolactin levels, it can cause rare but significant side effects, such as pituitary apoplexy, especially after rapid tumor reduction or physical and emotional stress.

Observation

A 45-year-old patient, with no significant family history, was diagnosed with a 7 cm invasive pituitary macroadenoma (Knosp 4), associated with a giant prolactinoma, hyperprolactinemia, and visual disturbances. Cabergoline was started due to surgical contraindication, resulting in a significant reduction in prolactin from 12,000 ng/ml to 246 ng/ml after one month. Three months later, ophthalmological exams were normal, except for the exclusion of a blind spot. Prolactin was below 0.5 ng/ml, and MRI showed a significant reduction in tumor size (35 mm). One year later, after a physically demanding move and significant psychoaffective stress, the patient developed headaches and vomiting. MRI revealed pituitary apoplexy with bilateral subarachnoid hemorrhage, without hydrocephalus. He was hospitalized, and in the absence of severe neurological signs or major visual disturbances, a conservative treatment approach was chosen.

Discussion

This case describes a giant prolactinoma treated with cabergoline, with an initially favorable response. However, after physical stress (moving), the patient developed pituitary apoplexy complicated by subarachnoid hemorrhage. Physical effort likely triggered the apoplexy due to the tumor's proximity to the subarachnoid space. Although cabergoline is effective, it can rarely cause apoplexy, especially with large adenomas, due to rapid changes in tumor vascularization. Close follow-up is essential.

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EP1240

JOINT3915

Co-occurrence of tuberous sclerosis and pituitary stalk interruption syndrome: a rare clinical presentation

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Background

Tuberous sclerosis complex (TSC) is a rare inherited neurocutaneous disorder characterised by a diverse range of benign growths, or hamartomas, affecting multiple organ systems. These can involve the brain, eyes, heart, lungs, liver, kidneys, and skin. The expression of TSC varies considerably between individuals. Clinical diagnosis is typically supported by imaging and genetic testing, with characteristic brain lesions such as glioneuronal hamartomas, subependymal nodules, subependymal giant cell astrocytomas, white matter lesions, and arachnoid cysts being commonly observed. Pituitary stalk interruption syndrome PSIS is **diagnosed primarily through magnetic resonance imaging (MRI)** of the brain which shows the characteristic abnormalities of the pituitary stalk and posterior pituitary location, while TSC diagnosis often involves genetic testing, clinical evaluation, and imaging studies to identify the characteristic brain lesions. Though both of TSC and pituitary stalk interruption syndrome (PSIS) is rare, the co-occurrence of these two conditions is even less frequent.

Clinical Case Description

A 41-year-old female with a medical history of TSC presented with polydipsia and polyuria. Laboratory tests revealed hypernatremia, alongside highly diluted urine, which led to a diagnosis of arginine vasopressin deficiency (AVP-D) (diabetes insipidus). The patient's history of TSC included bilateral renal angiomyolipomas (AML), learning difficulties, epilepsy, autism, and lymphangioleiomyomatosis affecting the lungs, kidneys, and lymphatic system. Upon initiation of Desmopressin treatment, her sodium levels normalised, and her carers reported significant improvement in her symptoms, including a reduction in excessive thirst and inappropriate fluid intake. In the past, she had been observed licking condensation from windows due to her heightened thirst. MRI of the pituitary gland, performed under sedation, **revealed a hypoplastic anterior pituitary, an absent infundibulum, and agenesis of the posterior pituitary gland, findings that are consistent with pituitary stalk interruption syndrome (PSIS).** Notably, the anterior pituitary profile was unremarkable.

Conclusion

This case highlights the rare and complex interplay between TSC and PSIS, the occurrence of both in a single patient is uncommon. Further research into the genetic mechanisms behind these conditions may provide insights into their co-occurrence and potential management strategies.

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EP1241

JOINT2064

A case of cushing disease presenting with pituitary apoplexy in an adolescent female

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This is a case report of a 16yo female presenting with pituitary apoplexy, secondary to an ACTH-secreting pituitary macroadenoma. On history, they reported an eighteen-month history of weight gain, hyperphagia and behavioural disturbance requiring psychiatric hospitalisation. Other noted features of Cushing Disease included oligomenorrhoea, acne, hirsuitism, abdominal striae, buffalo hump and acanthosis. She reports subjective visual changes premorbidly, although formal testing was not sought. During this time a clinical diagnosis of polycystic ovarian syndrome and Type 2 Diabetes Mellitus were made, and the patient commenced on metformin 2g daily. Relevant biochemistry included FSH 3IU/l,LH 2IU/l,Estradiol 174pmol/l,testosterone 2.1nmol/l,free testosterone 80pmol/l,progesterone 2.1nmol/l,17-OHP 0.8nmol/l,OGTT normal. They were reviewed for obesity shortly before presentation with apoplexy. A dexamethasone suppression test one week prior demonstrated an unsuppressed morning cortisol of 550nmol/lwith ACTH not recorded. Other Cushing Disease screening was planned. Past medical history was significant for precocious puberty with thelarche from 5 years of age, and GnRH treatment between 8 and 10.5 years of age. A contrast MRI at 9 years was reported normal with no evidence of pituitary lesion. Tall stature and obesity were present at this time, with a BMI Z-score consistently +2.5 SDs. Following triptorelin cessation they achieved menarche at 12 years of age and was discharged from the endocrinology service. At diagnosis they presented with thunderclap headache, visual loss, nausea and confusion. Apoplexy was demonstrated on CT and MRI. Urgent retrieval and neurosurgical evacuation of haemorrhage and tumour residue was performed, and the patient treated empirically with high-dose steroids. Histopathology confirmed the presence of ACTH-producing pit-NET. The post-operative course was complicated by venous thrombosis, posterior reversable encephalopathy syndrome (PRES), visual impairment, and glucocorticoid withdrawal syndrome. Early assessment of the hypothalamic-pituitary-adrenal axis suggests resolution of Cushing Disease and adrenal gland recovery, however, attempts to reduce post-operative hydrocortisone below 80mg/day (50mg/m^2/day) results in significant steroid withdrawal symptoms. Due to this, we are weaning steroids slowly at an increment of 5mg/m^2/day every other week. Other pituitary hormone functions are intact, although menses have not yet resumed. Additionally, an oral glucose tolerance test was normal. This case is interesting as both

ACTH-secretion macroadenomas and pituitary apoplexy are rare in the paediatric age group. This case highlights the high morbidity associated with such a diagnosis and opens discussion into the importance of considering Cushing Disease in the setting of an increasingly obese population.

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EP1242

JOINT2640

Analysis of obesity frequency in girls with central precocious puberty

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Context
Obesity and central precocious puberty (CPP) are linked, especially in girls, but its impact on CPP progression and treatment remains unclear.
Objectives
To assess obesity frequency in girls with CPP, analyze BMI evolution during GnRH analog treatment, and compare CPP parameters between eutrophic and overweight girls.
Methods
Data from 80 girls diagnosed with CPP and treated with GnRH analogs were analyzed (April 2017–November 2024). Anthropometric data, bone age, and pubertal staging were collected at diagnosis, treatment initiation, annually during treatment, at discontinuation, and after menarche. Height and BMI were expressed as z-scores (WHO, 2007).
Results
At diagnosis, 50% of patients were overweight. Mean (SD) zBMI was 1.1 (1.2) at diagnosis and 1.3 (1.1) at treatment discontinuation ($P = 0.067$). Girls were classified as eutrophic or overweight. zBMI increased only in eutrophic girls (0.455 vs. 0.585; $P = 0.012$). Thelarche age was similar (6.5 vs. 6.0 years; $P = 0.43$), but eutrophic girls had a shorter interval between thelarche and GnRH initiation (1.4 vs. 2.0 years; $P < 0.001$). At treatment initiation, overweight girls had higher height z-scores (1.8 vs. 1.0; $P = 0.003$). No differences were found in treatment initiation age (7.9 vs. 8.0 years; $P = 0.655$), GnRH discontinuation age (10.0 vs. 9.8 years; $P = 0.164$), or menarche age (11.3 vs. 10.8 years; $P = 0.320$). However, overweight girls had a greater difference between bone age and chronological age at treatment initiation (2.9 vs. 2.3 years; $P = 0.011$).
Conclusions
While no overall zBMI change occurred during GnRH treatment, eutrophic girls showed an increase. Despite similar thelarche ages, eutrophic girls started pubertal blockade earlier. Overweight girls had a greater bone age-chronological age difference, and their later treatment initiation may predict greater height loss. No differences were found in treatment discontinuation or menarche age. Further studies assessing final height are needed to evaluate the height loss risk in overweight patients.

Keywords
central precocious puberty, obesity, BMI, GnRH.

Abbreviations
CPP, central precocious puberty; BMI, body mass index; GnRH, gonadotropin-releasing hormone; SD, standard deviation.

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EP1243

JOINT2556

Copeptin and MR-proADM, do not show the risk of cardiometabolic disease in patients with acromegaly—preliminary results

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Background
Cardiovascular complications are a major cause of premature mortality in patients with acromegaly. Copeptin (CPP) is closely associated with plasma osmolality and is influenced by non-osmotic stimuli that play a role in the development of cardiovascular disease. Mid-regional proadrenomedullin (MR-proADM), primarily produced in the adrenal medulla, vascular endothelial cells, and the heart, has known vasodilatory effects. This study aimed to evaluate two cardiovascular biomarkers (CPP and MR-proADM) in patients with acromegaly concerning disease activity and to compare the results with those of a control group.
Methods
The study analyzed CPP and MR-proADM levels, along with hormonal and biochemical parameters, and the prevalence of cardiovascular and metabolic diseases in 53 patients with acromegaly and 26 controls.
Results
No significant differences were found in CPP or MR-proADM levels between the two groups. However, a positive correlation was observed between growth hormone (GH) and CPP levels, while a negative correlation was noted between fasting glucose and CPP levels among acromegaly patients. Additionally, there was a positive correlation between low-density lipoprotein (LDL) and MR-proADM levels, as well as between high-density lipoprotein (HDL) and MR-proADM levels in the study group. Atherogenic dyslipidemia was significantly more prevalent in patients with active acromegaly and pituitary macroadenomas compared to the control group. Acromegaly patients also exhibited significantly higher fasting glucose and insulin levels than controls.
Conclusions
Neither CPP nor MR-proADM serves as significant diagnostic or monitoring biomarkers for cardiovascular or metabolic complications in patients with acromegaly.

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EP1244

JOINT2756

Prevalence and clinical characteristics of central precocious puberty: experience of single academic center in Serbia

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Introduction
Central precociuos puberty (CPP) is a premature development of secondary sex characteristics (breast bud before 8 years in girls and enlargement of testicles before 9 years in boys), accompanied with growth and bone age acceleration. The gold standard for diagnosis is stimulated LH above 5 mU/lduring LHRH test. We observed the reports of increased incidence of CPP girls in the last decade.
Aim
To analyze patients with CPP diagnosed and treated in the last 10 years in the University Children's Hospital.
Methods
The design of the study was a retrospective chart review of patients treated in the University Children's Hospital between 2014 and 2024. We collected data about their birth history, family history, age at presentation of puberty, auxology data, basic LH, stimulated LH and bone age.
Results
We analyzed the prevalence of CPP patients treated at our hospital in the last decade. The available records revealed below 9 patients before 2019. In 2020 we treated 12 patients, with significant increase in 2021 (24) and stable number in the following years. In the last 5 years we noticed the rise of males with CPP and girls born small for gestational age (SGA). The average age at the initiation of the treatment with GnRH analogue treatment was 7.08 $\pm$ 2.21 years. Bone age was fairly advanced in all patients, basic LH was 1.64 $\pm$ 1.4 mU/land stimulated LH 12.7 $\pm$ 7.7 mU/L. Currently 43 (39 F/4M) patients are receiving GnRH analogue therapy every 3 months.
Conclusion
We noticed increasing numbers of CPP patients in the last decade, especially in the first years of COVID pandemic. The age at presentation remains the same, but

we observed increased number of girls born as SGA. We speculate that enlarged number of patients with CPP might be due to obesity rising trend.

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EP1245

JOINT2205

Fenestrated pituitary infundibulum in a young woman with ehlers-danlos syndrome: a case report

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Introduction

Fenestration of the pituitary infundibulum is a rare anatomical variant, often incidentally discovered on brain imaging. This case report describes a young woman with Ehlers-Danlos syndrome (EDS) who presented with frequent headaches. An magnetic resonance imaging (MRI) revealed a fenestrated pituitary infundibulum. The potential association between EDS and pituitary abnormalities is unknown. There is no known evidence about that connection in current literature.

Case Description

A 41-year-old woman with a known history of Ehlers-Danlos syndrome presented to the endocrinology clinic with MRI scan describing fenestrated pituitary infundibulum. The pituitary gland itself appeared normal in size and structure, with no evidence of adenoma or other lesions. Endocrine evaluation included assessment of the hypothalamic-pituitary-gland axes with no evidence of hormonal dysfunction.

Discussion

Fenestration of the pituitary infundibulum is a rare finding, often considered an anatomical variant without clinical significance. However, in this case, the presence of EDS raises the possibility of a connective tissue-related structural abnormality. EDS is characterized by defects in collagen synthesis, which may affect the integrity of the pituitary stalk and surrounding structures. Although functional MRI of the pituitary region could provide additional insights into potential microstructural or vascular changes, this imaging modality was not available in our clinical setting.

Conclusions

This case highlights a rare finding of a fenestrated pituitary infundibulum in a young woman with EDS. Although no endocrine dysfunction was identified, the potential link between EDS and structural pituitary abnormalities should be considered in patients with connective tissue disorders. Further studies are needed to explore this association and its clinical implications.

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EP1246

JOINT1931

Why was the hypopituitary patient's life not saved?

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56-year-old male patient visited his doctor as an outpatient with fatigue and chest complaints. Acute coronary syndrome was excluded. 3 weeks later, the patient voluntarily presented to the psychiatric clinic, from where he was immediately admitted to the ward for sleep disturbance and psychomotor slowing. On admission, hypotension, elevated cardiac necro enzymes, proBNP values and hyponatraemia were seen despite continuous Na supplementation. Low sodium levels despite sodium supplementation, the patient was referred to the endocrinology department for investigation of suspected hypoadrenia. His hormone profile confirmed panhypopituitarism, underlying cranial imaging confirmed a 9x12.5x10 mm pituitary macroadenoma, no neurosurgical intervention was performed. Despite adequate hormone replacement, no improvement was seen in the patient's condition, and the clinical picture was still characterised by a high degree of weakness and anaemia. Gastroscopy and biopsy raised the possibility of amyloidosis. Subsequently, the patient was referred to the cardiology department, where cardiac MRI confirmed the diagnosis of cardiac amyloidosis. Serum immunoelectrophoresis was performed due to elevated kappa light chain values and bone marrow biopsy was performed, which revealed the presence of multiple myeloma, and AL amyloidosis was described in the heart. Recovery from heart failure therapy was initiated, he developed another hypotensive crisis, Staphylococcus aureus infection, sepsis, resulting in patient's death. The picture of hypothyroidism as part of panhypopituitarism showed similar similar clinical symptoms to AL amyloidosis. Despite hormone replacement, the patient's life could not be saved due to the severe co-morbidity, AL amyloidosis and consequent heart failure.

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EP1247

JOINT2340

Diagnostic challenges in polyuria-polydipsia syndrome: a case from resource-limited setting

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Introduction

Polyuria-polydipsia syndrome is a rare medical condition, characterized by excessive urine output ($\geq$3 L/24 hour) with continuous ingestion of fluids. This syndrome can be due to defects in antidiuretic hormone production, secretion or renal response or from primary excessive fluid intake. Correct diagnosis is crucial, as treatment protocols differ significantly. A misdiagnosis may result in severe, life-threatening outcomes. However, the challenge lies in reaching an accurate diagnosis due to a significant overlap among the different forms of Diabetes insipidus (DI) and primary polydipsia, particularly in developing countries like Georgia, where access to diagnostic tests is limited.

Case presentation

We present an 18-year-old girl with history of polydipsia, polyuria, oligomenorrhea and binge eating. On physical examination, her vitals were within normal limits and body mass index was 28.8 kg/m^2. Additional evaluation was performed, including a negative urinary pregnancy test and the exclusion of urinary tract infection. Patient denied any history of head trauma. A 24-hour urine collection test was conducted, which confirmed polyuria (8.5 L/24 h). Additional testing excluded osmotic diuresis; electrolyte levels were within normal ranges, sodium being high-normal. Osmolality measurements revealed low urine osmolality-271mOsm/kg, while serum osmolality remained within normal limits. Based on the laboratory results neither primary polydipsia nor DI could be confirmed or excluded. The patient was advised to undergo further evaluation with water deprivation test. However, this test could not be fully performed in Georgia, as osmolality measurements are sent abroad, requiring days for results. Consequently, the second phase of the test, the desmopressin challenge, could not be conducted locally. Given the patient's clinical history and laboratory findings, it was decided to proceed with partial water deprivation test, focusing on the dehydration phase, with subsequent assessment of osmolality and copeptin levels. Additionally, psychiatric evaluation was recommended to further guide the diagnostic process. Following the partial water deprivation test, urine osmolality remained low, indicating the need for desmopressin phase. However, due to financial constraints, the patient was unable to travel abroad for further testing. As a result, psychiatric and psychological treatment were initiated with close supervision. Within a few weeks, the patient reported a noticeable reduction in water intake and an overall improvement in her symptoms.

Conclusions

This case highlights the complexities of diagnosing polyuria-polydipsia syndrome, especially in developing nations. Water deprivation test remains gold standard, with desmopressin phase providing essential diagnostic value. However, limitations in diagnostic resources in Georgia create substantial obstacles. Though the water deprivation test remained incomplete, the patient's gradual improvement following psychological intervention supports the diagnosis of psychogenic polydipsia. Main emphasis of this case is the relevance of a team-based approach in managing complex endocrine disorders, especially in countries where diagnostic tools are limited.

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EP1248

JOINT1034

Delayed diagnosis of pituitary apoplexy in a patient with migraine

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Introduction
Pituitary apoplexy is a rare clinical syndrome that occurs as a result of acute haemorrhage and/or infarction within a pituitary tumour. Classical presentation includes sudden onset headache, vomiting, visual impairment and possible partial or panhypopituitarism. Pituitary apoplexy is frequently spontaneous, but predisposing factors can be identified in 10–40% of cases. As the clinical syndrome overlaps with other presentations, recognition of pituitary apoplexy is challenging, which delay diagnosis and management. We describe the case of a pre-existing history of migraines leading to a late diagnosis of pituitary apoplexy.
Clinical case
A 34-year-old man presented to the hospital with sudden onset throbbing headache and several episodes of vomiting without fever, rash or neck stiffness. He had a background of chronic migrainous headache requiring hospital admission previously. Past medical history also included type 1 diabetes mellitus, and a 12mm non-functioning pituitary macroadenoma. Initial CT head imaging did not reveal any pathology and both an MRI and lumbar puncture were planned to exclude SAH. During admission, he developed hyperglycaemia with ketosis, which was managed by an intravenous insulin infusion. His headache did not demonstrate improvement and lumbar puncture was positive for xanthochromia. On the sixth day of admission, his sodium level dropped from 133mmol/lto 108mmol/L. The medical team assessed the patient to be hypovolemic and administered intravenous fluids. The possibility of pseudohyponatraemia secondary to hyperglycaemia was also raised. On the same day, the patient reported new visual deterioration. An urgent pituitary MRI was performed and intravenous Hydrocortisone was commenced. Anterior pituitary profile showed a cortisol of 19nmol/l,FSH 1.1IU/l,LH $<$1.0IU/l,testosterone 0.5nmol/l,prolactin 40mIU/l,free T4 12.5pmol/l,free T3 2.2pmol/land TSH 0.08mIU/L. MRI showed signs of apoplexy. Severe hyponatremia was managed in Intensive Care and he was commenced on hydrocortisone, levothyroxine and testosterone, and surgery done after that. Interval surveillance pituitary MRI showed significant reduction in the size of the lesion without mass effect on the chiasm. The patient remains on replacement therapy with Hydrocortisone, Levothyroxine and Testosterone.
Discussion
This case highlights the importance of considering apoplexy early within the differential of a patient with a pituitary adenoma presenting with sudden onset headache. Delayed diagnosis of pituitary apoplexy is common in the case of undiagnosed pituitary adenoma, but can be avoided in a patient with a known diagnosis. Hyponatraemia may occur secondary to cortisol insufficiency. Therefore, when apoplexy is suspected, the management should include administration of intravenous glucocorticoid therapy.

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EP1249

JOINT2460

Management of macroprolactinomas during pregnancy: about 2 cases

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Introduction
Prolactinomas are the most common pituitary adenomas and are a cause of infertility due to anovulation. Their treatment restores normal fertility. During a normal pregnancy, oestrogens cause hyperplasia of the lactotropic cells, responsible for hyperprolactinaemia and pituitary hyperplasia on MRI. Pregnancy in a patient with a prolactinoma poses several problems.
Observation
1st case: We report the case of a patient aged 40 years, followed for a macroprolactinoma, revealed at age 32, by secondary amenorrhea and bilateral galactorrhea, associated with a tumor syndrome. At the bill, hyperprolactinaemia at 305.60 ng/ml with pituitary MRI: a left lateralized pituitary nodular formation measuring: 10*8 mm. The patient was placed on cabergoline 0.5 mg: 4 cp/week, with a progressive decrease and then normalization of prolactinemia. After 7 years of treatment, the patient consults for pregnancy at 12 SA. The course of action was to reduce the dose of cabergoline to 0.5 mg/week and schedule monthly clinical follow-up. 2nd case: 33-year-old patient, followed for macroprolactinoma since the age of 25, revealed by a secondary amenorrhea, with a tumor syndrome, diplopia and galactorrhea. With an MRI pituitary adenoma occupying the entire saddle cavity measuring 11x 10 x 11 mm and a prolactinemia at 563.80 ng/ml. Treated with cabergoline, the course was marked by pregnancy. The course of action was to continue the cabergoline and schedule regular follow-up.
Discussion
When a patient has a prolactin adenoma, pregnancy will be achieved in the vast majority of cases with precautions depending on the initial tumor size. The risk of developing microprolactinomas is low, allowing for a discontinuation of dopamine agonists once pregnancy has been diagnosed. The approach differs in the case of macroprolactinomas, where the risk of progression is higher and therefore the continued dopaminergic agonist therapy during pregnancy is justified. Monitoring involves monthly clinical check-up and possibly a detailed neuroophthalmological examination, the frequency of which will depend on visual symptoms and the pre-pregnancy situation (size of the tumour; proximity of the optic pathways; presence or absence of a visual deficit before pregnancy). A pituitary MRI without contrast should be performed in case of symptoms suggestive of tumor progression or apoplexy (headaches; deficit of acuity or visual field; oculomotor disorders..).
Conclusion
Management of macroprolactinomas during pregnancy should be cautious and monthly, because the increase in tumor volume, with a risk of apoplexy, is observed in cases reported in the literature.

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EP1250

JOINT2625

Non functional pituitary macroadenoma expressing GH, LH and ACTH

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Introduction
Non-functional pituitary adenomas are benign neoplasms that arise from adenohypophyseal cells and are not associated with clinical signs of hormonal hypersecretion. They form a broad and heterogeneous group Plurihormonal adenomas can be classified into two groups: “PIT1-positive adenomas” (formerly known as subtype 3 silent pituitary adenomas); and plurihormonal adenomas with more than one transcription factor, known as ‘plurihormonal adenomas with unusual immunohistochemical combinations’. WE present the case of a rare plurihormonal combination of a non-functioning macrodenoma.
Observation
Patient aged 27 The onset of symptoms dates back to July 2023, with the onset of a drop in visual acuity, prompting the patient to consult an ophthalmologist for a visual field test, which revealed a bitemporal hemianopia, followed by a pituitary-hypothaloid MRI, which showed an invasive pituitary macroadenoma. adenoma, initially measuring 42*49*25mm, referred urgently for neurosurgery in view of the visual repercussions. Moreover, the patient reported no signs or symptoms related to tumour hypersecretion identified by a preoperative work-up, including IGF1, which returned normal at 184ng/ml for his age. HISTOCHIMIC study was in favour of a plurihormonal pituitary adenoma strongly expressing GH, weakly ACTH and LH, with KI67 estimated at 2% The evolution in 03 months post-op was marked by the persistence of a pituitary residue measuring 15*14*12mm on control MRI, completed by an endocrine work-up showing gonadal, thyroid and corticotropic anteropituitary insufficiency. and IGF levels normal for age. In addition, the patient did not report any tumour symptoms, such as headaches or reduced visual acuity.
Discussion
Patients with non-functional pituitary adenomas have less chance of remission than patients with functional pituitary adenomas. Adenomas can progress after surgical treatment, with regrowth rates of 15-66% in patients with non-functional adenomas treated with surgery alone, and 2-28% in those treated with surgery and radiotherapy. Long-term radiological monitoring after treatment of these adenomas is therefore recommended. No convincing prognostic factors for recurrence of these adenomas have yet been found. Clinical factors such as age, gender, tumor size and tumor invasion have limited predictive value for tumor progression. On the other hand, Ki-67 has been described as an independent cellular marker of tumor progression and recurrence.
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EP1251

JOINT2796

Discordant disease activity indicators in a patient with acromegaly

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Introduction
Acromegaly is a neuroendocrine disorder characterized by chronic hypersecretion of growth hormone (GH). Insulin-like growth factor 1 (IGF-1) is currently the primary marker for assessing disease activity and treatment effectiveness due to its strong correlation with GH levels. However, cases with discordant GH and IGF-1 levels pose diagnostic and therapeutic challenges.
Clinical Case Description
At 22 years old, Patients. reported back pain, recurrent fever, skin hyperpigmentation, breast discomfort with nipple discharge, and progressive enlargement of facial features, hands, and feet. Laboratory tests revealed hyperprolactinemia (1,701.0 mIU/l; reference range: 66.0–436.0) and non-elevated IGF-1 (164.0 ng/ml; reference range: 82.0–283.0). Brain MRI identified a pituitary macroadenoma measuring 26×41×34 mm. Treatment with cabergoline 0.5 mg twice weekly was initiated. At 23 years old, despite a normal IGF-1 level (85.4 ng/ml), the patient demonstrated active acromegaly with markedly elevated basal GH (80.0 ng/ml; reference range: 0.02–1.23) and insufficient suppression during an oral glucose tolerance test (OGTT) (minimum GH: 60 ng/ml at 120 minutes). MRI showed tumor progression (32×35×23 mm). The patient was started on long-acting octreotide 20 mg every 28 days. Subsequent assessments revealed persistently elevated GH (26.6 ng/ml) despite a normal IGF-1 (120.9 ng/ml). MRI showed tumor regression (32×29×23 mm), prompting an increase in the octreotide dose to 40 mg. Six months later, the patient underwent transnasal adenomectomy. Postoperatively, maximum GH suppression during OGTT was 0.6 ng/ml at 90 minutes. Immunohistochemical analysis confirmed a sparsely granulated somatotropinoma, with GH expression in tumor cells, Ki-67 <1.0%, strong somatostatin receptor subtype 2 and 5 expression (>80% of tumor cells, IRS-8), and CAM 5.2 expression in fibrous bodies. At 25 years old, laboratory results confirmed persistent disease activity: IGF-1 remained within the normal range (85.7 ng/ml), but GH was elevated (5.1 ng/ml) with inadequate suppression during OGTT (minimum GH: 3.28 ng/ml at 90 minutes). MRI showed only postoperative changes. The patient continued treatment with long-acting octreotide 20 mg daily.
Conclusion
This case highlights the need for an expanded diagnostic approach in acromegaly, particularly in cases with discordant GH and IGF-1 levels. Alongside IGF-1 measurement, GH levels—both basal and during OGTT—should be systematically evaluated to ensure accurate disease monitoring and treatment optimization.

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EP1252

JOINT3990

Delayed diagnosis of pituitary apoplexy: a case report

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Introduction
Pituitary apoplexy is a rare but life-threatening endocrine emergency, often revealing an underlying pituitary adenoma. It results from hemorrhagic or ischemic necrosis of the pituitary gland and requires prompt diagnosis and management.
Case Presentation
We report the case of a 60-year-old man with a history of COVID-19 infection one year prior, presenting with sudden onset severe headaches, vomiting, and profound asthenia. He initially consulted the emergency department, where he was treated symptomatically and discharged. However, his symptoms worsened over the next few days, and he developed anorexia and bilateral blurred vision. Subsequently, he consulted a general practitioner, who prescribed injectable corticosteroid therapy. This treatment led to a significant improvement in his symptoms, but during the course of treatment, he developed a polyuria-polydipsia syndrome. After the corticosteroid therapy was discontinued, the patient experienced a sudden deterioration of his condition, including generalized tonic-clonic seizures. This prompted further investigations. Brain MRI revealed an intra-sellar lesion with hemorrhagic components compressing the optic chiasm, consistent with pituitary apoplexy. Hormonal assessment confirmed anterior pituitary insufficiency, including corticotropic, thyrotropic, and gonadotropic deficiencies, as well as a probable central diabetes insipidus.
Conclusion
Pituitary apoplexy is most commonly associated with macroadenomas, particularly non-functional ones. Identifying the secretion profile post-apoplexy can be challenging, as it may resolve hypersecretion caused by an adenoma. In our patient, it is important to consider potential triggering factors; a recent COVID-19 infection was suspected as a possible contributing factor. Corticotropic insufficiency is the most frequent endocrine deficit and poses a significant risk to survival. Central diabetes insipidus can be unmasked by corticosteroid therapy, which may further complicate the clinical picture. Early recognition and prompt hormonal replacement therapy are crucial for patient survival and functional recovery. While surgical decompression remains an option in severe cases, conservative management may be effective in selected patients.

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EP1253

JOINT2456

More than thirst: diagnosis of central diabetes insipidus in a young woman without comorbidities

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Introduction
Central diabetes insipidus is a condition caused by vasopressin deficiency, which results in an inability to concentrate urine and consequently manifests with polyuria and polydipsia. In most cases it arises after trauma, tumours or autoimmune processes[1]. The water deprivation test is the most widely used test. The test is considered positive if peak serum osmolality is > 295 mmol/kg or if peak urine osmolality is < 300 mmol/kg or if the copeptin dosage is < 2.6 pmol/L[2].
Case Study
38-year-old patient with polyuria and polydipsia that had arisen about two years previously and worsened over the last year. The patient reported a fluid intake of about 8 litres per day. No previous history of trauma. Blood tests showed normal electrolyte values, but urine tests showed a lower specific gravity than normal. An MRI with contrast of the pituitary gland showed a normal gland. Therefore, considering the patient's symptoms, we decided to perform a water deprivation test, lasting approximately 14 hours. Blood samples were taken every two hours for dosing copeptin, serum osmolarity, sodium, as well as urine samples for urinary osmolarity and urine specific gravity. From the start to the end of the test: the patient's body weight decreased by approximately 1.2 kg (92.8 Kg vs 91.6 Kg) . Serum osmolarity increased from 288 mOsm/Kg to 301 mOsm/kg and urinary osmolarity increased from 487 mOsm/Kg to 611 mOsm/Kg. The urine specific gravity increased from 1005 to 1014 g/L; sodium values increased slightly during the test from 141 to 144 mmol/L; and, finally, the copeptin value remained below 2 pmol/lthroughout the test.
Treatment
The patient started therapy with desmopressin acetate 90 mg/day.
Thake Home Message
Vasopressin is an unstable hormone and it's difficult to measure it in laboratory in contrast to copeptin, the c-terminal fragment of the vasopressin precursor, which provides a reliable indirect measure of bioactive hormone[3]. Although in our clinical case already the serum osmolarity value allowed us to make a diagnosis, the copeptin assay was essential to make a definite diagnosis of central diabetes insipidus.
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EP1254

JOINT2517

A persistent headache in acromegalic patient: the positive result of combination therapy with pasireotide LAR, pegvisomant and cabergoline

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Acromegaly is a rare condition characterized by the excessive exposure to GH and IGF-1 due to a pituitary adenoma in most of the cases. The disease is associated with numerous symptoms including headache, which is frequently difficult to manage. We aim to report the clinical history of a young woman who received the diagnosis of acromegaly when she was 11 years-old and started to refer headache, localized in the right frontal and orbital area, associated with nausea and emesis and finally got hospitalized in March 2011 because of a tonic-clonic seizure. The preliminary investigations included cerebral CT scan and RM which showed a voluminous lesion of the sellar and suprasellar region, located behind optic chiasm which compressed the third ventricle with consequent hydrocephalus and shifting of the midline, and hormonal dosage (IGF-I: 1008 ng/ml; PRL 3861 ng/ml with no macroprolactin). After the execution of an endoscopic septostomy and right ventriculoperitoneal shunt, the case was collectively discussed and considering the elevated risk related to neurosurgery, the patient started cabergoline, lanreotide ATG and pegvisomant first, pasireotide LAR as only therapy secondly and then shifted again to the first combination therapy. Despite the partial biochemical control, in consideration to the low lesion shrinkage, in December 2012 a partial resection of the macroadenoma was obtained. Over the years, the patient continued the medical therapy with lanreotide, cabergoline and pegvisomant in combination with good biochemical control and stability of the residual adenoma. In 2022, the patient started to refer headache that couldn't be attributed to acromegaly progression nor ventriculo-peritoneal shunt malfunctioning. In December 2023, lanreotide was substituted with pasireotide. In the last check-ups, the patient referred optimal control of headache by the combination therapy cabergoline, pegvisomant and pasireotide LAR. Pasireotide is known to be able to improve symptoms not sufficiently controlled by fg-SRLs and it can be used as monotherapy or in combination therapy in patients with severe headache not responsive to first-generation SRL therapy, as reported in several studies. Our case report enforces knowledge about pasireotide benefits in headache treatment.

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EP1255

JOINT3884

Giant macroprolactinoma mimicking a craniopharyngioma: a remarkable evolution with persistent hyperprolactinemia due to big big prolactin

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Introduction
Giant macroprolactinomas are rare pituitary tumors that can present with atypical radiological features, sometimes mimicking craniopharyngiomas. While dopamine agonist therapy typically leads to significant tumor shrinkage and normalization of prolactin levels, persistent hyperprolactinemia despite radiological resolution may indicate macroprolactinemia, particularly due to Big Big Prolactin (1).
Case Presentation
We present the case of a 27-year-old male with progressive visual disturbances, headaches, and hypopituitarism. MRI revealed a large sellar and suprasellar mass with cystic components and calcifications, initially suggestive of a craniopharyngioma. However, markedly elevated prolactin levels (300 ng/ml) led to the diagnosis of a giant macroprolactinoma. Due to significant visual impairment, surgical intervention was performed, followed by cabergoline therapy (2 mg weekly). After two years, complete radiological tumor resolution was achieved, with no clinical signs of hyperprolactinemia. Despite this, prolactin levels remained elevated (170 ng/ml), prompting further analysis. Polyethylene glycol (PEG) precipitation confirmed the presence of Big Big Prolactin, a high-molecular-weight prolactin complex with reduced bioactivity (2,3). After confirmation, cabergoline was gradually tapered and discontinued.
Conclusion
This case underscores the importance of distinguishing true hyperprolactinemia from macroprolactinemia in patients with persistent hyperprolactinemia despite tumor resolution. Recognizing the Big Big Prolactin phenomenon can prevent unnecessary treatment continuation and misinterpretation of disease activity. Systematic screening for macroprolactinemia should be considered in similar cases to optimize patient management (4).
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EP1256

JOINT2407

Effects of abnormal growth hormone secretion treatment on bone metabolism and structure in acromegaly and adult growth hormone deficiency-a preliminary report

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Introduction
Both the excess of growth hormone (GH) in acromegaly (Acro) and its deficiency (GHD) may lead to impaired bone metabolism and bone mineral density (BMD) and fragility. However, the exact mechanism remains unclear.
Aim
To evaluate the effects of Acro and GHD treatment on bone metabolism, including bone turnover markers, BMD and bone microarchitecture.
Methods
In this single-center prospective study 26 patients were recruited: 13 (8 males, 5 females) with Acro and 13 (6 males, 7 females) with GHD. Calcium, phosphorus (serum), parathyroid hormone (PTH), 25-hydroxy- and 1,25-dihydroxy-vitamin D and bone turnover markers: serum b-cross laps (Ct-x), Procollagen type I N-terminal propeptide (P1NP), Sclerostin (Scl) and Dikkopff-1 (Dkk-1), and BMD and trabecular bone score (TBS) measured by dual-energy X-ray absorptiometry were assessed baseline and 6 months after adequate treatment (a6m).
Results
Mean age was 50.18 ± 14.45 and 32.17 ± 10.85 yrs. in Acro and GHD group, respectively. In Acro group 7 patients had hypogonadism, whereas in the GHD group 6 patients had multiple pituitary hormonal deficiency. Median baseline GH and IGF-1 levels in Acro were 12.1 µg/l[2.91-74.4] and 652 µg/l(2.86 xULN), respectively. In the GHD group median baseline IGF-1 was 80.4 µg/l(0.95 xLLN). In Acro group a6m of treatment we observed a reduction in serum phosphorus (1.41 vs 1.06 mmol/L). We also observed increase in PTH (29.3 vs 46.4 pg/ml) and decrease in 1,25(OH)2 vitamin D (60.65 vs 54.3 pg/ml). A6m of treatment we noticed an increase in bone turnover markers: Ct-x (26.4 vs 55.7 ng/L), P1NP (290.5 vs 405.5 ng/ml), and Scl (60 vs 68 pg/ml), but a decline in Dkk-1 levels (4198 vs 3873 pg/ml). BMD increased only at the lumbar spine (1.237 vs 1.308 g/cm^3). In GHD group there was increase in serum phosphorus (1.03 vs 1,14 mmol/L). A6m of treatment decrease in P1NP (276.8 vs 256.1 ng/ml), and increase in Ct-x (26,8 vs 47,5 ng/ml), Scl (47,6 vs 64,6 pg/ml) and Dkk-1 (3394 vs 4016 pg/ml) was observed. There was no change in BMD and TBS a6m in the GHD group.
Conclusion
We present preliminary results of the study showing the impact of GH changes on bone turnover markers in patients treated for Acro and GHD.

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EP1257

JOINT2482

Sarcoidosis diagnosis after succesful treatment of cushing's disease

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Introduction
Cushing's syndrome (CS) corresponds to a state of glucocorticoid excess. Endogenous CS can be either adrenocorticotropic hormone (ACTH) dependent or independent, with Cushing's Disease (CD) being the most common cause of ACTH dependent CS. Along with increased mortality, cardiovascular, metabolic, and musculoskeletal complications, CS also leads to some degree of immunosuppression, mainly by a decrease in lymphoid tissue and lymphopenia. CS cure, on the other hand, stimulates the immune system and may result in the exacerbation of immune mediated diseases.
Case Report
A 49-year-old woman was sent to the endocrinology clinic for a left adrenal incidentaloma. Personal history was notable for severe osteoporosis (spine T-score -2.5 and femur –2.2) and an episode of panuveitis at the age of 18. Further enquiry revealed recent significant weigh gain, buffalo hump, easy bruising, lower limb oedema and hypertension. Abdominal CT scan and MRI described a 1.1cm adenoma in the left adrenal gland. Laboratorial work-up suggested ACTH-dependent hypercortisolism. Desmopressin stimulation was suggestive of CD and pituitary MRI confirmed a right pituitary adenoma with 8 × 11 × 12mm. Transsphenoidal tumorectomy was performed confirming a corticotroph adenoma. Postsurgical serum cortisol was 0.7 mg/dl, and the patient was discharged with hydrocortisone 20 + 10mg and desmopressin 60mg daily. In the following weeks a cervical/shoulder girdle discomfort appeared with progressive development of arthralgias, persistent coughing and xerostomia. Additional evaluation revealed an erythrocyte sedimentation rate of 120 mm, with a C-reactive protein of 1.84 mg/dl and an angiotensin converting enzyme of 77 IU/L. CT scan confirmed the presence of supraclavicular, mediastinal and hilar lymph nodes, with diffuse areas of consolidation and densification of the pulmonary parenchyma, mainly in the lower lobes. Transbronchial lymph node biopsy was carried out and confirmed the presence of a non-necrotizing granuloma. The bronchoalveolar lavage had lymphocytosis (26%) with a CD4/CD8 ratio of 3. Lung function tests showed a slight decrease in DLCO of 68%. ALL these findings are consistent with sarcoidosis.
Discussion and conclusion
Autoimmune disorders are a possible complication after CS cure. Thyroid disorders and rheumatological diseases are the most common occurrences. Sarcoidosis has been described, usually presenting with skin findings, pulmonary involvement or both. Glucocorticoid-withdrawal syndrome is an important alternative diagnosis with symptoms like myalgia and asthenia being common to CS, adrenal insufficiency and autoimmune disorders. A close follow-up is of utmost importance in the posttreatment period of CS and a high level of suspicion is required when clinical presentation deviates from what is expected.

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EP1258

JOINT3554

Multidisciplinary approach in the management of cardiac metastasis from small intestinal neuroendocrine tumour: a case report

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Introduction
Neuroendocrine tumours (NETs) are rare and more frequently metastasize to the abdominal lymph nodes or liver. Extra-abdominal metastases are now increasingly detected due to ^{68}Ga-SSA-PET/CT's high sensitivity. Right sided valvular dysfunction is the hallmark of carcinoid heart disease (CHD) caused by high serotonin levels secreted by liver metastasis. Cardiac metastases (CMs) are rare, occurring in about 1-4% of NETs, primarily from small intestine. They can occur in association with typical valvular involvement or may be the only manifestation of CHD. Patients may be asymptomatic or presenting with nonspecific symptoms depending on tumour location and burden.
Case
66-year-old-male, presenting with abdominal distension, diarrhea and weight loss. Underwent right hemicolectomy due to a tumour in the terminal ileum detected on colonoscopy. Histopathology revealed G2 NET (2 mitoses/10 HPF), pT4N0 LVI2 R0. Abdominal-pelvic CT showed no abnormalities; ^{68}Ga-SSA-PET/CT revealed focal uptake in the apical region of the left ventricle, initially not considered significant. 1-year post-surgery, developed diarrhea, flushing and weight loss. Second evaluation with ^{68}Ga-SSA-PET/CT continued to show myocardial uptake and identified mesenteric densification, raising suspicion of lymph node involvement. Cardiac MRI (CMR) revealed an intramural cardiac mass (12x25mm) near the apex without cleavage plans from myocardium, interfering with wall motion and suggestive of a rhabdomyoma or cardiac lymphoma. The patient was referred to our center, with chromogranin A (CgA) 703.9 ng/ml ($\leq$102), on PPI, 5-hydroxyindoleacetic acid (5-HIAA) 5.6 mg/24h ($\leq$15) and normal B-type natriuretic peptide. ECG revealed sinus rhythm and complete left bundle branch block. Transthoracic echocardiogram showed no evidence of CHD but demonstrated increased left ventricular wall thickness (apical septal segment), with localized reduced contractility. Using Sonovue contrast we observed the referred mass. A 24h ECG monitoring didǹt show significant arrhythmias. The patient had no cardiac symptoms. Based on integrated clinical assessment, CMR was revised and the mass reclassified as a CM from the known NET; cardiac biopsy (considered high-risk) was not performed and surgical intervention was not performed due its unresectability. Lanreotide 120 mg was initiated with improvement of abdominal symptoms and CgA. At 12 months, contrast echo and CMR continue to show stable intramyocardial mass.
Conclusions
CMs from NETs are rare and typically found in advanced disease. In this case, the heart was the first site of distant metastasis. Multidisciplinary discussion enabled clinical diagnosis and appropriate therapy. Despite the usual aggressive nature of other CM, NETs often have an indolent course with prolonged survival.

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EP1259

JOINT3576

Radiotherapy as first line therapy for pituitary adenomas

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Introduction
Transsphenoidal surgery is the first-line treatment for non-functioning pituitary adenomas (NFPAs) in case of visual impairment or progressive tumor growth, for GH-secreting and ACTH-secreting adenomas, as well as for prolactinomas when medical treatment is not possible. Radiotherapy is generally proposed as second- or third-line treatment and is rarely performed before surgery. The objective of our study was to evaluate the efficacy on tumor volume control of pituitary radiotherapy as first-line treatment for patients with pituitary adenomas.
Methods
We retrospectively reviewed files from 10 patients with pituitary adenoma, who had radiotherapy as first-line treatment in a tertiary center between 2011 and 2019. We documented patient and tumor characteristics, time and reason for radiotherapy, duration of follow-up and calculated tumor volume change after radiotherapy.
Results
A total of 10 patients with pituitary adenomas (60% male) treated with first-line radiotherapy were included. Mean age upon diagnosis was 63.5 years (SD: 20.3). Five patients (50%) had NFPA, 2 had acromegaly and 3 had macroprolatinomas. Seven patients received conventional fractionated radiotherapy (VMAT) with median radiation dose of 54 Gy (Range: 45-54), while 3 patients received stereotaxic radiosurgery with median dose of 18 Gy (R: 18-24). Radiotherapy was performed after a mean follow-up of 70.9 months from diagnosis (SD: 91.6), and median maximal diameter before radiotherapy was 24.8 mm (R: 10-40). Among 5 patients with NFPAs, 3 had visual field defects upon diagnosis, 3 had panhypopituitarism and the choice of radiotherapy as first-line treatment was based on age (median age at diagnosis: 78 years, R: 61-83), in addition to comorbidities or patient preference. Among 5 patients with macroprolactinomas and acromegaly, the choice of radiotherapy was based on resistance to medical treatment and refusal of surgery. During a mean follow-up of 61.8 months after radiotherapy (SD: 46.3), tumor size decreased in 8 patients (80%), and was stable in 1 patient. Only 1 patient with a macroprolactinoma had a 6.5% increase in tumor size, 69 months after radiotherapy. Pituitary function was difficult to evaluate at last follow-up as data were missing, which was related to patients' age. Still, most had hypopituitarism at baseline and no improvement is expected with radiotherapy as with pituitary surgery. No patient had salvage pituitary surgery during follow-up.

Conclusions
Radiotherapy can be performed as first-line treatment in patients with pituitary adenomas when surgery is not an option because of patient preferences or comorbidities and achieves tumor volume stabilization or decrease.

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EP1260

JOINT3408

Symptomatic rathke's cleft cyst

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Introduction
Rathke's cleft cysts (RCC) are frequent benign cystic sellar lesions (13 - 22%). Most RCC are small, intrasellar and asymptomatic. Larger cysts may compress adjacent structures and rarely become symptomatic. We report the case of hypopituitarism revealing a RCC.
Observation
A 74-year-old hypertensive menopausal patient, followed for rheumatoid arthritis and treated with corticosteroids, presented at our endocrinology department with recurrent hypoglycaemia, chronic headaches and visual disturbances. On clinical examination, visual field abnormalities are found. Hormonal testing showed basal cortisol level at 17ng/ml confirming corticotropic, thyrotropic, gonadotropic insufficiencies with a normal prolactin level at 17ng/ml. A hypothalamic-pituitary MRI revealed a cystic lesion occupying the sella turcica, measuring 27mm, with a pure liquid signal that was unmodified by gadolinium injection, displacing the optic chiasm and posterior pituitary. Therefore, the diagnosis of RCC complicated with hypopituitarism and visual compression was made and the patient was started on hydrocortisone 15mg/day and levothyroxine 75µg/day, with a follow-up MRI to monitor the cyst's long-term progression.
Conclusions
The vast majority of Rathke's pouch cysts remain small, asymptomatic, and are often discovered incidentally. Only about 1% to 5% of Rathke's pouch cysts become symptomatic, typically when they enlarge and compress nearby structures such as the optic chiasm or pituitary gland. This makes symptomatic Rathke's pouch cysts relatively rare, with their occurrence being significantly lower than that of asymptomatic cases.

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EP1261

JOINT3465

Immune checkpoint inhibitor-induced hypophysitis: a case report of panhypopituitarism and acute neurological manifestations

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Background
Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment, but they can cause significant endocrine-related adverse events. Hypophysitis, an inflammation of the pituitary gland, occurs in 5-10% of patients receiving combination CTLA-4/PD-1 blockade. However, recent studies suggest that the incidence may be higher, with rates up to 25% reported in patients treated with ipilimumab plus nivolumab for melanoma. This higher incidence may reflect increased awareness and recognition of this immune-related adverse event in real-world clinical practice.
Case Report
A 41-year-old male with stage IV BRAF wild-type melanoma developed severe neurological symptoms during his fourth cycle of ipilimumab/nivolumab therapy. The patient presented with progressive headache, gait ataxia, and generalized tonic-clonic seizures. Initial assessment revealed profound hyponatremia (119 mmol/l)and altered consciousness (GCS E1V1m[3]). Endocrine evaluation demonstrated complete anterior pituitary failure, consistent with panhypopituitarism. Pituitary imaging showed radiological evidence of hypophysitis. The patient's presentation illustrates that rapid-onset panhypopituitarism can manifest without classical visual field defects typically associated with pituitary enlargement. Management included high-dose glucocorticoids (IV methylprednisolone 1mg/kg), hormonal replacement therapy (levothyroxine, hydrocortisone, testosterone), and discontinuation of ICI treatment. This approach aligns with current guidelines for managing ICI-induced hypophysitis.
Conclusion
This case report illuminates several critical insights into ICI-induced hypophysitis. Rapid-onset panhypopituitarism can occur without typical visual field defects, challenging traditional diagnostic expectations. The presentation demonstrated that hyponatremia secondary to adrenal crisis may precede radiographic changes, emphasizing the critical importance of early and comprehensive endocrine evaluation. Moreover, the occurrence of seizure activity represents an uncommon neurological manifestation of acute hypophysitis, highlighting the need for heightened clinical vigilance in patients undergoing immune checkpoint blockade. The case underscores the paramount importance of multidisciplinary collaboration between oncologists and endocrinologists in managing complex immune-related adverse events. Implementing protocolized pituitary axis monitoring for patients receiving dual immune checkpoint blockade is essential. This should include rigorous baseline assessments and frequent follow-up testing to enable early detection and intervention. Ultimately, this case reinforces the critical nature of early recognition and prompt management of ICI-induced hypophysitis. Timely and comprehensive medical intervention can prevent potentially life-threatening complications and ensure optimal patient outcomes in the evolving landscape of immunotherapy.

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EP1262

JOINT631

Unmasking the giant: a pediatric macroprolactinoma mimicking a craniopharyngioma

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Background
Macroprolactinomas and craniopharyngiomas are two sellar and suprasellar tumors that may share clinical and radiological similarities, often making differential diagnosis challenging.
Case Presentation
An 8-year-old boy presented with progressive frontal headache, visual loss, intermittent vomiting, but no galactorrhea or gynecomastia, without polyuric-polydipsic syndrome. He was not on any medication and had no family history of endocrinopathies. Clinically, with no growth delay, at Tanner stage G1P1. Brain MRI revealed a sellar and suprasellar mass 57 × 55 × 55 mm, with solid-cystic components without calcifications compressing the pituitary gland against the sellar floor, and involving the opto-chiasmatic cisterns, optic nerves, chiasm, with triventricular dilation. Biological tests showed a corticotropic deficiency. Prolactinemia was not initially assessed. The tumor was considered a likely craniopharyngioma. The patient underwent transsphenoidal surgery for tumor resection with hydrocortisone substitution. Immunostaining revealed neoplastic cells positive only for prolactin (100%) with a Ki-67 index of 4%. Three months post-surgery, MRI showed a 70% regression of the cystic component (22 cc vs 70 cc), with persistence of the solid component measuring 40 × 33 × 31 mm. The Prolactin level was 1736 ng/ml. The patient was started on Cabergoline 0.25 mg twice a week, gradually increased to 2 mg/week, Aiming to lower prolactin, shrink the tumor, improve visual function, and reverse corticotropic deficiency. Genetic testing for AIP mutation and Menin could not be performed due to unavailability.
Discussion
Unlike the craniopharyngioma, considered as the most common non-malignant sellar and suprasellar tumors in childhood, Pituitary adenomas are less common. Prolactinomas represent 50% of pediatric pituitary adenomas. Males tend to develop larger tumors with higher prolactin levels. The neuroradiological appearance of a non-homogeneous signal with a cystic component in prolactinomas can be mistaken for a craniopharyngioma. Genetic studies show that 10% of patients under 18 have mutations in AIP and MEN1 genes. The 2024 Consensus Guideline for the Diagnosis and Management of Pituitary Adenomas in Childhood and Adolescence recommends systematic serum prolactin measurement and the use of cabergoline as a first-line dopamine agonist therapy, even in the presence of visual disturbances or pituitary apoplexy. Treatment involves a progressive dose increase up to 1.5–2 mg per week. In cases of intolerance or resistance to high doses, surgery or radiotherapy may be considered as alternative options.

Conclusion
Craniopharyngiomas, though common in children, can mimic macroprolactinomas. Routine prolactin testing is crucial when assessing sellar masses to guide treatment before considering invasive surgery.

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EP1263

JOINT2635

A case report of an infant with congenital hypopituitarism presenting with hypoglycemia and low beta-hydroxybutyrate

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Introduction
Congenital hypopituitarism is defined as the deficiency of one or more hormones produced by the pituitary gland. Diagnosis in neonates is often challenging as they often present with non-specific symptoms. We describe a case of a 7-week-old baby girl with congenital hypopituitarism presenting with hypoglycemia.
Case
A 7-week-old baby girl presented to the Children's Emergency for jitteriness, increasing lethargy and poor feeding. She was born full term with a birth weight of 3.4kg. Postnatally, she had hypoglycemia and conjugated hyperbilirubinemia diagnosed in another hospital, but was lost to follow-up after discharge. At presentation in the emergency at 7 weeks old, baby was jittery with poor peripheral perfusion. She was dehydrated with depressed fontanelles. Her tone was increased with brisk reflexes. She was not hyperpigmented, not dysmorphic and had normal female genitalia. Blood sugar at presentation was 2.4 mmol/L. At time of hypoglycemia, baby's beta-hydroxybutyrate was low at $<$0.6 mmol/land her urine ketones were trace in the urine dipstick. Insulin production was suppressed at $<$1.6 mU/l(2.6 – 24.9) and C-peptide was low at 25 pmol/l(70-1448). Cortisol was inappropriately low at 116 nmol/l(14-458) and growth hormone level was 1.58mg/l(0.12 – 7.79). Lactate was normal at 1.6 mmol/l(0.5 – 2.2), sodium 141 mmol/l(133-144), potassium 6.1 mmol/l(3.6 – 5.8), chloride 111 mmol/l(97-110), bicarbonate 17 mmol/l(16-29), urea 7.8 mmol/l(1.2-6), creatinine 24 umol/l(11-36), ALT 130 U/l(6-51), AST 232 232 U/l(23-83), total bilirubin 164 umol/l(1-12) and direct bilirubin 130 umol/l($<$5). Her plasma concentrations of several acylcarnitines were elevated. Free carnitine was within normal limits. Her urine organic acid revealed that the excretions of ketone bodies were markedly elevated in the presence of a moderate dicarboxylic aciduria (C6$>$C8$>$Cl0) and slight lactic aciduria. Overall, this profile was not indicative of a specific disorder and is suggestive of severe ketosis. MRI pituitary showed hypoplasia of the pituitary gland. Baby was subsequently started on hydrocortisone, thyroxine and growth hormone replacement, and was discharged well.
Conclusion
Hypoglycemia seen in hypopituitarism is typically ketotic. In this case report, this baby presented with hypoglycemia with low beta-hydroxybutyrate (the predominant ketone body) and urine ketones despite low insulin level and high free fatty acids. The presence of ketones was instead detected in her plasma acylcarnitines profile and urine organic acids, which was consistent with her subsequent diagnosis of central hypocortisolism.

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EP1264

JOINT2506

Delayed puberty: the coin other side

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Background
Delayed puberty in girls is defined as a lack of development of secondary sexual characteristics by the age of 13 years or absence of menarche by the age of 16 years. one of the missed causes of delayed puberty is the condition caused by Mullerian duct anomalies. They are congenital uterine anomalies presented by delayed puberty, infertility, or recurrent miscarriage. Imaging can help to identify patients who can benefit from interventions.
Objectives
This report describes the presentation and hormonal profile of a girl diagnosed with one type of Mullerian duct anomalies. Moreover, it describes the role of MRI pelvis to identify the best intervention for the girl.
Case description
A 16-year-old girl was presented with an attack of acute abdominal pain. There were recurrent cyclic attacks of pelvic pain for a few days which resolved with only analgesics. According to Tanner maturity rating, she has T4 breast development, T4 pubic hair, and T3 axillary hair. Still, she had primary amenorrhea. She had a normal hormonal profile for her age. The conclusive diagnosis was reached by doing MRI pelvis. MRI showed no well-formed uterus, two rudimentary horns with absent cervix and upper vagina.
Conclusions
Mullerian duct anomalies can be a hidden cause of delayed puberty that must be kept in mind when confronting a girl with primary amenorrhea. MRI is the gold standard to diagnose these patients and to put the optimal surgical plans as trials to save fertility.

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EP1265

JOINT1560

First report of a case of post-surgical pituitary neuroendocrine tumor residue confined within the pituitary stalk

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Pituitary neuroendocrine tumors (PitNETs) located solely in the pituitary stalk, without affecting the pituitary gland, are exceptionally uncommon. To date, only a limited number of cases has been documented in the literature. Herein, we report a case of a post-surgical PitNET residue confined solely to the pituitary stalk, observed during a morphological follow-up two years after endoscopic transsphenoidal surgery. We describe the case of a 23-year-old woman who initially presented with secondary amenorrhea and galactorrhea, leading to a diagnosis of prolactin-secreting PitNET. Owing to the failure of medical therapy with cabergoline, the patient underwent endoscopic transsphenoidal surgery. Postoperatively, her prolactin levels decreased to 30 ng/ml ($n$$<$26,5), with no evidence of pituitary dysfunction. However, one year after surgery, hyperprolactinemia recurred, accompanied by secondary amenorrhea and galactorrhea, prompting the reinitiation of cabergoline therapy to suppress prolactin secretion. Two years after the surgical intervention, routine morphological surveillance revealed a thickening of the pituitary stalk. Magnetic resonance imaging (MRI) demonstrated a 4-mm thick mass of homogeneous signal intensity on both T1-weighted and T2-weighted imaging, localized within the pituitary stalk. The patient remains free of diabetes insipidus. Comprehensive evaluation excluded alternative etiologies of pituitary stalk thickening, including lymphoma, craniopharyngioma, germ cell tumors, and granular cell tumors. The patient declined endoscopic transsphenoidal biopsy. Consequently, an annual MRI-based follow-up is recommended. During the surveillance period from 2010 to 2024, the pituitary stalk thickening remained stable. Following a multidisciplinary team review including an expert neuroradiologist, a definitive diagnosis of PitNET residue confined within the pituitary stalk was established. The patient's prolactin level remained stable at 60 ng/ml under a weekly dose of 0.75 mg of cabergoline. Although PitNET residues confined to the pituitary stalk are rare, awareness of their existence is essential for accurate postsurgical assessment. Recognizing this condition can guide appropriate management, prevent unnecessary surgical biopsies, and ensure optimal long-term follow-up.

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EP1266

JOINT2020

A rare case report of an intravascular large B-cell lymphoma causing a panhypopituitarism

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A rare and aggressive form of B-cell lymphoma known as intravascular large B-cell lymphoma (IVLBCL) is characterized by the growth of large cells within the lumen of blood vessels. While previous studies have documented a wide range of symptoms caused by neoplastic cells obstructing small vessels in various organs, there is limited literature on IVLBCL cases with hypothalamic-pituitary functional impairment. Here, we present a rare case of IVLBCL that provoked hypopituitarism. A 58-year-old male patient presented with symptoms that progressively developed over several weeks, including deteriorated general condition, intermittent episodes of confusion, daily high fever, and polyuropolydipsia syndrome (5 liters per day). Laboratory investigations revealed mild hypernatremia (sodium, 149 mEq/l)as well as elevated serum levels of lactate dehydrogenase (LDH; 566 IU/l)and β2 microglobulin 8.31 mg/l(0.8-2.34). Basal hormone analysis demonstrated hypopituitarism. Brain magnetic resonance imaging (MRI), however, showed a lesion infiltrating the floor of the third ventricle (21 × 18 × 15 mm), extending to encompass the entire pituitary stalk. The lesion appeared homogeneous and exhibited strong contrast enhancement after gadolinium administration. ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography revealed enhanced FDG uptake of the lesion infiltrating the floor of the third ventricle, extending to encompass the entire pituitary stalk. In the biopsy of the clinically unaffected skin, immunohistochemistry revealed the presence of intravascular neoplastic cells positive for B-cell markers CD20, CD5, and MUM1, confirming the diagnosis of intravascular large B-cell lymphoma. Corticotropic and thyrotropic deficiencies were supplemented, and diabetes insipidus was treated with desmopressin. Additionally, the patient underwent R-CHOP chemotherapy, which resulted in a complete response. The patient remained in remission for six months following the cessation of chemotherapy. Hypopituitarism associated with IVLBCL was first described in 1986. A limited number of cases of IVLBCL involving functional abnormalities of the hypothalamic-pituitary axis have been reported. IVLBCL with hypothalamic or pituitary involvement can be effectively managed with hormone replacement therapy followed by chemotherapy. Consequently, timely identification of clinicopathological features is crucial for reducing mortality rates.

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EP1267

JOINT2376

The First genetically confirmed case of wolfram syndrome in the philippines - a case report

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Wolfram syndrome is a rare disease characterized by constellation symptoms progressing from childhood to adulthood. These symptoms brought forth its other name DIDMOAD which comprises Diabetes insipidus, Diabetes mellitus, Optic atrophy, and deafness. It is a rare form of monogenic diabetes with an estimated prevalence of 1 in 770,000 in the United Kingdom, 1 in 100,000 in North America and 1 in 710,000 in the Japanese population. In this report, we describe a 26-year-old Filipina woman diagnosed with Type 1 diabetes and optic atrophy who consulted due to severe headache, fever, urinary frequency, and urgency. During her admission, she had symptoms of persistent thirst, polyuria, and nocturia. Further workup confirmed that she had urological abnormalities and Diabetes insipidus leading to the clinical diagnosis of Wolfram Syndrome. Genetic testing was then performed which showed that she had two pathogenic or disease-causing variants identified in the WFS1 gene. As healthcare providers, a high suspicion for Wolfram Syndrome should be a standard in patients who present with juvenile-onset diabetes mellitus and optic atrophy which are the primary symptoms of Wolfram Syndrome. Early recognition and diagnosis will guide us to the proper management and help improve the patient and their family's quality of life. Although there is no known cure yet for Wolfram Syndrome, treatment of manifestations includes supportive care which is often provided by multi-disciplinary specialists. The surveillance involves regular monitoring of existing manifestations, the response of an individual to supportive care, and the emergence of new manifestations.

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EP1268

JOINT2349

Hormonally inactive pituitary adenomas: clinical and laboratory features and predictors of surgical treatment effectiveness

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Introduction

The proportion of hormonally inactive pituitary adenomas (IPA) is about 10-20% of all cases of central nervous system tumors. Transsphenoidal adenomectomy is the primary treatment; however, complete tumor resection is not always achievable. The purpose of the study. To analyze the clinical, laboratory, and morphological characteristics of IPA patients and identify prognostic factors for surgical treatment outcomes.

Materials and methods

This retrospective dynamic study included 75 patients with IPA treated between 2016 and 2020. We analyzed medical history, hormonal profiles (cortisol, ACTH, TSH, free T4, LH, FSH, prolactin), imaging results (MRI), and histopathological and immunohistochemical findings. All patients underwent transsphenoidal adenomectomy as their primary treatment.

Results

Among the examined group of patients, the most common preoperative symptoms were headache (75.7%) and visual impairment (71.6%). Hypopituitarism of varying severity was diagnosed in 44% of cases, with the most frequent combination being secondary hypocortisolism, hypothyroidism, and hypogonadism. Secondary hyperprolactinemia was observed in 62.8% (49 patients). All tumors were macroadenomas, with a median volume of 7612.5 mm^3 [4180.0; 15015.0]. Giant adenomas were found in 13 patients. Histological examination confirmed the diagnosis of pituitary adenoma in 68 out of 70 cases. The predominant histological subtypes were chromophobic (38.2%) and basophilic adenomas (35.3%). Immunohistochemical analysis (performed in 27 patients) revealed staining for one or more pituitary tropic hormones in 92% of cases, indicating secretory potential. The most common morphological subtype was "silent" gonadotropinomas (56%). Ki-67 immunoexpression was analyzed in 33 patients, with a median level of 4.4% [2%; 7%]. A Ki-67 index $<3\%$ was found in 33.3% of patients, while 66.7% had values $>3\%$. Among 36 evaluated patients, non-radical tumor resection was observed in 18 (50%). Patients with no residual tumor had significantly higher Ki-67 levels (median: 6.3%) compared to those with residual tissue (median: 2.0%) ($P = 0.038$). Recurrence occurred in 8 patients with residual tumor, with a median time to recurrence of 14.5 months. Larger tumor volume before surgery was associated with a higher recurrence rate ($P = 0.017$, Mann-Whitney U-test).

Conclusions

Currently, no reliable markers predict IPA recurrence postoperatively. The presence of residual tumor tissue is a negative prognostic factor. We found no significant correlation between Ki-67 levels and recurrence; paradoxically, patients with residual tumor tissue had lower Ki-67 values. The role of Ki-67 in predicting IPA recurrence remains controversial and warrants further investigation.

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EP1269

JOINT766

The overlooked iceberg in hyponatremia in the elderly: the pituitary gland The overlooked iceberg in hyponatremia in the elderly: the pituitary gland

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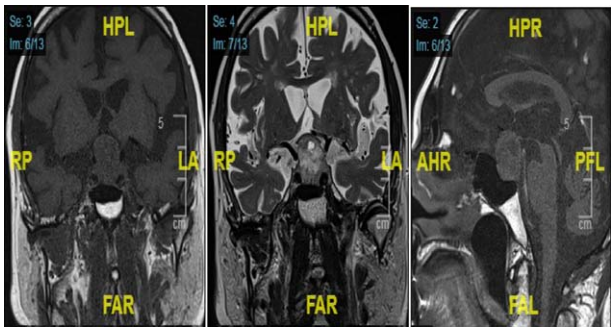
Hyponatremia, characterized by low serum sodium levels, is a frequent electrolyte abnormality encountered in clinical settings. In this report, we elucidate the case of a 91-year-old patient presenting with hyponatremia. The patient has been experiencing postprandial fatigue and weakness for the past 3-4 years, with symptoms worsening after meals. The patient has been managing hyponatremia for about 6 years with dietary treatment and fluid restriction, despite a regular appetite and normal food intake. 1.5 years ago, and the patient experienced complete vision loss in the left eye in 2021 due to macular degeneration. Recent hospital admission revealed a sodium level of 125, indicating hyponatremia, along with postprandial hypoglycemia. The patient was diagnosed with SIADH and was placed on a fluid restriction and given dietary salt supplementation. Blood sugar monitoring was initiated due to concerns about early-onset diabetes. After a Holter monitor study, the patient's fatigue worsened, and blood pressure dropped to 68/48 mmHg with a heart rate of 112 bpm. IV saline improved their blood pressure, and investigations pointed toward adrenal insufficiency and hypothyroidism. Diagnosis was confirmed as secondary adrenal insufficiency and central hypothyroidism, and treatment with prednisolone and thyroid hormone replacement was started. A pituitary MRI showed a possible macroadenoma with a cystic lesion extending into the cavernous sinus and impacting the optic chiasm. The patient's sodium levels and clinical condition, including hypotension and hypoglycemia, improved with treatment.

Figure-1 Magnetic resonans imaging of pituitary revealing centrally cystic-necrotic macroadenoma



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EP1270

JOINT1707

An unsual case of hypopituitarism coincidental with rasmussen's encephalitis and rathke's cleft cyst

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Rasmussen's encephalitis is ultra-rare with precocious puberty reported in approximately 20% of cases but not endocrinopathy. Sodium valproate has been reported as causing impaired gonad, thyroid and adrenal axes function. Rathke's cleft cysts affect pituitary function to varying degrees. We report a case of a patient with Rasmussen's encephalitis, long-term valproate treatment and a Rathke's cleft cyst. A 41 year old female presented with a 1 year history of secondary amenorrhea, scalp hair loss and leg oedema. Menarche occurred at 12 years of age with subsequent regular menses. At 8 months of age she developed a right hemiparesis and epilepsy but no appertaining records were available. She had received treatment with valproate for 27 years. Examination: weight 57.6 kg, mild right hemiparesis, scalp alopecia and moderate leg oedema. Investigations at 09:00h: cortisol 202 nmol/l,ACTH 48.8 ng/l(arose at 07:00h), fT4 10.3 pmol/l,fT3 5.3 pmol/l,TSH 2.02 mmol/l,FSH 3.0 IU/l,LH 1.0 IU/l,oestradiol <100 pmol/l,prolactin 394 mU/land IGF-1 6.3 nmol/L. Renal function, liver function, bone profile and full blood count were normal. Her symptoms, signs and hypogonadotropic hypogonadism were attributed to valproate side-effects. Anticonvulsant change was declined as she had been seizure-free for 23 years, as was HRT. No clinical or endocrine changes were recorded at 1 year. She subsequently presented with general deterioration, anorexia, weight loss (weight 52.6 kg), decreased mobility, worsening leg oedema and hypotension. Investigations at 09:00h: cortisol 93 nmol/l,ACTH 10.6 ng/l,fT4 6.7 pmol/l,TSH 2.98 mU/l,FSH 1.8 IU/l,LH 0.6 IU/l,oestradiol <100 pmol/l,valproate 201 mg/land pancytopenia. MRI was declined. Treatment with hydrocortisone and change in anticonvulsant to lamotrigine resulted in improved clinical status. HRT was declined. At follow up thyroid function and IGF-1 returned to normal but ACTH, cortisol, and gonadotrophins remained low. MRI was accepted and demonstrated the presence of an intrasellar Rathke's cleft cyst.

Discussion

1. This patient's varying endocrine dysfunction is difficult to explain. Valproate could explain the original endocrine abnormalities but not those that have persisted.
2. The Rathke's cleft cyst could be responsible if it had changed in size on stopping valproate.
3. An episode of hypophysitis would be an alternative explanation.

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EP1271

JOINT2605

AVP deficiency secondary to herbal remedies

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Introduction

Arginine vasopressin (AVP) deficiency involves decreased release of arginine vasopressin (AVP) which could lead to polyuria. Hence, patients usually present with polyuria and polydipsia. Lack of AVP can be resulted from disorders that act at one or more of the sites involved in AVP synthesis and secretion. AVP deficiency is a rare disorder with prevalence of 1 in 25,000 individuals and most cases are acquired. The most common acquired causes include autoimmune neurohypophysitis, primary or secondary tumours, infiltrative diseases (such as Langerhans cell histiocytosis and sarcoidosis), neurosurgery and head trauma Here we discuss a case in which AVP deficiency possibly secondary to herbal remedies.

Case Presentation

A 53-year-old male was admitted with polyuria and polydipsia. Passing around 7Litres of urine daily which was disturbing his sleep. He had no significant past medical history. He was taking herbal remedies which including Rhodiola rosea root extract, cranberry extract, royal jelly extract and resveratrol 1.5months earlier he also completed 14 days of ciprofloxacin antibiotics for prostatitis. CT head showed no acute pathology. MRI pituitary showed no acute lesions or pathology. Bloods showed hypernatraemia 147 mmol/L. Urine osmolality of 162 and serum osmolality of 304, urinary sodium was <20. He was given a trial of oral desmopressin which did not help, however when changed to intravenous desmopressin 1 microgram the patients symptoms significantly improved and was able to concentrate the urine. Discharged with nasal spray desmopressin 10micrograms twice daily and his symptoms continued to improve. Discussed in Neuro-pituitary MDT.

Conclusion

AVP deficiency is one of the main entities of the polyuria-polydipsia syndrome. Most cases are acquired and commonly include head injury, neurosurgery, cranial tumours and neurohypophysitis. There have been very limited case reports on herbal remedies causing AVP deficiency such as olive extract. There are also few cases reporting on transient diabetes insipidus in patients using quinolone antibiotics. It is important especially in these rare cases to use an MDT approach to help manage patient's symptoms.

Questions for discussion

Have you come across herbal remedies induced AVP deficiency?
Could quinolones contribute to AVP deficiency?

Input/output chart.

	Input volume (Litres)	Output volume (Litres)
Before desmopressin	9.2	9.9
After desmopressin	5.1	5

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EP1272

JOINT3660

Secondary corticotropic insufficiency due to arachnoid cyst: a reversibility to explore"

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Introduction
Arachnoid cyst is a rare condition characterized by the accumulation of fluid in the subarachnoid space, located between the membranes surrounding the brain and spinal cord. This condition can lead to compression of brain structures and disrupt the functioning of the pituitary gland, resulting in hormonal production abnormalities. In some cases, hormonal disorders, such as corticotropic insufficiency, can be the first clinical sign revealing an arachnoid cyst.
Observation
We report the case of a 56-year-old woman with no notable medical history, who consulted for intense asthenia, headaches, and slight weight gain. Biological tests revealed low TSH, low FT4 and FT3 levels, and a decreased 8 a.m. cortisol, suggesting corticotropic insufficiency. Pituitary MRI showed an arachnoid cyst associated with atrophy of the anterior pituitary, confirming hypothalamo-pituitary dysfunction. Substitution treatment with hydrocortisone and Levothyrox was initiated, with gradual dose increases. This treatment led to regression of symptoms and a significant improvement in the patient's quality of life.
Discussion
Arachnoid cyst is a rare and often underdiagnosed condition, characterized by abnormal accumulation of fluid in the subarachnoid space. This accumulation can exert pressure on brain structures, particularly the pituitary gland, leading to hypothalamo-pituitary dysfunction. Clinical manifestations can vary, with corticotropic insufficiency being a significant feature. The uniqueness of this case lies in the reversibility of corticotropic insufficiency after substitution therapy. This reversibility, though rare, suggests that mechanical compression of the pituitary gland does not necessarily lead to irreversible damage. It opens up interesting perspectives on the underlying pathophysiological mechanisms, such as transient hypoxia, disruption of neuroendocrine signaling, or the plasticity of pituitary cells.
Conclusion
Arachnoid cyst, although rare, can lead to severe hormonal disorders, which may sometimes be reversible. Early diagnosis, along with appropriate management and careful follow-up, is essential to optimize clinical outcomes and improve patients' quality of life.
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EP1273

JOINT3486
Misdiagnosis: a case of craniopharyngioma revealed by diabetes insipidus
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Introduction
Craniopharyngioma is a rare benign epithelial tumor in children, typically located near the pituitary stalk. Although benign and extracerebral, this tumor remains serious due to frequent visual, neuro-intellectual, and endocrine sequelae, including pituitary insufficiency, growth retardation, pubertal delay, and diabetes insipidus. However, significant progress in surgery, radiotherapy, and medical management has markedly improved the prognosis of this disease.
Case report
This is a 14-year-old patient who, in 2019, developed a polyuric-polydipsic syndrome (PUPD) that significantly impaired his daily life. This led his family to consult a pediatrician, where a screening assessment for diabetes was conducted, which returned normal results, leading to a diagnosis of psychogenic PUPD. Three years later, the condition worsened, with the onset of a visual disturbance (bilateral diplopia), prompting an ophthalmologic examination followed by a brain CT scan, which suggested the presence of a craniopharyngioma, leading to his transfer to our facility for specialized care.
Discussion
Diabetes insipidus (DI) is a polyuric-polydipsic syndrome (PUPD) characterized by the excretion of large volumes of diluted, hypotonic urine due to a deficiency of antidiuretic hormone (ADH), leading to thirst and polydipsia. This condition is caused by damage to the posterior pituitary gland, often due to tumors such as craniopharyngiomas, infiltrative, traumatic, or vascular lesions, resulting in a deficiency in the production of antidiuretic hormone (arginine vasopressin). DI has been shown to occur in 46.8% of pediatric craniopharyngiomas. This central form of diabetes insipidus must be distinguished from other causes of polyuria and polydipsia, particularly psychogenic and nephrogenic causes, which are more common Treatment is primarily based on hormonal replacement, with desmopressin (Minirin) being the preferred synthetic analogue of ADH, offering a potent antidiuretic effect. In addition, proper hydration and treatment of the underlying etiology must be ensured, along with regular clinical monitoring. Nowadays, optimal management of cranopharungioma is based on a multimodal strategy involving a combination of surgery and, in some cases, radiotherapy, with the aim of controlling the disease and limiting morbidity.
Conclusion
DI is a rare condition that requires a thorough etiological investigation, with MRI playing a crucial role in diagnosis From our observation, we note that diabetes insipidus can be the first clinical sign of a craniopharyngioma, which must be differentiated from psychogenic causes. Early recognition is essential for effective treatment. Recognizing this association is crucial for early diagnosis and effective treatment, which can lead to improved long-term outcomes.
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EP1274

JOINT3371
A case of metastatic PITNET. diagnosis, treatment and outcomes
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Introduction
Metastatic PitNET (mPitNET) is extremely rare endocrine neoplasm, defined by the presence of craniospinal and/or systemic metastases, accounting for less than 0.2% of all pituitary tumors. Its low incidence makes both diagnosis and treatment challenging. The prognosis is generally poor, with an estimated 5-year survival rate as low as 35%. Symptoms of mPitNET are often a mixture of effects of hormonal activity, local invasiveness and distant metastasis. Surgery remains the first-line treatment - more than 80% of mPitNET cases require at least two surgeries, while more than 25% require at least four. However, depending on the individual case, additional therapeutic options may include radiotherapy, somatostatin analogs, dopamine agonists, and temozolomide (TMZ). It has been observed that patients receiving TMZ are more likely to achieve 5-year survival compared to those on alternative treatment regimens that do not include TMZ. However, since mPitNET remains a clinical challenge and frequently do not respond to first-line treatment, other therapeutic options, such as peptide receptor radionuclide therapy, immune checkpoint inhibitors, and tyrosine kinase inhibitors, have been tried.
Case Presentation
A 15-year-old, Caucasian male patient, was referred to endocrinology department due to gynecomastia, recurrent headaches, and visual disturbances. Laboratory tests did not reveal any abnormalities, while MRI revealed a large sellar mass suggestive of craniopharyngioma. The lesion was surgically removed, and histopathological examination identified a chromophobe pituitary adenoma with low ACTH expression (5% of cells). The clinical course of disease was aggressive, with numerous recurrences and mass effect. The patient had a total of seven debulking surgeries, complicated by infections (Acinetobacter baumannii) and acute hydrocephalus. Adjuvant stereotactic radiotherapy was delivered. Seven years after diagnosis, metastases were detected in the cerebellopontine angle, frontal lobe, and anterior vagal trunk. Scintigraphy showed expression of somatostatin receptors and lanreotide therapy was introduced for treatment. The patient subsequently received TMZ resulting in partial tumor regression and disease stabilization, however, severe side effects (myelosuppression, gastrointestinal symptoms) were observed. After twenty years of treatment, the patient remains clinically stable but struggles with visual impairment, epilepsy, and hypopituitarism. Current treatment includes lanreotide, antiepileptic drugs and thyroxine and hydrocortisone replacement.
Conclusion
By presenting this case, we wish to emphasize how advancements in diagnostic and therapeutic techniques, we can prolong patient's life - even in the disease with such a poor prognosis.
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EP1275

JOINT2422
Combining hormone replacement therapy and adjuvant treatment for a patient with resistant prolactinoma: a new clinical strategy
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Introduction
Prolactinomas make up nearly 50% of all pituitary tumors, with up to 20% of cases showing resistance to traditional therapy. Hormone replacement therapy (HRT) poses unique challenges in female patients with prolactinomas, as hormonal fluctuations can impact tumor behavior and treatment effectiveness. This case highlights a potential therapeutic approach for this clinical scenario.
Material and Methods
A 39-year-old female presented with complaints of pronounced fatigue, decreased libido, persistent pain in the breasts, and a weight gain of 6 kg over the past six months. The menstrual cycle was absent due to a previous hysterectomy with left ovary resection. In 2019, the prolactin (PRL) level was 50.5 ng/ml (<26.7 ng/ml). We administered cabergoline starting at 0.5 mg per week. In 2020, pituitary MRI revealed microadenoma 2.5 × 2.5 mm. Cabergoline was increased to 4.5 mg weekly, but no significant improvement was seen. In 2021, the PRL level was 1900 mU/l,also bilateral galactorrhea of Grade 2 was noted, along with pronounced breast pain and excess body weight. An MRI scan revealed an increase in pituitary adenoma size up to 3.5 mm. Bromocriptine was added, starting at 1.25 mg twice daily and increased to 2.5 mg twice daily. After a year of combined therapy, PRL decreased to 740 mIU/l,though it didn't reach the reference range, but the patient experienced relief from breast pain. Considering the previous hysterectomy and ongoing complaints of discomfort in the breast area, tamoxifen was added to the combination therapy. In the following months, due to improved PRL levels, the cabergoline dosage was discontinued by 2022. In 2023–2024, with bromocriptine (5 mg/day) and tamoxifen (20 mg/day), PRL remained within the normal range. There were no signs of galactorrhea or breast pain, and a 10 kg weight loss was noted. Due to complaints of low mood and menopausal hot flashes, the patient was offered HRT with tibolone 2.5 mg daily with discontinuation of tamoxifen. After one month, she reported improved mood, sleep, and relief from symptoms that had troubled her for 5 years, with the PRL level also within the reference range.
Results
Tibolone, unlike traditional HRT, selectively activates estrogen receptors, minimizing prolactin secretion and tumor risk. This makes it a safer option for menopausal women with well-controlled prolactinomas.
Conclusions
HRT helps manage vasomotor symptoms and prevent osteoporosis, but estrogen can stimulate tumor growth. Tibolone's dual action—antiestrogenic on breasts, estrogenic on the hypothalamus—suggests its potential use in menopausal prolactinoma patients.

DOI: 10.1530/endoabs.110.EP1275

EP1276

JOINT1155

A case of arginine vasopressin deficiency following immunization with mrna-covid-19 vaccination

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Introduction
Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have been rapidly developed with several novel and conventional technologies. The full profile of adverse effects is yet to be elucidated. Recently, there are sporadic but increasing reports of endocrinopathy in relation to SARS-CoV-2 vaccination, including a few cases of pituitary abnormalities such as hypophysitis. Hypophysitis following SARS-CoV-2 vaccination is exceptionally rare with less than ten cases being reported in the literature and typically presents as arginine vasopressin (AVP) deficiency emerging shortly after vaccine administration.
Aim
We present a novel rare case of infundilo-neurohypophysitis related to SARS-COV-2 vaccination which led to permanent isolated AVP deficiency.
Case Presentation
A 31-year-old previously healthy man presented with polyuria and polydipsia twenty days after his third dose of SARS-COV-2 vaccine with mRNA type (Moderna). He reported increased urine output and liquid intake, almost 7 liters per day. The previous two doses of SARS-COV-2 vaccine administrated to the patient, nine and seven months before, were viral rector type (AstraZeneca). On admission physical examination was normal. Biochemical tests and endocrine work up revealed no other abnormalities except for low urine osmolarity. Sella region magnetic resonance imaging (MRI) revealed diffusely enlarged pituitary gland and thickening of the pituitary stalk. Additionally, the bright spot of the neurohypophysis was not visible. After exclusion of the majority of causes of hypophysitis and taking in consideration the time-related symptoms in the absence of other symptoms, AVP deficiency was suspected in the context of SARS CoV-2 vaccine induced hypophysitis. Thus, treatment with oral desmopressin (DDAVP) was commenced, leading to rapid resolution of symptoms and also confirming our provisional diagnosis of AVP deficiency. Currently, at 3-year-follow-up there is persistence of pituitary stalk thickening on MRI with no other abnormalities. and the patient necessitates treatment with DDAVP 60 mg twice daily in order to remain asymptomatic.
Conclusion
Although rare, there are limited data suggesting a possible association between SARS CoV-2 vaccination and the development of AVP deficiency. Increased vigilance among clinicians is crucial for early recognition and intervention. To date, AVP deficiency following the SARS CoV-2 vaccine is a rare, temporally linked event with its pathophysiology still hypothetical. Further studies are needed to explore a potential causal relationship.

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EP1277

JOINT1529

Unusual endocrine trio: a case report of down syndrome with autoimmune hypothyroidism and prolactinoma

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Introduction
Down syndrome (DS) is a genetic disorder leading to a range of physical and cognitive impairments. Endocrine abnormalities such as thyroid disorders are prevalent among patients with DS. (1).
Case presentation
We report the case of a 26-year-old female patient, previously followed for DS since childhood, referred to the endocrinology department at the age of 19 after developing clinical symptoms suggestive of hypothyroidism. Laboratory tests revealed a TSH level of 11 µU/ml, FT4 of 15 pmol/l,and positive anti-TPO antibodies. A cervical ultrasound showed a heterogeneous, hypoechoic, pseudonodular thyroid gland of normal size, with decreased vascularity on color Doppler. The patient was started on Levothyroxine. At the age of 26, the patient presented with menstrual irregularities. Laboratory tests showed a TSH level of 2.02 µU/ml and hyperprolactinemia with a prolactin level of 977 mUI/ml. A pituitary MRI revealed a 5 mm anterior pituitary microadenoma. The patient was started on Cabergoline.
Discussion and Conclusion
This case highlights the complex interplay between Down syndrome and endocrine disorders, particularly hypothyroidism and hyperprolactinemia. Individuals with Down syndrome are at increased risk for thyroid dysfunction, with autoimmune hypothyroidism being one of the most common endocrinopathies observed in this population. Additionally, the development of hyperprolactinemia in this patient is of particular interest. Hyperprolactinemia is often secondary to thyroid dysfunction, especially in cases of untreated or poorly managed hypothyroidism. Prolactinomas are observed more frequently in DS compared to general population according to some observational studies (1). The patient's prolactin level of 977 mUI/ml and the MRI findings of a pituitary microadenoma led to the diagnosis of a prolactin-secreting adenoma. Treatment with Cabergoline resulted in both clinical and biochemical improvement of hyperprolactinemia. This case also underscores the importance of regular endocrine monitoring in individuals with Down syndrome, as they are susceptible to multiple endocrine abnormalities. Early diagnosis and treatment of these conditions can significantly improve the patient's quality of life and prevent long-term complications, especially in the presence of premature mortality in these patients (1).
(1) Rivelli A, Fitzpatrick V, Wales D, Chicoine L, Jia G, Rzhetsky A, Chicoine B. Prevalence of endocrine disorders among 6078 individuals with Down syndrome in the United States. J Patient Cent Res Rev. 2022;9:70-4. doi: 10.17294/2330-0698.1877.

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EP1278

JOINT4010

Contribution of MRI in the diagnosis of puitary stalk interruption syndrome

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Introduction

Pituitary stalk interruption syndrome is a rare etiology of antero-pituitary insufficiency. Somatotropic insufficiency may be isolated or immediately combined with wide clinical heterogeneity. The aim of this study is to determine the importance of hypothalamo-hypophyseal MRI in the positive diagnosis of SITP.

Materials and methods

Retrospective analysis of 7 observations (4 males and 3 FEMALES) ranging in age from 6 to 26 years Investigated by pituitary MRI for Antero pituitary insufficiency.

Results

Pituitary MRI revealed no visualization of the pituitary stalk in 5 patients, and a very thin stalk in tow. An ectopic hypothalamic post-hypophysis was found in 5 patients. Post-hypophyseal extinction was noted in two patients. Hypoplasia of the anterior pituitary glandular parenchyma with a small sella was noted in 4 patients. Isolated growth hormone (GH) deficiency was noted one patient with thin stalk, whereas the absence of a pituitary stalk was associated with combined hormone deficiency (panhypopituitarism was noted in tow patients).

Discussion

SITP is a rare congenital malformation which is characterized by antero-pituitary deficiencies. Etiologic diagnosis is performed radiologically by an MRI showing the association of a thin or absent pituitary stalk, an ectopic post-hypophysis and/or a hypoplastic or absent anterior pituitary. It provides a morphological study of the hypothalamo-hypophyseal axis and helps to establish clinic-radiological correlations.

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EP1279

JOINT2405

A clinical case: chromosomal abnormalities and hypogonadism

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Introduction

An inversion of chromosome 9 is a change in the structure of a chromosome caused by a 180° rotation of one of its internal sections. It is the result of two simultaneous breaks in a given chromosome. It is not known where the break occurs, and which nucleotide sequences change during this process. The prevalence of this karyotype feature is 1-3% of the total population. A clinical case. The patient went to the doctor in November 2024 at the medical center of Endocrinology of in Tashkent, Uzbekistan, complaining of an absence of menstruation. From the medical history: the patient was born in 2010 with a weight of 3100 grams with a normal pregnancy. Since birth, she has been under the supervision of an orthopedist with a diagnosis of congenital dislocation of the hip joint. In September 2024, uterine hypoplasia was detected at a medical examination at the school and was sent for further follow-up to the endocrinology center. An objective examination by a gynecologist-endocrinologist revealed that the external genitalia corresponded to the female sex. Mammary glands and secondary hair were poorly developed. Sexual development according to Tanner: Ax-1, Pb-2, Ma-2, Me-0. Her body type was normosthenic, with a shortened torso and a massive lower jaw. Laboratory data showed a significant decrease in hormone levels: Androstenedione 0.39 ng/ml, Sex hormone binding Globulin 108 nmol/l,LH 0.03 mIu/ml, Progesterone 0.46 ng/ml, Prolactin 2.71 ng/ml, Testosterone 0.13 nmol/l,Estradiol 12.9 pmol/l,Free Androgen index 0.12 %. The level of FSH was within the normal range - 4.88 mIu/ml. Instrumental studies have shown on ultrasound of the uterus and appendages a decrease in the volume of the uterus (infantile uterus 3-4 grade) and on MRI of the pelvic organs - MRI-signs of hypoplasia of the uterus. Based on the results of the geneticist's observation, karyotyping was performed, where cytogenetic examination data showed Karyotype XX, inv 9 (p12;q13) and based on the results of all laboratory and instrumental studies and the geneticist's conclusion, the final diagnosis was made: Hypogonadotropic hypogonadism (chromosomal aberration, inversion of chromosome 9 p12;q13). Complication: Primary amenorrhea. Delayed sexual development.

Conclusions

The patient is currently receiving hormone replacement therapy, vitamin therapy, and she is under the supervision of an endocrinologist and gynecologist. It is recommended to follow up again after 3 months, follow a healthy lifestyle, regular physical activity, and a balanced diet.

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EP1280

JOINT2246

Psychosis as a rare clinical presentation of sheehan syndrome: case report and review of the literature

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Introduction

Sheehan syndrome is hypopituitarism due to pituitary necrosis resulting from hemorrhagic choc during pregnancy. The clinical picture is characterized by post-partum amenorrhea and absence of lactation. Psychotic presentations are rare. This article reports an exceptional case of sheehan's syndrome with a psychiatric presentation.

Case report

The patient was 65 years old, not known to have an endocrinopathy. She had been known to be diabetic for 24 years and was being followed for heart disease. She had been menopausal for 25 years following her last delivery, which was complicated by post-partum haemorrhage, absence of milk production and return from childbirth. Admitted to the emergency department, she presented with psychomotor agitation consisting of delusions of persecution and bizarre delusions, auditory and visual hallucinations, repetitive gestures and aggressive behaviour. This picture was preceded by asthenia and a digestive picture of abdominal pain, vomiting and diarrhea. Clinical examination revealed a disoriented patient, pale skin and mucous membranes, hypotension, depigmentation of the nipples, axillary and pubic depilation, and edema of the lower limbs. Biological tests revealed normocytic normochromic anemia with hemoglobin at 8g/dl, hyponatremia at 117mmol/l,8 hour cortisol level at 2.9µg/dl, ultrasensitive thyroid stimulating hormone at 0.55mUI/l,T4L less than 5.15pmol/land T3 less than 1.64 pmol/l. Magnetic resonance imaging revealed an empty sella turcica. The patient underwent hormone replacement with glucocorticoids and thyroxine, with a spectacular evolution.

Discussion

The pathophysiology of the psychiatric manifestations of Sheehan syndrome is unclear. It seems to result from a complex interaction between hormonal deficiencies and metabolic and electrolyte changes in the central nervous system, such as hyponatremia. The latter is known to cause cognitive deficits and is not usually associated with psychotic symptoms in the absence of disturbances of consciousness and neurological signs. Hypothyroidism may play a more important role in pathogenesis, as it is systematically associated with neuropsychiatric manifestations. It is associated with mood symptoms rather than psychosis, although psychotic presentations without mood disorders have been reported. Dramatic improvement with glucocorticoids and thyroxine suggests a possible link with these hormonal deficiencies.

Conclusion

Psychosis in patients with Sheehan's syndrome is uncommon. This rare presentation of Sheehan syndrome with psychosis not only represents the close association of organic pathology to psychiatric manifestations but also illustrates the possible psychiatric adverse effects of panhypopituitarism and its metabolic consequences. Clinicians should have a high index of suspicion in case of postpartum- psychosis presenting with significant obstetric history.

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EP1281

JOINT2127

Cushing's disease due to invasive macroadeoma with crooke cellular transformation and mgmt methylation

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We present the case of a 41-year-old woman with clinical symptoms of asthenia, proximal muscle weakness, behavioral changes, Cushingoid facies, visual disturbances and weight gain of 1.5 years. She also had a previous pelvic fracture with osteopenia in densitometry and hypertension of three months' evolution. In the study due to clinical suspicion of Cushing's syndrome, an elevation of urinary free cortisol was observed five times above the upper limit of normal, a dexamethasone suppression test of 1 mg of 26 mg/dl, elevated nocturnal salivary cortisol and inappropriately elevated ACTH repeated on three occasions. In ophthalmological study showed bilateral homonymous left quadrantanopia with bilateral left hemianoptic loss of sensitivity compatible with right parietotemporal lesion. Pituitary resonance imaging describes a giant pituitary mass measuring 5.1 × 3.5 × 4.2 cm with extensive growth to the interpeduncular cistern and prepontine cistern, extension through the floor of the sella turcica to the sphenoid sinus, invasion of the right cavernous sinus with hydrocephalus and signs of intracranial hypertension requiring placement of a shunt valve. Surgery was performed in 2022 first with transcranial surgery and required a second transsphenoidal surgery one month later due to significant tumor remnant. The main complications of the surgery were diabetes insipidus and hypothalamic syndrome with psychomotor agitation that was difficult to control, as well as secondary hypothyroidism and central catheter infection. The pathological study showed Ki67 of 4%, positivity for ACTH, alpha subunit, presence of Crooke cells and MGMT methylation and negativity for p53. In the hormonal study one month after surgery, the patient presented data of adrenal insufficiency with cortisol < 1 mg/dl and in the continuous resonance, the tumor residue was 3.7x2.7x2.2 cm. She received treatment with radiotherapy-protontherapy on the tumor residue, which remained stable in the following three years. Cushing's disease due to invasive macroadenoma with positivity for Crooke cells occurs rarely. The positivity of these cells and MGMT methylation predispose to invasive macroadenomas with persistence of tumor residues and, in general, recurrence of Cushing's disease. In our case, the patient remains without data of hypercortisolism and the tumor residue remains stable after three years of surgery and protontherapy.

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EP1282

JOINT3435

Kallmann-morsier syndrome: a genetic mystery behind amenorrhea and anosmia

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Introduction
Kallmann-Morsier syndrome is a rare genetic condition characterized by the association of hypogonadotropic hypogonadism (HH) with anosmia or hyposmia. This condition results from a defect in the embryonic migration of GnRH-producing neurons and olfactory neurons. Diagnosis is often delayed due to the significant variability in clinical manifestations.
Case Report
We present the case of a 17-year-old single female patient who consulted for primary amenorrhea. The medical history revealed anosmia present since childhood, with a family history of anosmia reported in her father. Clinical examination revealed normal development of secondary sexual characteristics, corresponding to Tanner stage S3P3. Biological assessments showed hypogonadotropic hypogonadism, with low LH and FSH levels, indicating dysfunction of the hypothalamic-pituitary axis. Paraclinical evaluations revealed:.
- A normal breast ultrasound,.
- A normal transthoracic echocardiogram,.
- An MRI of the olfactory bulbs showing complete agenesis of the left olfactory bulb and hypoplasia of the right olfactory bulb, thereby confirming the diagnosis of Kallmann syndrome. The treatment implemented was progressive hormone replacement therapy. Estradiol was gradually introduced over two years to promote the development of secondary sexual characteristics and ensure bone health. Subsequently, progesterone was added to simulate a physiological menstrual cycle.
Discussion
Kallmann syndrome was first described in 1944 by Franz Josef Kallmann, a German-born geneticist who emigrated to the United States. This condition results from a defect in the embryonic migration of GnRH-producing neurons and olfactory neurons, caused by genetic mutations, particularly in the **KAL1**, **FGFR1**, and **PROKR2** genes. Although rare, this syndrome should be considered in any patient presenting with primary amenorrhea associated with hypogonadotropic hypogonadism and anosmia or hyposmia.
Conclusion
This case highlights the importance of suspecting Kallmann syndrome in adolescent girls presenting with primary amenorrhea accompanied by anosmia. Early and appropriate management, including hormone replacement therapy, optimizes pubertal development, improves bone health, and ensures a better quality of life.

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EP1283

JOINT2580

Acromegaly and kidney cancer what is the link?

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Introduction
Acromegaly is a chronic disease associated with an increased risk of cancer. A recent survey study conducted in Italy demonstrated an increased incidence of all malignant tumors in acromegalic patients, as well as gender differences in the incidence of malignant tumor types, with an increased incidence of thyroid, colorectal and breast cancer in women, while thyroid, kidney and colorectal cancer in men.
Observation
73-year-old patient with history of Enucleation for papillary renal carcinoma in 2013. Diagnosed in our training for Acromegaly clinically confirmed by dysmorphic syndrome acro-facial biologically IGF1 rate elevated to 2.6N with morphologically a hypotalamo-hypophyseal MRI in favor of a left paramedian pituitary micro-adenoma. Acromegaly: severe obstructive sleep apnea syndrome. 28-year history of hypertension complicated by non-sequelae ischemic stroke on dual therapy. Diabetes for 02 years on Metformin. Colonoscopy: presence of a histologically resected pedunculated polyp compatible with a tubulovillous adenoma with low-grade dysplasia. The patient was referred to neurosurgery for transphenoidal removal of the adenoma.
Discussion
IGF-1 synthesized locally in connective tissue adjacent to renal epithelial cells acts as a paracrine or autocrine factor in the kidney. The degree of IGF1R gene expression is different throughout the nephrogenic zone, with stronger expression in glomeruli and tubular epithelium of the medulla, and weaker expression in proximal tubules [12]. IGF1R affects the transformation of renal cells to malignancy by inducing cell proliferation, dedifferentiation and inhibiting apoptosis. RCC cells are sensitive to exogenous IGF-1 stimulation. Expression of IGF1R and the development of ccRCC were found to be associated, indicating that it may be a possible molecular prognostic marker as well as a potential target for new therapeutic interventions. Therefore, treatment of acromegaly and control of disease progression in acromegalic patients with any type of cancer are mandatory.

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EP1284

JOINT3842

Height blood pressure and acromegaly: about 78 cases

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Introduction
Acromegaly is a rare condition secondary to hypersecretion of GH often by a pituitary adenoma. High blood pressure is frequently found, aggravating the cardiovascular complications of acromegaly and improving its risks of morbidity and mortality.
The objective
Is to specify the frequency and evaluate the clinical and paraclinical characteristics of High blood pressure in acromegalic patients.
Patients and methods
This is a retrospective, descriptive study of 78 patients hospitalized in the endocrinology, diabetology and metabolic diseases department of Ibn-Rochd University Hospital, Casablanca from January 2007 to December 2024.
Results
Elevated blood pressure – hypertension was found in 27 cases (21%), with a mean age of 54 years (36–72) and a sex ratio: F/M of 2.45. Mean blood pressure was

150/90 mmHg. Grade 1 was found in 51%, grade 2 in 34% and grade 3 in 15%. Hypertension was well controlled in 58% under monotherapy and in 32% under dual therapy. Hypertension was resistant in 22% under dual therapy and in 12% under triple therapy and was associated with diabetes or prediabetes in 79% of cases, and with dyslipidemia in 52%. Hypertensive retinopathy was found in 38% of cases, positive microalbuminuria (42%) and hypertensive heart disease (19%). Hypertension did not regress in any patient after surgical management.
Conclusion
In a third of cases, high blood pressure is found and is an integral part of the cardiovascular complications that determine cardiovascular morbidity and mortality.

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EP1285

JOINT2444
Parhon's syndrome: the difficult path to finding the root cause
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Introduction
Parhon's syndrome, also known as the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or antidiabetes insipidus, is a rare disorder characterized by excessive secretion of antidiuretic hormone (ADH) from the posterior pituitary gland or an ectopic source. This results in dilutional hyponatremia, which requires hospitalization in 15–20% of cases.
Materials and methods
Patient S., a 66-year-old male, has been hospitalized multiple times since March 2024 due to recurrent episodes of hyponatremia, with serum sodium levels dropping to 108 mmol/l,accompanied by seizures and falls. Parhon's syndrome was suspected.
Results
In June 2024, the patient was admitted to the Department of Neuroendocrinology at the Endocrinology Research Centre. Hormonal studies showed no evidence of hypothyroidism (TSH: 0.487 mIU/l,free T4: 16.8 pmol/l)or adrenal insufficiency (ACTH: 28 pg/ml, cortisol: 326.7 nmol/L). Heart failure was ruled out (NT-proBNP: 10 pg/ml; reference range: 0–125 pg/ml). Upon admission, laboratory findings included serum sodium of 119.9 mmol/l,blood osmolality of 247–249 mOsm/kg (reference: 280–300), and urine osmolality of 415–603 mOsm/kg (reference: 300–1200). Initial treatment involved an infusion of 3% NaCl, followed by oral therapy with 0.9% solution of NaCl. After five days, sodium stabilized at 133.6 mmol/lwith fluid restriction (800 mL/day) and furosemide (80 mg/day). As prior imaging showed no brain, thoracic, or abdominal tumors, further tests were done to explore a possible ectopic ADH source. A whole-body PET/CT (June 2024) revealed a hypermetabolic lesion in the right back, diagnosed as elastofibroma, but a follow-up PET/CT (July 2024) showed no tumors. A core biopsy failed due to insufficient tissue visibility. A surgeon suggested the 18F-FDG uptake was due to nonspecific changes from prior falls linked to hyponatremia. With fluid restriction, furosemide (80 mg/day), and NaCl (200 mL/day), serum sodium levels remained stable (138–141 mmol/L). Reducing furosemide to 40 mg/day led to sodium levels of 135–138 mmol/l,but stopping it caused a drop to 132.8 mmol/l,requiring reintroduction at 40 mg/day to maintain normal levels. Ongoing sodium monitoring was advised.
Conclusions
Despite the absence of a confirmed source of ADH hypersecretion, this case underscores the importance of early diagnosis, understanding the pathophysiology of Parhon's syndrome, and implementing an effective treatment strategy. Proper management prevents severe complications associated with hyponatremia and inappropriate therapy, ultimately improving the patient's quality of life.

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EP1286

JOINT2843
Metyrapone as a bridge therapy after pituitary radiation for aggressive Cushing's disease: a case report
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Primary therapy in Cushing's disease consists of transsphenoidal surgery but when the tumor is aggressive, patients can undergo targeted radiotherapy. Due to its late effect, medical therapy like metyrapone is an option for managing hypercortisolism till radiotherapy is achieving maximal therapeutic effect, limited because of poor tolerability and lack of data regarding long-term efficacy. To document the significant changes on metyrapone in our patient we used: body weight, systolic blood pressure, ability of doing squats, Quality of Life, Beck Depression Inventory assessment, glycosylated hemoglobin test (HbA1c) along with biochemical parameters. The patient is a 56-year-old female with medical history of severe psychiatric symptoms (major depression, episodes of hypomania) and cognitive impairment along with proximal muscle weakness and metabolic complications: obesity, uncontrolled type 2 *diabetes, resistant hypertension, all caused by* pituitary adenoma diagnosed in February 2022. In April 2022 the patient was referred to neurosurgery for transsphenoidal pituitary surgery. The immunohistochemistry was positive for ACTH with high proliferative index (ki-67: 14%). Postsurgical MRI scan indicated residual tumor presence. A second and third surgery attempts couldn't control hypercortisolism. In August 2023 she started stereotactic pituitary radiation followed by metyrapone, initially 250 mg daily then titrated up to 250 mg twice/day, well tolerated. We documented the changes before and after initiating metyrapone treatment: weight loss was 13 kg, diabetes was controlled with metformin and GLP-1 analogue (HbA1c from 10.1% to 6%), proximal muscle strength increased from 1 to 5 squats, maximum systolic blood pressure was 150 mmHg. Psychiatric symptoms ameliorated, concentration, comprehension, verbal control and spatial abilities improved. Regarding biochemical changes: plasma ACTH decreased from 132.9 pg/ml to 64.58 pg/ml, 24-hour urinary free cortisol from 172.51mg/24h to 52.2mg/24h, morning serum cortisol normalized (20.76mg/dl) as well as late-evening salivary cortisol (0.18mg/dl). She continues with 500 mg metyrapone per day with a favorable evolution. Neurosurgery in tertiary centers is the first line treatment in Cushing's disease and should remain the mainstay of its management, followed by radiotherapy in aggressive cases. Only few medications have been proven to be beneficial as a bridge therapy while waiting for the effect of stereotactic pituitary radiation to be complete and metyrapone could be one of them.

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EP1287

JOINT1203
Combined therapy of somatostatin analogue with pegvisomant for the management of acromegaly
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Combined therapy of somatostatin analogue and growth hormone receptor antagonist for the management of acromegaly. A 35-year-old woman was diagnosed with acromegaly in January 2021. She was consulted by an endocrinologist due to enlarged hands and feet. She also complained of a change in facial features, weight gain, excessive sweating, and severe headaches. Laboratory tests confirmed the diagnosis of acromegaly. MRI of the pituitary gland revealed a pituitary tumor of 22 × 32 × 26 mm. She was referred to the neurosurgery department. The surgery was not complete, the remnant tumor was 25 × 28 × 16 mm and comprised the right cavernous sinus. The patient was suggested to start radiotherapy but did not agree. A first generation somatostatin analogue was introduced. IGF-1 concentration was 492 ng/dl (115-307). Due to the lack of improvement, a second generation of somatostatin analogue was started. At the beginning patient received 40 mg of pasireotide. After a few months, IGF-1 concentration was still elevated [416 ng/dl, (115-307)]. Then the dose was increased to 60 mg. During the nine months of treatment, a normal IGF-1 level was observed only once (306 ng/dl, (115-307)], in January 2023. The patient was dismissed from this treatment due to the lack of normalization of IGF-1 and the poor tumor shrinkage. The patient underwent radiotherapy in June 2023. It was not possible to introduce Gamma Knife radiosurgery. It was decided to apply irradiation with a total dose of 54 Gy. Severe headache appeared soon after cessation of pasireotide and aggravated after radiotherapy. It was decided to administer pegvisomant until the effects of radiotherapy appeared. Before administration of pegvisomant, an MRI was done and revealed a residual tumor measuring 17 mm x 20 mm x 20 mm infiltrating the right cavernous sinus and almost completely encasing the internal carotid artery segment. The tumor grew between the base of the right frontal lobe and the inner surface of the right temporal pole toward the optic canal. It did not infiltrate the right optic nerve or the optic chiasm. The initial dose was 10 mg in October 2023. The permanent reduction in IGF-1 level was achieved with a dose of 20 mg. Due to a headache

that impaired quality of life significantly, pasireotide was administered again as emergency therapy in November 2023. It was very effective in managing headaches. The patient continues therapy addressing both IGF-1 concentration and the most disturbing symptom.

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EP1288

JOINT1414

Barriers to timely diagnosis of cushing's disease in the outpatient setting

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Introduction

Cushing's disease is a rare condition, particularly when compared to Cushing's syndrome, with an incidence of 0.7 to 2.4 cases per million individuals. Due to its rarity, diagnosis is frequently delayed, which results in a notable increase in morbidity. First line treatment is pituitary surgery, and remission in obtained in 80% of patients with microadenoma, and 60% of those with macroadenoma. In the event of failure of surgical treatment, and if reoperation is not feasible, the introduction of steroidogenesis inhibitors and radiotherapy may be considered.

Case report

We present the case of 38-year-old female patient with hypercorticism which was reffered to our institution from outpatient endocrinologist. She was diagnosed with diabetes mellitus type 2 at the age of 33, and hypertension at the age of 30. Due to irregular mestrual cycles, she was followed by endocrinologist and gynecologist as a polycistic ovary syndrome. At the age of 38, due to worsening of diabetes and obesity, her outpatient endocrinologist obtained Dex screening cortisol levels which were unsupressed, and reffered her for further testing. We did extensive hormonal work up which confirmed ACTH dependent hypercortisolism. Pituitary NMR showed pituitary macroadenoma sized 3,1 cm. The patient also presented with an adrenal incidentaloma, and subsequent evaluation confirmed the presence of a nonfunctional tumor with radiological characteristics consistent with an adenoma. She was operated on by experienced neurosurgeon, and postoperative follow up comfirmed that did not achieve remission, and since tumor invaded cavernous sinus, gama knife was performed. Subsequently, patient in still not in remission regarding Cushings disease, while she has well controlled diabetes and hypertension.

Conclusion

In conclusion, as previously mentioned, the diagnosis of Cushing's disease is frequently delayed due to its rarity, particularly in less experienced centers. Consequently, in young women presenting with amenorrhea and diabetes, secondary causes of diabetes should be considered to ensure timely diagnosis and appropriate treatment.

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EP1289

JOINT2363

The interplay of hormones and neuroplasticity: how hormonal changes shape brain adaptation to stress and learning

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Introduction

Neuroplasticity responds to hormonal shifts through brain self-adaptation and reorganization resulting in substantial influence on stress responses along with learning and environmental change adaptation capability. This article investigates how hormones affect neuroplasticity through examination of five significant hormones including cortisol together with estrogen and testosterone and oxytocin and thyroid hormones based on data from literature.

Material and Methods

Published data from past two decades from source such as MedLine, PubMed, Scopus, WebofScience, Google Scholar regarding hormonal changes in neuroplasticity were analysed and presented as summary.

Results

Stress-induced cortisol regulation affects both synaptic plasticity and memory consolidation processes in the brain while estrogen and testosterone support neurogenesis activities and synaptic remodeling and cognitive functions throughout the areas that include hippocampus and hypothalamus. The hormone estrogen specifically controls serotonin manufacturing processes in the brain as well as controlling serotonin receptor operation to affect cognitive functioning. The stress and memory responses are directly influenced by progesterone and its metabolites although their performance changes throughout the menstrual cycle. When a woman takes hormonal birth control the medicine changes the way her brain looks by modifying gray and white matter structure. The research paper examines sexual brain differences in network connections particularly regarding the default mode network while demonstrating how sex hormones control such functional brain networks. Researchers need to understand how hormones influence brain function because this knowledge enables proper development of treatment methods for neuropsychiatric disorders such as depression and anxiety where sex-specific differences are prominent. Research needs more focus on hormonal treatments of brain disorders because this review establishes that hormone changes affect neural flexibility and mental wellness at varying stages of life.

Conclusion

Changes in brain neuroplasticity can affect in dual way: neuroplasticity can changes hormones secretion, hormones disregulation can changes brain functional activity. Underlying molecular mechanisms should been taken in account in treatment neurologic and endocrine diseases. Deep understanding that process can help in improving preventive managements in adaptation to stress and learning.

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EP1290

JOINT585

Corticotherapy revealing a pituitary adenoma

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Introduction

Prolonged corticosteroid therapy exerts a negative feedback control on the hypothalamic-pituitary axis, resulting secondary adrenal insufficiency. Recovery of normal adrenocortical axis function is most often spontaneous. We report here a case of non-secreting pituitary adenoma revealed by corticosteroid therapy.

Observation

A 20-year-old woman was referred to us for the management of a pituitary microadenoma evolving in the context of Cushing's syndrome. During questioning, a skin allergy is reported for which long-term corticosteroid therapy had been prescribed. Not having been properly informed, the patient abruptly interrupted her treatment and consulted her doctor because of the sudden onset of asthenia and arterial hypotension, in which case a requested hormonal assessment revealed a low cortisol level at 40.19 nmol/lwith non-increasing ACTH level at 9.67 pg/ml. Having been convinced of the central origin of the adrenal insufficiency, and disregarding corticosteroid intake notion, magnetic resonance imaging was requested, revealed a 4 mm pituitary microadenoma left side. It should be noted that the rest of pituitary assessment did not objectify any hypo or hypersecretion of the other axes. After a withdrawal protocol, cortisol levels at 3 months had returned to 339.50 nmol/l,and the patient was still being followed-up.

Discussion

Pituitary adenomas of any type are rare. intrasellar lesions prevalence in the general population is 6-10%, mainly microadenomas. Non-functional pituitary adenomas are pituitary tumours that do not secrete any hormone. Since 1948, synthetic corticosteroids are widely used in medical practice due to their anti-inflammatory, anti-allergic and immunosuppressive properties. Addition to their therapeutic effects, corticosteroids exert a negative feedback effect on the corticotropic axis, inhibiting the secretion of ACTH and cortisol. This phenomenon is also called iatrogenic or exogenous Cushing's syndrome.

Conclusion

Better management of prolonged corticosteroid therapy will help us to assess the real adrenal insufficiency incidence, and to propose adequate prevention of this side effect.

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EP1291

JOINT3877

Craniopharyngioma in adolescence: from diagnosis to ongoing care

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Introduction
Craniopharyngiomas are rare, benign tumors that arise near the pituitary gland, predominantly affecting children and adolescents. Although benign, these tumors can lead to significant morbidity due to their proximity to critical structures like the hypothalamus and pituitary gland. Early diagnosis and appropriate treatment are essential, particularly when hypothalamic involvement occurs, as it can complicate management and influence long-term endocrine function.
Case Description
A 15-year-old female presented with a history of severe, recurrent headaches and syncope. Initial blood and biochemical tests were within normal limits. Endocrine testing revealed normal thyroid function, undetectable LH and subnormal FSH levels, Tanner stage 2 sexual development and decreased height velocity (SDS -1.9 in 2025 vs. SDS -1.3 in 2023). Magnetic resonance imaging (MRI) revealed hydrocephalus and a mass located in the chiasmatic region, suggesting a craniopharyngioma. The patient underwent surgical resection of the mass, and histological examination of the resected tissue confirmed the diagnosis of craniopharyngioma. Postoperatively, the patient developed polyuria, which raised concerns for arginine vasopressin deficiency, thus desmopressin was initiated. Electrolyte disturbances (including sodium and potassium shifts) and low urine specific gravity were observed as well. Given the persistent polyuria (20 L per day), the dose of desmopressin was increased, and within 2-3 days the patient was improved (diuresis 3L per day). Her laboratory results have since normalized. The patient is under ongoing follow-up care by both an endocrinologist and an oncologist for continued monitoring of her recovery and management of potential long-term endocrine effects, including the evaluation of sexual development as part of her follow-up care.
Conclusions
Craniopharyngiomas should be considered in the differential diagnosis of adolescents with unexplained neurological symptoms and growth delay. While the patient's craniopharyngioma was managed with initial success, the case underscores the necessity of lifelong multidisciplinary follow-up to address hormonal deficiencies, metabolic complications, and psychosocial challenges. It is important to find the balance between tumor control and preserving quality of life in adolescents with this condition.

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EP1292

JOINT909

Non-surgical management of patients with pituitary macroadenomas: case report

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Introduction
Particular clinical difficulties are presented by patients with mixed hyperproduction, as well as situations with secondary hyperprolactinemia due to compression of the pituitary stalk. Thus, the aim was to study the results of using of dopamine receptor agonists in patients with macro-adenomas and hyperprolactinemia.
Material and Methods
An observational study was performed on clinical cases of three patients referred for management and treatment at the Republican Endocrinology Centre. The observation period was from the beginning of 2022 to the present.
Results
Patient 1. A 38-year-old man consulted a doctor due to a constant, terrible headache. During the interview, he noted a change in appearance over the past 4 years. The headache has increased worse since March 2022, nasal congestion appeared. In the sellar region, a tumor with uneven clear contours with overall dimensions of 67*53*85mm, a heterogeneous structure with the presence of calcifications and small cystic components, measuring up to 7 mm, is determined. Serum tests: TSH 1,27 mIU/nL, Free T4 14,21pmol/l,Prolactin 10000mIU/l,-Cortisol 214.5nmol/l,IGF-1: 956.6 ng/ml, HbA1 – 6,24%. *Ophthalmologist's report*: long-standing papilledema; OD - absolute scotoma in the posterior pole next to the optic disc, OS - widening of the blind spot. In a year treatment prolactin 369.7mIU/l,GH 0.556ng/ml, IGF-1 251.7, then prolactin 282mIU/L. Dynamics Pt MRI: 67*53*85mm (May2022) vs. 35*18*40mm (October2022) vs. 27*15*25 mm (March2023). Patient2. A 23-year-old man with any symptoms and changes in health. In February 2021 he consulted a doctor with the results of a hormonal analysis: TSH 1,98 mIU/nL, fT4: 15,3 pmol/l,prolactin: 6 395mkIU/l,-MonoProlactin: 5650mIU/l87%, FSH 33,43 mIU/l,total testosterone – 1,97pmol/l,cortisol: 419nmol/l,HbA1C 5.3%. PT MRI: a pituitary adenoma was detected in the left half measuring 7.5x10x9.5 mm without displacement of the pituitary stalk. Cabergoline 0.5mg twice a week was prescribed. Patient3. A 38-year-old woman consulted a doctor about dizziness and lack of menstrual cycle. Hormonal status parameters: TSH 3,09mIU/nL, FreeT4: 14.72pmol/l,Prolactin: 123100 mkIU/ml, MonoProlactin: 97736mkIU/ml–79.4%, FSH 5.54 mIU/l,Estradiol: 57.71pmol/l,Cortisol: 389.8nmol/l,IGF-1: 135.5ng/ml. PTMRI: a pituitary adenoma 22x20x19mm with clear contours of a solid structure, suprasellar growth, compression of the chiasm. Normalization of prolactin occurred after several months of treatment, but to resume the menstrual cycle it was necessary to increase the dose of cabergoline.
Conclusion
The use of cabergoline is an effective and safe treatment for pituitary macroadenomas in the first step.

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Reproductive and Developmental Endocrinology

EP1293

JOINT836

The relationship between reproductive hormones, testis size, mating strategy, and spermatogenesis efficiency across primates

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Background
In humans, it is well-described that spermatogenesis is tightly regulated by reproductive hormones. Spermatogenesis is also an evolutionarily conserved process, which ultimately results in the production of spermatozoa. Common across all mammals are processes that maintain a stem cell pool, a proliferation phase, meiosis and a final differentiation process. Despite being a conserved process, spermatogenesis also undergoes rapid evolutionary changes driven by selective pressures favouring male reproductive success. Primates represent an excellent population to investigate spermatogenesis since many species are evolutionary close but also differ considerably regarding testis size and mating strategies. Comparison of the spermatogenic efficiency across primates can provide valuable insights into how evolution has influenced the complex interplay between reproductive hormones and testicular function and potentially provide insight into why human male fertility has decreased.
Methods
Hormones were measured in serum samples from nine primate individuals representing six different species using ELISA or LC-MS/MS. Histological evaluations of testicular tissue were performed by immunohistochemistry using antibodies against melanoma-associated antigen 4 (MAGE-A4) to stain spermatogonia and nuclear transition protein 1 (TNP1) to stain elongated spermatids. A total of thirteen individuals representing eight species. Germ cells positive for the two antibody markers were quantified using the Qupath software, and the ratio of TNP1-positive spermatids and MAGE-A4-positive spermatogonia was calculated.
Results
Whereas the percentage of MAGE-A4-positive spermatogonia was similar between all individuals, there were remarkable differences in the percentage of TNP1-positive spermatids. Species that have a monogamous mating strategy had lower TNP1/MAGE ratios, indicating a lower spermatogenic efficiency and species with a harem mating strategy showed intermediate ratios, whereas species

with polygynandrous mating systems showed the highest TNP1/MAGE ratios, suggesting a more efficient spermatogenesis when multiple males are present per female. Interestingly, all primates showed high levels of the spermatogenesis hormone marker, inhibin B compared to human reference ranges. The inhibin b levels were particularly high in the chimpanzees, likely caused by their large testis size. The harem-living species had the highest testosterone levels and their dihydrotestosterone (DHT) levels were above human reference ranges suggesting that these hormones could reflect male dominance.
Conclusions
Our preliminary data indicates that the mating strategy among primates affects both testis size and the efficiency of spermatogenesis, which again is reflected by inhibin B levels. Humans had the lowest inhibin B levels of all investigated primates, which corroborates the poor testicular function observed among humans.

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EP1297

JOINT879

Characterization of intracrine androgen production in human genital skin fibroblasts

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Introduction
Differences of sex development (DSD) comprise a heterogeneous group of conditions with an atypical sex development. Disorders of steroid biosynthesis are often directly or indirectly involved. Steroid hormones are typically measured in the bloodstream, while locally produced intracrine steroids in peripheral tissues remain underexplored. 5-α-Reductase type 2(SRD5A2) converts testosterone to dihydrotestosterone (DHT), a potent androgen critical for male genital development in the fetal period and puberty. Deficiency of this enzyme, caused by mutations in the SRD5A2 gene, leads to an autosomal recessive DSD with varying degrees of undervirilization in individuals with a 46, XY karyotype. This study focuses on the analysis of the intracrine steroidome associated with SRD5A2 deficiency in cultured genital skin fibroblasts (GSF) to improve the understanding of peripheral androgen biosynthesis.
Method and Cell culture
GSFs from molecular proven SRD5A2-deficient persons (labioscrotal folds) and controls (scrotum) were cultured in DMEM-based medium at 37°C, 5% CO_2. Cells were seeded in 6-well plates (6×10^4 cells/2 ml/well) and incubated with testosterone, DHEA, and 17-hydoxyprogesterone (17OHP) at three concentrations (1, 10 and 100 nM). Supernatants were analyzed by LC-MS/MS after 24 h pre-incubation (before hormone incubation) or after additional 72 h of hormone incubation.
- **ARD515**: homozygous p.Arg227Gln.
- **ARD249**: homozygous Gly196Ser.
- **GS451**: homozygous p.Ile199Asn.

Results
DHT production was significantly reduced in SRD5A2-deficient cells compared to control cell lines confirming the underlying molecular defect. At 100 nM testosterone, the mean DHT production in SRD5A2-deficient cells was 5.54 nM $\pm$ 2.69 ($n = 3$), while in control cells it was 46.65 nM $\pm$ 30.58 ($n = 3$). Additionally, there was a notable back-conversion to androstenedione in the SRD5A2-deficient cells, with levels of 8.84 nM $\pm$ 2.79 ($n = 3$), compared to 0.15 nM $\pm$ 0.22 ($n = 3$) in control cells. Similarly, the metabolism of DHEA and 17OHP showed distinct differences between the SRD5A2-deficient and controls.
Conclusion
A limited but detectable conversion of testosterone to DHT occurs in SRD5A2-deficient cells, suggesting that residual enzymatic activity may be involved. The observed back-conversion of testosterone to androstenedione highlights the complexity of steroidogenesis in SRD5A2 deficiency. To fully explain this back-reaction, Further androgen biosynthesis pathways should be included in steroid measurements to understand androgen biochemistry in these cells better.

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EP1298

JOINT2083

Reproductive hormones in 46, XY differences/disorders of sex development and healthy populations

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Background
Reproductive hormones evaluation plays a critical role in diagnosing 46 XY Differences/Disorders of Sex Development (DSD). However, there is limited data on hormonal levels in both prepubertal and pubertal stages, particularly when compared to healthy cohorts.
Objective
The aim of this study was to investigate the differences in hormonal levels between 46 XY DSD patients and healthy controls during prepuberty and puberty, specifically focusing on luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), estradiol (E2), anti-müllerian hormone (AMH), and inhibin B (INHB).
Methods
In this retrospective, semi-longitudinal study, serum samples were collected from two cohorts: 46 XY DSD patients (i) 201 with steroid 5α-reductase deficiency (5aRD), (ii) 120 with Androgen Insensitivity Syndrome (AIS), (iii) 95 with NR5A1 mutations, and 52 healthy male controls. Hormonal measurements of LH, FSH, T, E2, AMH, and INHB were performed using chemiluminescent immunoassays (Immulite 2000, Siemens Healthcare, Sudbury, UK).
Results
Compared to age-matched healthy controls, patients with 5aRD exhibited significantly elevated LH and FSH levels between 1 and 9 years of age, higher LH and INHB levels from 9 to 11 years, and a notable increase in T levels. Between 11 and 13 years, 5aRD patients had higher levels of LH, T, E2, AMH, and INHB, with elevated LH, T, and E2 levels observed in those older than 13 years. AIS patients demonstrated increased levels of LH, T, and E2 between 1 and 9 years, higher T and INHB levels between 9 and 11 years, and elevated LH, T, and E2 levels in those aged over 11 years. *NR5A1* mutation patients showed higher levels of LH, FSH, and T, along with lower AMH levels between 1 and 11 years. After 11 years, these patients exhibited elevated LH, FSH, and E2 levels, with decreased AMH and INHB levels.
Conclusions
Distinct hormonal secretion patterns were observed in all three 46 XY DSD conditions compared to healthy controls. The 5aRD patients exhibited signs of earlier pubertal development, characterized by elevated LH, INHB, and a rising trend in T levels between 9 and 11 years. The AIS cohort demonstrated features of androgen resistance in their hormonal profiles. In patients with *NR5A1* mutations, early pubertal development was noted between 1 and 11 years, but the absence of a significant increase in T levels, alongside decreased AMH and INHB levels after 11 years, suggests the onset of gonadal dysfunction.

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EP1299

JOINT2996

Evaluating the FIB-4 score as a screening tool for NAFLD in PCOS: a cross-sectional study

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Patients with polycystic ovary syndrome (PCOS) have an increased risk of non-alcoholic fatty liver disease (NAFLD), which often results in more severe hepatic steatosis and liver fibrosis. The prevalence of NAFLD in PCOS patients ranges from 34% to 70%, and the possible mechanisms behind this association involve

insulin resistance, inflammation, and hyperandrogenism. This study aimed to analyze the FIB-4 score, a widely recognized tool for assessing NAFLD risk, in a cohort of women with PCOS.
Methods
PCOS was diagnosed according to the ESHRE/ASRM criteria, and patients were classified into four phenotypes: PCOS-A (anovulation, hyperandrogenism, polycystic ovary morphology), PCOS-B (anovulation, hyperandrogenism), PCOS-C (hyperandrogenism, polycystic ovary morphology), and PCOS-D (anovulation, polycystic ovary morphology). FIB-4 score was calculated to assess NAFLD risk, with a cut-off value of >1.3 used to suggest advanced fibrosis.
Results
A total of 168 women with PCOS were included in the study, with a mean age of 26.1 ± 6.4 years and a mean BMI of 24.5 ± 5.8 kg/m^2. The most prevalent phenotypes were PCOS-A (40.7%), followed by PCOS-D (22.6%), PCOS-C (23.2%), and PCOS-B (13.6%). The mean HOMA score was 3.3 ± 1.86, and 58.8% of patients had confirmed hyperandrogenism. The median FIB-4 score was 0.397 ± 0.152, and no participants had a FIB-4 score above 1.3. Statistically significant differences were observed only between phenotypes A and C ($P < 0.05$). Significant correlations were found between FIB-4 and SHBG ($\rho = 0.335$, $P < 0.001$), free androgen index (FAI) ($\rho = -0.257$, $P < 0.001$), triglycerides ($\rho = 0.199$, $P < 0.05$) and androstendione ($\rho = -0.259$, $P < 0.001$). In multiple regression analysis, SHBG ($B = 0.001$, $Beta = 0.184$, $P < 0.05$) and androstendione ($B = 0.002$, $Beta = 0.277$, $P < 0.05$) showed small but significant associations with FIB-4, whereas FAI and triglycerides did not appear to be significant predictors.
Conclusion
The study suggests that the FIB-4 score may not be an effective screening tool for NAFLD in younger women with PCOS, as none of the participants had a FIB-4 score above 1.3. Although SHBG and androstendione showed small but statistically significant correlations with FIB-4, further research is needed for better understanding the role of metabolic factors in NAFLD risk in PCOS.

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EP1300

JOINT967

Evolution in the health-care demand at the transgender care unit of malaga after 25 years of experience

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Introduction
The first unit for transgender health-care within the Spanish public health system was created in 1999 in Andalusia. The Transgender Care Unit (TCU) of Malaga is functionally dependent on the Endocrinology and Nutrition service and is composed of a multidisciplinary team, including specialists in Endocrinology, Clinical Psychology, Plastic Surgery, Gynecology, Urology, Otorhinolaryngology, and Phoniatrics.
Objective
To compare the sociodemographic profile of transgender people undergoing endocrinological follow-up at the TCU of Malaga during the period from 1999 to 2024.
Methodology
Descriptive, retrospective, and cross-sectional study that include transgender people under endocrinological follow-up at the TCU of Malaga from 1999-2024. The inicial assessment is performed by Endocrinology for individuals over 14 years of age, with psychological evaluations being voluntary in accordance with current legislation. The collected data included the number of consultations (initial and follow-up) in the last two years, the mean age $\pm$ standard deviation at the first consultation, the ratio of transgender women/transgender men (MTF/FTM), the frequency of psychopathology, and the psychological support received.
Results
The number of consultations has increased exponentially, reaching 1,609 and 1,794 consultations per year in 2023 and 2024, respectively. First consultations accounted for 18% of visits, while the remaining 82% were follow-ups. The average age of individuals attending for the first time has decreased, from 28.5 years in the first decade to a range of 22.2–23.9 years in 2023–2024. The proportion of individuals under 18 years old increased from 8.2% in the first decade to 30% in the second decade, reaching 40% in 2024. A reversal in the biological sex ratio of individuals seeking transition was also observed. The MTF/FTM ratio initially stood at 2.45 but gradually decreased to a ratio of 0.66 in 2024, with 39.5% identifying as MTF and 60.5% as FTM. It is noteworthy that a high percentage of individuals presented psychopathology (43–50%). The most common conditions were anxiety-depression disorder, attention deficit hyperactivity disorder, and autism spectrum disorder. The rate of suicidal ideation and/or attempts was 22%. The majority of people (50.6% to 80.8% in 2023–2024) accepted receiving psychological support at the onset of their medical transition.
Conclusion
The high demand for health-care by transgender people, combined with the significant proportion of minors with psychopathology, highlights the complexity of assessing the gender identity. It is essential to provide transgender care in specialized multidisciplinary teams.

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EP1301

JOINT3372

The impact of gender dysphoria diagnosis on parents of transgender youth: the role of heteronormativity and mentalization

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Purpose
The diagnosis of gender dysphoria (GD) can be a traumatic experience for parents of transgender youth. The aim of this cross-sectional study was to examine the role of heteronormative beliefs and attitudes on the traumatic impact of GD diagnosis in mothers and fathers of transgender youth, as well as the mediating role of mentalization, i.e. the ability to psychologically understand one's own and others' behaviors and emotions.
Methods
A total of 75 couples of mothers and fathers ($N = 150$) of adolescents who received a GD diagnosis answered questions about heteronormativity, mentalization, and the traumatic impact of diagnosis. Mean age of adolescents at diagnosis of GD was 16.3 ± 1.0 years, 49 were assigned male at birth (AMAB) and 26 were assigned female at birth (AFAB) Heteronormativity was assessed using the Italian version of the Heteronormative Attitudes and Beliefs Scale Mentalization was measured using the Italian version of the Reflective Functioning Questionnaire. The traumatic impact of the GD diagnosis was assessed using the Italian version of the Impact of Event Scale-Revised.
Results
Results showed that heteronormative attitudes were significantly higher in fathers than in mothers. Moreover, heteronormative beliefs were positively associated with greater traumatic impact of GD diagnosis only in fathers, whereas heteronormative attitudes were associated with greater traumatic impact of GD diagnosis in both mothers and fathers. Finally, an impaired mentalizing functioning mediated the relationship between heteronormative attitudes (but not beliefs) and the traumatic impact of a child's GD diagnosis only in fathers, but not in mothers.
Conclusion
When transgender youth enter the health care system because of their gender incongruence, their entire family must be supported to create an accepting and affirming environment in which gender-related stress and negative emotions can be effectively processed. ubmitted.

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EP1302

JOINT3987

Mental health assessment in women with PCOS: evaluating anxiety and depression using GAD-7 and PHQ-9

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Introduction
Polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disorder, affecting 6–10% of women of reproductive age worldwide. It is defined by clinical and/or biochemical features, including hyperandrogenism (HA), ovulatory dysfunction (OD), and polycystic ovarian morphology (PCOM), with patients classified into four distinct phenotypes. Despite the physical symptoms, PCOS is also associated with psychological challenges. The aim of this study is to evaluate the mental health of women with PCOS using the Generalized Anxiety Disorder 7-item scale (GAD-7) and the Patient Health Questionnaire-9 (PHQ-9), focusing on anxiety and depression.
Subjects and methods
We analyzed 111 female patients, divided into two groups: PCOS ($n = 70$, age: 26.14 ± 6.734 years) and the control group ($n = 41$, age: 26.98 ± 6.912 years), matched by age. We assessed anthropometric parameters (BMI and waist circumference), androgen levels (total testosterone, SHBG, FAI) and mental health questionnaires (GAD-7 and PHQ-9). The analysis was performed using SPSS software.
Results
The two groups showed differences in BMI values (PCOS:Controls: 25.581 ± 5.742 vs. 23.007 ± 4.411) and waist circumference (PCOS:Controls: 81.53 ± 14.417cm vs. 76.17 ± 10.998cm). A clear difference was observed in androgen levels, which were notably higher in patients with PCOS ($P < 0.01$). No significant differences were found in the results of the GAD-7 and PHQ-9 questionnaires between the groups ($P > 0.05$). There was no significant correlation between the mental health questionnaires (GAD-7 and PHQ-9) and BMI, waist circumference, or androgen levels in either group ($P > 0.05$). Furthermore, no correlation was found between these parameters within the PCOS group.
Conclusion
The results of this study did not reveal a significant correlation between mental health assessments (GAD-7 and PHQ-9) and anthropometric parameters or androgen levels in either group. This suggests that, although physical differences are evident in patients with PCOS, psychological factors such as anxiety and depression may not be directly linked to these specific body indicators. These findings highlight the complexity of the relationship between PCOS and mental health, suggesting that further research is required to explore potential underlying factors.

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EP1303

JOINT3491

Leptin levels may not have a role in the development of pubertal gynecomastia

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Introduction
Leptin(L) is a signal from adipose tissue in the regulation of energy metabolism. Except of this other peripheral tissues contribute to its level and are being influenced through L receptors. Such have been found in the anterior lobe of the pituitary, gonads and in mammary epithelial cells. There is characteristic sexual dimorphism in L in both lean or obese individuals. Men have lower serum levels than women and this difference is found from puberty. L has a complex and bidirectional interplay with sex steroids. It has the ability to increase the activity of CYP19 aromatase thereby leading to increased estrogen (E) and in turn estrogens increase mRNA synthesis and L level. In addition, an inverse correlation with androgens has been reported and further in high-grade obesity high L has a suppressive effect on testosterone(T). On the basis of these data it could be speculated that L is part of the control of breast parenchymal proliferation and with other factors, could be involved in the development of pubertal gynecomastia (PG).
Aim
To investigate L in adolescents with PG at different stages of pubertal development with normal weight or obese and to compare it with L in a control group at the same age and BMI. To find a correlation between L and levels of sex steroids.
Methods
A total of 50 boys with PG, admitted to tertiary Pediatric endocrinology department in a single university hospital were included. They were divided into three groups according to pubertal stage: Tanner stage 2, mid pubertal stages 3-4 and a group with completed puberty. Anthropometric measurements, leptin and hormonal investigations were collected and compared with a group of 64 controls without PG matched in pubertal stage and anthropometrics.
Results
The investigation of leptin level in the three groups, matched for BMI and pubertal stage, did not prove statistically significant difference. Correlation was sought between L and sex hormones, free and biologically activeT, as well as the ratio of T and E2. Correlations were not found in all three groups of PG patients with normal weight or obese. A correlation was found in adolescents 3-4 Tanner stage in the control group with normal BMI: a strong positive between L and SHBG($r = 0{,}915$, $P < 0{,}01$) and correspondingly a strong negative correlation between L and freeT($r = -0{,}730$, $P < 0{,}05$), bioavailable T($r = -0{,}734$, $P < 0{,}05$), FAI($r = -0{,}914$, $P < 0{,}01$).
Conclusion
The presented study did not prove the role of L on development of PG, but confirmed its role on androgen levels in boys without PG.

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EP1304

JOINT1708

Long term pubertal outcome of patients with prenatal diagnosis of ovarian cysts

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Prenatal ovarian cysts (POC) require close postnatal follow-up and sometimes surgery in case of complications. Long-term outcome and pubertal development have not been reported in these patients and would be useful to rationalize treatment, follow-up and parental counselling. This study aims to compare pubertal development and plasmatic AMH level of patients with POC compared to healthy controls. This prospective case-control study included patients with diagnosis of POC and healthy controls without endocrine disease. Each child underwent a clinical evaluation of pubertal development (Tanner stages, age of onset), a dosage of plasmatic AMH, LH and FSH. Early puberty was defined as thelarche before 9y and late as after 13y. 105 children were included (56 cases). Mean age was 13.8 yearsd. Mean ages of thelarche (10.85 vs 11.04, $P = 0.630$), pubarche (10.96 vs 11.03, $P = 0.860$) and menarche (12.4 vs 12.23, $P = 0.845$) were not different between cases and controls. Neither early (4 vs 2, $P = 0.643$) nor late (2 vs 7, $P = 0.080$) puberty was more frequent in case of POC. Plasmatic AMH was comparable between cases and controls (36.75 vs 39.90, $P = 0.742$), FSH and LH concentrations were not increased in cases (FSH:4.43 vs 3.87, $P = 0.31$; LH: 4.05 vs 3.37, $P = 0.38$), even in ovariectomy group (FSH:4.7 vs 3.94, $P = 0.23$; LH:4.17 vs 3.45, $P = 0.22$). Patients with POC develop a normal puberty and have levels of plasmatic AMH and gonadotropic hormones similar to controls. These data are reassuring for the pubertal outcome of these patients and that may alleviate their follow-up, at least for those without ovariectomy.

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EP1305

JOINT3641

The impact of thyroid autoimmunity on clinical outcomes in euthyroid women undergoing ART: a systematic review

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Introduction
Data on whether thyroid autoimmunity negatively affects assisted reproduction outcomes in euthyroid women are conflicting: Some meta-analyses suggest antithyroid autoantibodies (ATA) negatively impact ART outcomes, while others find no effect. A closer look shows that TSH levels and the degree of ATA elevation are key factors to consider. Another crucial element is the better ART outcomes in ATA(+) women with ICSI compared to IVF. The rise of ICSI and evolving definitions of SCH may explain the trend of reduced impact of ATA in recent studies, as well as the contradictions with older studies. These opposing data have prompted us to formulate the following research question: In euthyroid women of infertile couples undergoing ART, does the presence of ATA lead to fewer pregnancies, more miscarriages, and ultimately fewer live births?.
Material and Methods
Following PRISMA guidelines, we searched PubMed, Embase, and Cochrane databases from January 2006 to April 2024 for observational studies comparing the impact of ATA on clinical outcomes in euthyroid ATA(+) vs. ATA(-) women undergoing ART, using strict inclusion and exclusion criteria. Possible confounding parameters were extracted from each study, and quality was assessed with the NOS scale. Due to variability among studies, a qualitative synthesis was employed. Desired outcomes were clearly defined, and the calculation method (based on participants, pregnancies, or total ART cycles) was carefully evaluated.
Main Results
35 studies were eligible for inclusion. Of 14 studies on the biochemical pregnancy rate, 3 found significant differences. For clinical pregnancy rate, 4 of 29 studies showed lower CPR in ATA(+) women. 1 of 6 studies on ongoing pregnancy rate found a decrease in ATA(+) women. In delivery rate, 1 of 4 studies reported a lower rate. 7 of 28 studies on miscarriage rate indicated higher MR in ATA(+) women. The live birth rate was lower in 2 of 15 studies. None of the 3 studies on cumulative live birth rate showed adverse effects. To improve comparability, studies with similar features were grouped. Emphasis was placed on studies examining cumulative live birth rate, first IVF attempt, and large sample size.
Conclusion
Most studies found no negative impact of ATA on IVF outcomes. Although some data suggest otherwise, particularly for MR, studies with larger sample sizes or those focusing on the first IVF attempt show no adverse effect of ATA. Similarly, ATA positivity does not appear to affect CLBR.

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EP1306

JOINT2666

Spironolactone repurposing in the management of benign premature adrenarche with facial acne

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Background
Premature adrenarche (PA) is common among 5-9 years old children, mainly females. The outcome is usually benign in the absence of a definable cause for androgen excess, but some patients seek management for their symptoms of hyperandrogenism, body odor, axillary or pubic hair but some experience significant distress and seek for treatment for facial acne. Management of hyperandrogenism (including acne) among pubertal and adult females includes "off label" use of spironolactone, a steroidal aldosterone antagonist. licenced for use as a diuretic but has also an anti-androgenic effect in higher doses. As such, it has been used for treatment of prepubertal acne associated with benign PA at the Royal Children Hospital, Melbourne.
Aim
To characterize those patients who received spironolactone compared to a similar population who received standard of care dermatological preparations only, or no treatment at all, and to assess their growth, puberty, short and long term outcome parameters and safety.
Methods
A retrospective case-control study included all patients diagnosed with benign PA between 2000 and 2024. Case/control ratio was 1:2. Data included clinical, growth and laboratory assessments.
Results
Study population included 8 females who were treated with spironolactone, median age 8.3 years (range 7.5,11.7), and 16 female who were not treated with spironolactone, median age 6 years (range 4.2,9.2). The spironolacton group was significantly older at presentation, $P < 0.001$. Spironolactone doses ranged from 25 to 100 mg/day, with most patients stabilizing at 50 mg/day. 75% of those treated experienced initial improvement in acne severity. However, 62.5% required additional therapies as additional topical creams, retinoic acid, oral antibiotics and oral contraceptive pill at follow-up visits, suggesting partial long-term efficacy. Minor adverse events occurred in 25% of treated patients but resolved without discontinuation. No significant electrolyte abnormalities or renal dysfunction were reported. Both groups initiated central puberty at comparable ages (mean 9.2 vs. 9.3 years), indicating that spironolactone did not delay puberty onset. Final heights aligned with mid-parental targets in both cohorts, alleviating concerns about growth suppression. The study noted that most patients stabilized at lower doses (1–1.5 mg/kg) compared to adult acne regimens (2.5 -3mg/kg), potentially balancing efficacy and safety in children.
Conclusions
spironolactone offers a viable option for benign PA-associated acne. Our findings support cautious off-label adoption, while advocating rigorous longitudinal monitoring and further prospective trials to solidify a role for spironolactone in pediatric acne management.

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EP1307

JOINT3664

Efficacy of preoperative hormonal treatment in severe cases of hypospadias: a case-control study

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Background
Severe proximal hypospadias repair remains a surgical challenge due to the elevated risk of complications. Success rates vary according to the severity of the malformation, with glans width (GW) < 14 mm recognised as an independent risk factor for poor outcomes. Preoperative hormonal treatment (PHT) has been proposed to enhance penile size and improve tissue quality prior to surgery, although its efficacy and the optimal regimen of administration remain controversial. This case-control study evaluates the efficacy of a tailored PHT regimen in patients with severe hypospadias and compares surgical outcomes between patients who received PHT and those who did not.
Methods
A retrospective study of the medical records of patients with proximal (PXH) or midshaft (MSH) hypospadias who underwent surgical repair in the same centre between August 2001 and May 2024. Since June 2020 patients with GW < 14 mm and/or significant ventral curvature (> 30°) at preoperative assessment received PHT as daily treatment with 2% transdermal testosterone gel(2 mg/day) for 30–60 days, except for one patient who received topical androstanolone 2.5% due to 5alpha-reductase deficiency. Hormonal treatment was discontinued at least 1 month prior to surgery(mean 55 ± 23 days). Penile length(PL), GW, and adverse effects were recorded pre- and post-treatment by the same Paediatric Endocrinologist. Surgical outcomes and short-term postoperative complications were assessed by the same surgeon.
Results
A total of 42 patients were included: 14 received PHT (5 MSH, 9 PXH) and 28 no-PHT (10 MSH, 18 PXH). Mean age at surgery was 2.68 ± 1.75 and 2.09 ± 1.13 years, respectively (p:0.38). In the PHT group no adverse effects due to the hormonal treatment were reported. A mean increase of 45 ± 27mm(+50%) for GW and of 80 ± 42mm(+41%) for PL were measured, with a relevant Cohen's effect size for both parameters(d = 0.75 and d = 1.10, respectively). The overall complication rate (CR) between the two groups was 66% in PHT (urethrocutaneous fistula 78%, glandular dehiscence 22%) and 71% in no-PHT (urethrocutaneous fistula 75%, glandular dehiscence 15%, urethral stenosis 15%) (p:0.4), over a mean follow-up period of 31 ± 15 months. For MSX cases, CR was 20% for PHT while 50% for no-PHT.
Conclusions
PHT was found to be a non-invasive, well-accepted, and effective treatment for enhancing penile size prior to surgical repair of severe hypospadias. Although a direct

impact on complication rates could not be established for PXH, due to the reduced sample size, the improvement in MSX cases is significant.

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EP1309

JOINT1995

Evaluation of cardiovascular risks in people with gender dysphoria who received gender-affirmig hormone therapy

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Objective

Cardiovascular diseases are proven to be the most common cause of death in the world. A number of scoring systems have been proposed to predict this risk. The prevalence of cardiovascular disease in individuals with gender dysphoria (GD) has been investigated in many small-group studies. In this study, we aimed to assess the cardiovascular risk scores of female-to-male (FtM) GD receiving gender-affirming hormone therapy (GAHT).

Materials and Methods

This was a cross-sectional study. Individuals with GD who received GAHT for at least 1 year were included in the study. A total of 43 FtM GD who consequtively applied were included. In addition, healthy cis-men ($n = 15$) and cis-women ($n = 15$) with the same body mass index and age were included in the study. Sociodemographic data, smoking status, glucose, lipid profiles, total testosterone levels of those who received GAHT for at least 1 year were measured. The atherogenic index of plasma (AIP), atherogenic coifficent (AC) and visceral adiposity index (VAI) were calculated for each participant.

Results

The mean age of FtM GD was 29.1 $\pm$ 5.7, the mean age of cis-women was 25.7 $\pm$ 3 years and the mean age of cis-men was 25 $\pm$ 0.8 years. In the present study, the neck circumference of cis men was significantly higher than that of cis-women and FtM GD ($P = 0.005$; $P = 0.002$, respectively). In addition, the neck circumference of FtM GD was statistically higher than that of cis-women ($P < 0.001$). While there was no statistical difference between FtM GD and cis-men in terms of waist-to-hip ratio ($P > 0.05$), the waist-to-hip ratio was significantly increased in FtM GD compared to cis- women ($P < 0.001$). When comparing the waist-to-height ratio, the waist-to-height ratio was statistically significantly increased in FtM GD compared to cis-women ($P < 0.001$). FtM GD had a statistically significantly higher TG/HDL ratio than cis-women ($P = 0.006$). When comparing the groups in terms of AC, there was no statistically significant difference between cis-women and cis-men, and between cismen and FtM GD ($P > 0.05$ for all). AC was statistically significantly increased in FtM GD compared to cis- women ($P = 0.007$).

Conclusion

This study suggests that FtM GD who received GAHT may have an increased cardiovascular risk compared to cis women. Our findings emphasize the importance of routine cardiometabolic risk assessment in FtM GD who have undergone GAHT.

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EP1310

JOINT1124

Safety of puberty blockers and testosterone therapy for cardiovascular health in adolescents with gender dysphoria

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Puberty blockers (GnRH analogues) are used to delay pubertal progression in adolescents with gender dysphoria, alleviating distress associated with undesired physical changes. However, concerns about their long-term safety, efficacy, and potential irreversible effects have led to their use being halted for adolescents in the UK, except within the context of approved clinical trials. This study evaluates cardiovascular safety in adolescents on GnRH analogues, with a focus on mean blood pressure measurements obtained through ambulatory blood pressure monitoring (ABPM). Thirteen adolescents (birth-assigned: 6 males, 7 females), including 3 trans men on testosterone therapy, were assessed. Clinic systolic blood pressure (SBP) and 24-hour ABPM were measured. Analyses included comparisons between smokers and non-smokers, correlations between SBP/ABPM and BMI, and differences between trans men with and without testosterone therapy. One patient did not tolerate ABPM, and analyses were conducted for the remaining participants. Clinic SBP and 24-hour ABPM measurements were comparable between birth-assigned males and females (Clinic - Male: 124.8$\pm$1.90 mmHg *vs* Female: 125.6$\pm$2.50 mmHg; ABPM - Male: 86.22$\pm$2.54 mmHg *vs* Female: 84.63$\pm$1.47 mmHg). Smoking status (tobacco and vape) did not affect clinic SBP or 24-hour ABPM measurements (Clinic - Non-smokers: 123.12$\pm$1.52 mmHg *vs* Smokers: 129.50$\pm$3.03 mmHg; ABPM - Non-smokers: 83.57$\pm$1.66 mmHg *vs* Smokers: 88.72$\pm$1.32 mmHg). ABPM measurements showed minimal association with BMI ($R^2 = 0.31$, $P = 0.06$). Those assigned female at birth with and without testosterone therapy had similar ABPM results, including awake and asleep periods (Testosterone naive: 85.51$\pm$2.20 mmHg *vs* Testosterone: 83.46$\pm$1.54 mmHg). A nocturnal dip > 10% was observed in both those birth-assigned male and female. These findings suggest that puberty blockers and, in some cases, testosterone therapy, are safe regarding cardiovascular function in adolescents with gender dysphoria. This study offers valuable evidence supporting the cardiovascular safety of these treatments in this population and underscores the importance of further longitudinal research in larger cohorts to strengthen these conclusions.

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EP1311

JOINT2211

Circulating adipokine concentrations aid in distinguishing functional hypothalamic amenorrhoea and polycystic ovary syndrome in women presenting with oligo/amenorrhoea

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Introduction

Adipokines, such as leptin and adiponectin, are secreted from adipose tissue and signal to the hypothalamus to indicate sufficient energy availability, which is requisite for reproductive health. Leptin is a permissive signal for hypothalamic GnRH function. Functional hypothalamic amenorrhoea (FHA) is caused by insufficient energy availability and is a low leptin state. Indeed, leptin administration restores pulsatile LH secretion in FHA. Conversely, adiponectin levels decrease with bodyweight, especially central obesity with associated insulin resistance. Polycystic ovary syndrome (PCOS) is strongly associated with insulin resistance and central adiposity. Herein, we directly compare circulating leptin and adiponectin concentrations in women presenting with oligo/amenorrhoea due to either FHA or PCOS.

Methods

Women aged 18-35yrs were classified as Healthy ($n = 47$), FHA ($n = 44$), or PCOS ($n = 73$; stratified by BMI as lean [BMI: $<25 kg/m^2$; $n = 33$], overweight [BMI:25-30kg/m^2; $n = 15$] or obese [BMI: $>30 kg/m^2$; $n = 25$]). Serum adiponectin and leptin were measured by DELFIA assay. Insulin and glucose were collected following an 8-hour overnight fast. Reproductive hormones were collected during the follicular phase, or following a progesterone-induced bleed in PCOS. Groups were compared by Kruskal-Wallis and associations assessed by linear regression.

Results

Leptin was positively related to BMI in all groups, whereas adiponectin was negatively related to BMI only in Healthy and PCOS groups. Despite similar BMI (Healthy 21.2, FHA 20.4, Lean PCOS 21.1kg/m^2), women with FHA had lower leptin and higher adiponectin levels. Median (IQR) leptin (ng/ml) was: Healthy 12.50 (5.80-18.25), FHA 5.20 (3.05-8.78), Lean PCOS 8.90 (6.40-17.10) ($P < 0.0001$); and adiponectin (mg/ml) was: Healthy 9.90 (7.80-13.30), FHA 14.05 (10.98-17.10), Lean PCOS 9.20 (7.10-10.90) ($P < 0.0001$). Women with FHA were more insulin sensitive than Healthy and Lean PCOS groups (HOMA-IR 0.63 vs 1.05 and 0.94 respectively, $P = 0.002$). Adiponectin was inversely associated with HOMA-IR in Healthy ($r = -0.06$; $r^2 = 0.25$, $P = 0.002$) and PCOS ($r = -0.14$; $r^2 = 0.18$, $P = 0.0004$), but this relationship was reversed in FHA ($r = +0.04$;

$r^2=0.18$, $P = 0.013$). Adiponectin was inversely associated with free androgen index (FAI) (r=-0.32; $r^2=0.11$, $P = 0.005$), whereas leptin was positively associated with FAI (r=+0.06; $r^2=0.22$, $P < 0.0001$) in PCOS. Adiponectin was positively associated with LH in PCOS (r=+0.26; $r^2=0.14$, $P = 0.001$), but not in FHA. Leptin was positively associated with LH (r=+0.09; $r^2=0.14$, $P = 0.014$) and oestradiol in FHA (r=+1.27; $r^2=0.14$, $P = 0.012$), but negatively associated with LH in PCOS (r=-0.03; $r^2=0.10$, $P = 0.007$).

Conclusion

These data highlight the divergent interaction between adipokines and reproductive/metabolic markers in women with FHA and PCOS, providing novel insights into the value of adipokines in the assessment of women with oligo/amenorrhoea.

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EP1312

JOINT3348

Pharmaceutical disruption of steroidogenesis

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Concern has been raised over negative endocrine side-effects of synthetic chemicals, as active pharmaceutical ingredients (APIs), on the health of humans. While studies have investigated side-effects of APIs in humans and animals, these employed different analytical methods, measured different endpoints, investigated only one or few APIs together and often overlooked their direct effect on hormonal production. This makes it difficult to assess the scale of the problem that APIs might have on endocrinology. Additionally, comparing existing data from different studies is often challenging due to differences in analytical methodologies, such as hormone quantification techniques or the use of different model systems. Here, we present findings from a comprehensive investigation on the effects of APIs on human steroidogenesis, the quintessential hormonal pathway at the center of endocrinology. We examined the effects of 70 APIs, representing all major pharmaceutical classes used worldwide, on 16 hormones involved in steroidogenesis at physiological relevant concentrations. Our analysis identified five distinct clusters of APIs based on their effects on steroidogenesis, with only 17 APIs showing no impact. The initial enzyme in steroidogenesis, CYP11A1, was identified as the most concerning target due to its promiscuity in binding lipophilic and nitrogen-rich compounds, including prevalent pharmaceutical classes such as fungicides, antidepressants, antibiotics, and lipid-lowering statins. As pharmaceutical use continues to rise and environmental pollution with APIs becomes more pervasive, these findings show that APIs might pose a significant threat to humans through the disruption of steroidogenesis at physiological relevant doses.

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EP1313

JOINT1306

The role of autocrine androgen signalling for leydig cell function

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Introduction

Patients with CAIS have a genetic defect in the androgen receptor, resulting in an external female genitalia with the presence of intra-abdominal testicles. While these testes do not exhibit functional spermatogenesis, they seem to serve as an important source of steroid hormones that also induce puberty. However, it remains unclear in how far the defective AR-mediated signalling impacts Leydig cell steroidogenic activity and function.

Research Aim

Here we aim to characterize the production of steroid hormones in a Leydig cell line and the responsiveness to different stimuli to establish a robust model system to test possible autocrine mechanisms.

Material and Methods

The MLTC-1 cell line was stimulated with progesterone, 8-Br-cAMP, hCG, LH, and a combination of LH and hCG or inhibited with ketoconazole. Moreover, the cells were transfected with plasmids encoding a dominant negative androgen receptor as well as enzymes affecting steroid production. Supernatants were collected at 4 and 24 hours post-stimulation, and androgen concentrations were quantified using liquid chromatography–mass spectrometry (LC-MS). Additionally, RNA and protein expression of steroidogenic enzymes were analysed 24 hours after stimulation.

Results

Stimulation of MLTC-1 cells generally resulted in a significant increase in androgen concentrations at the 4-hour time compared to 24 hours, suggesting that the initial stimulatory effect diminishes over time. Stimulation with LH exhibited the most pronounced effect, increasing androgen concentrations in the supernatant 50-fold compared to untreated control cells. In contrast, progesterone and 8-Br-cAMP did not induce a significant increase in androgen production. The inhibitor ketoconazole, however, effectively reduced androgen concentrations at 1 μM and 10 μM without compromising cell viability, whereas 100 μM negatively impacting cell growth. Transfection with plasmids expressing a dominant negative androgen receptor or enzymes modulating steroid hormone production demonstrated that the steroid profile could be successfully modulated in these cells.

Conclusion and Outlook

Our findings demonstrate that MLTC-1 cells can be used as a robust Leydig cell model for steroidogenesis, as evidenced by their responsiveness to LH. Moreover, transfecting these cells as a first step towards a gene therapy to modulate steroid production in CAIS patients is generally feasible.

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EP1314

JOINT2305

Fertility information needs in adult survivors of childhood cancer - first results of the FeProCAYA study

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Background

Endocrine late effects impacting reproductive function are a major concern for childhood cancer survivors. Despite increasing research, significant knowledge gaps persist regarding thresholds and risk factors for hypogonadism, genetic predispositions, fertility preservation efficacy, and the role of communication and decision-support tools.

Methods

FeProCAYA, a cohort study within the FePro-Ulm research center at the University Medical Center Ulm (funded by the Federal Ministry of Education and Research, BMBF), examines fertility risks in individuals treated for childhood and adolescent conditions associated with impaired adult fertility. This analysis assessed endocrine late effects, fertility-related quality of life (WHOQOL-BREF), and reproductive concerns (RCAC) in long-term childhood cancer survivors ($\geq$20 years post-diagnosis) via an online questionnaire.

Results

From clinical records, 225 eligible survivors (diagnosed $<$18 years) who received potentially gonadotoxic treatment at the University Medical Center Ulm between 1999 and 2004 were identified. Of these, 169 with valid postal addresses were invited to participate, and 51 (30 female; response rate 30.2%) completed the survey. The median age was 28.0 years (range 20–40), with a median follow-up of 23.0 years (range 20–26). Endocrine conditions were self-reported by 60.8% ($n = 31$), most commonly hypothyroidism ($n = 15$), osteoporosis/repeated fractures ($n = 12$), sex hormone replacement ($n = 6$), and growth hormone deficiency ($n = 4$). A BMI $\geq$25 kg/m^2 was reported by 41.2% ($n = 21$). While 21.6% ($n = 11$) had children, 66.7% ($n = 34$) expressed significant fertility concerns, and 62.8% ($n = 32$) reported unmet information needs regarding fertility after cancer. Notably, only 49% ($n = 25$) recalled receiving fertility counseling before treatment or during follow-up care.

Conclusions

Structured and repeated reproductive health counseling during long-term follow-up may help address unmet information needs and improve fertility-related quality of life in childhood cancer survivors, a population already facing a high disease burden.

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EP1315

JOINT1361

Effect of FSH therapy on semen parameters in male idiopathic infertility: a real-life experience

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Introduction
Infertility is the inability to conceive following one year of unprotected intercourse. About 30% of cases are related to male factors alone, and in 30% of these no specific cause for subnormal semen parameters can be found. However, a meticulous diagnostic process is essential before diagnosing the patient as having idiopathic infertility. The use of FSH treatment has been suggested in idiopathic infertile men with FSH plasma levels < 8 IU/lto increase sperm quantity and quality and pregnancy rate.
Methods
Twenty-three males with idiopathic infertility were assessed. Data on specific causes of infertility and genetic, environmental and lifestyle risk factors for infertility were investigated, along with basal hormonal and semen parameters. Patients with FSH plasma levels < 8 IU/l,oligo/asthenozoospermia and no seminal tract obstruction were treated with FSH. New semen analyses were assessed three and six months after treatment in 18 and 6 patients, respectively.
Results
Mean age of the 23 enrolled patients was 37.4 ± 4.8 years. We evaluated risk factors for infertility and found that 5 patients (21.7%) were current smokers, 10 (43.5%) had BMI ≥ 24.9 kg/m^2, 4 (17.4%) had either impaired fasting glucose or diabetes. 12 patients (52.2%) had sonographic evidence of varicocele (10 $\leq$ II grade, 2 III grade), furthermore 4 underwent surgical correction. Median testosterone levels were 4.62 ng/ml (IQR 4.0-5.8). Baseline semen analysis showed that 20 patients (86.9%) had oligozoospermia [median spermatozoa concentration: 4.6×10^6/ml (IQR 1.2-13); median total number: 16.2×10^6 (IQR 5.1-32.7)]; 21 (91.3%) had asthenozoospermia [median total motility: 26% (IQR 12-37)]; 22 (95.6%) ha teratozoospermia. Patients were treated with FSH 150 UI 3 times per week. After 3 months of treatment there was no statistically significant improvement in semen parameters. Six patients were evaluated after 6 months of treatment and showed an improvement in semen parameters, although not significant probably due to the small sample size [median spermatozoa concentration: 8.1×10^6/ml (IQR 1.9 – 14.9)($P = 0.46$); median total number: 24.6×10^6 (IQR 6.5-47.5)($P = 0.46$); median total motility: 43% (IQR 30.8-60.5) ($P = 0.71$)].
Conclusion
The careful search for factors related to altered semen parameters could reduce the number of men diagnosed as having idiopathic infertility, allowing better management in the clinical practice. Our data, even though on a limited number of patients, seem to suggest that prescribing FSH therapy for more than 3 months could lead to an improvement in semen parameters. Further studies on larger series are needed.

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EP1316

JOINT3547

Impact of thyroid autoantibodies on ovarian reserve and embryo quality in euthyroid women undergoing assisted reproductive technology

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Introduction
The impact of thyroid autoimmunity on female fertility and assisted reproductive technology (ART) outcome is still controversial.
Aim
The aim of this study was to evaluate the impact of thyroid autoantibodies (TAA) on ovarian reserve, ovarian response and oocyte quality in euthyroid infertile patients undergoing ART.
Material and Method
Retrospective study on 294 women undergoing ART at the University Hospital of Padua. Every patient underwent to the evaluation of FSH, LH, 17β-estradiol, TSH, free thyroxine (fT4), anti-thyroid peroxidase antibody (anti-TPO), anti-tireoglobulin antibody (anti-TG) and anti-Müllerian hormone (AMH) on the 2nd–5th day of menstrual cycle. In the same moment, pelvic sonography was performed to estimate antral follicle count (AFC). All patients underwent a standardized controlled ovulation stimulation (COS) process and the number and quality of retrieved oocytes was evaluated. Exclusion criteria: TSH >4 mUI/L; previous or concomitant medications for thyroid disease.
Results
The mean age of the patients was 37.6 years and the BMI was 23.7 kg/m^2. Three patients with TSH>4 mUI/lwere excluded. Of the 199 patients undergoing CS, 42 presented at least one thyroid autoantibody (TAA+): 22 were positive for both TAA, 6 for anti-TG only, 14 for anti-TPO only. Based on Bologna criteria, 60% were normo-responders, 19% poor-responders, and 21% high-responders. A total of 1348 oocytes was retrieved, including 285 in patients with TAA+ and 1063 in patients with negative antibodies (TAA-). Comparison of normo, poor and high-responders showed no statistically significant differences in BMI and TTA positivity. Considering the two groups TAA+ and TAA-, no statistically significant differences emerged for AMH levels, AFC, total oocyte count and rate of mature oocytes at pick-up. TSH was higher on average in the TAA+ group than in the TAA-. AMH and AFC values were significantly lower in patients with anti-TPO only compared with those with anti-TG only. In contrast, there was no evidence of a difference in the number of total and mature oocytes according to TAA positivity.
Conclusions
The presence of anti-TPO is associated with a decreased ovarian reserve, but it seems to be not correlated to a poor response in ART. Further studies are needed to better evaluate the impact of anti-TPO on female fertility and ART outcomes.

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EP1317

JOINT2958

Body proportions, hypothalamic-pituitary-gonadal function, testicular morphology and the risk for gonadal malignancy in males with 46,XX testicular DSD and 47,XXY Klinefelter syndrome

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Background
Individuals with 46,XX testicular DSD (T-DSD) and 47,XXY Klinefelter syndrome (KS) have a male phenotype, but sex chromosome aneuploidy with a supernumerary X chromosome. In contrast to KS, T-DSD males lack a major part of the Y chromosome. In both conditions, testicular dysgenesis leads to hypogonadism with infertility. While biological paternity can be achieved in a subset of KS men using assisted reproductive technology, this is impossible in men with T-DSD, where spermatogenesis cannot take place due to the absence of the Y chromosomal AZF region.
Aim of the study
To gain insight into the effects of X-linked supernumerary genes with and without additional Y-chromosomal gene deficiency on human body proportions, hypothalamic-pituitary-gonadal (HPG) axis function, testicular morphology and the risk of gonadal malignancy.
Patients and Methods
Retrospective and cross-sectional data from ($n = 50$) males with T-DSD aged 14-67 years and ($n = 91$) males with KS were evaluated, including medical history data, anthropometric and hormonal data, testicular ultrasound imaging and histological images of testicular biopsies.
Results
Men with T-DSD had a shorter stature than predicted from parental target height (TH). In contrast, final height of the KS men exceeded their TH. Both males with T-DSD and KS had significantly reduced testicular volumes and ultrasound

imaging of their testes showed reduced echogenicity of the gonadal parenchyma, with multiple hypoechogenic areas in older men. Biopsies from these areas within the testes evidenced benign Leydig cell hyperplasia. There were no cases of testicular malignancies observed in either cohort. Hypergonadotropic hypogonadism developed during adolescence in both conditions, with decompensation of testicular endocrine function occurring at different times in life. LH serum concentrations were inadequately low for serum testosterone concentrations mainly in older men with T-DSD. The vast majority of T-DSD males had Inhibin B concentrations below the detection limit at any age, in contrast, Inhibin B was measurable in some young KS males.
Conclusions
Final height in males with T-DSD and KS does not result from hypogonadism, which occurs similarly in both conditions, but rather from the absence or presence of Y chromosomal genes. In both KS and T-DSD, decompensation of endocrine testicular function occurs at variable times in the course of life, but a relative central HPG axis deficiency contributes to this only in T-DSD. Focal areas of reduced echogenicity within the testes of men with KS and TDSD on ultrasound are not indicative of malignancy but correspond to clusters of hyperplastic Leydig cells.

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EP1318

JOINT2932

What can we learn from the largest north african cohort of testicular disorders of sex development?

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Introduction
Testicular disorders of sex development (T-DSD) represent a heterogeneous group of congenital anomalies affecting sexual differentiation. In North Africa, these conditions have long been underexplored due to limited access to genetic analysis. This study aims to describe the epidemiology, phenotypic characteristics, and genetic features of T-DSD in this region.
Methods
We conducted a cross-sectional descriptive study including patients diagnosed with DSD and confirmed testicular tissue, followed at the endocrinology reference center in southern Tunisia. All patients underwent clinical assessment of sexual maturation using Tanner and Prader staging, as well as steroid hormone profiling. Genetic analysis was performed using next-generation sequencing (NGS) at the genetics department.
Results
We identified 50 North African patients from 40 families, with two-thirds of cases involving consanguineous unions. The most common etiologies were testosterone biosynthesis defects (38%) and gonadal dysgenesis (32%). The mean age at first consultation was 17.98 ± 11.89 years (range: 1 day–60 years), with no significant difference between etiological subgroups. The most frequent reason for medical consultation was primary amenorrhea (62%), except in 46,XX DSD cases. Complete pure gonadal dysgenesis showed a strong phenotypic correlation with mutations in key sex differentiation genes (SRY and NR5A1), whereas partial pure gonadal dysgenesis exhibited variable male phenotypes associated with MAP3K1 mutations. Androgen receptor abnormalities (AIS: 10%; 5α-reductase deficiency: 12%) presented with diverse phenotypes, with genotype-phenotype correlation established only for the R753X mutation in the AR gene. Patients with testosterone biosynthesis defects showed variable phenotypic expression, but specific traits such as pubertal virilization suggested 17βHSD3 deficiency in which we proved the founder effect for the C206X mutation. Strong phenotype-genotype correlation was observed only in cases of LH resistance. In 46,XX T-DSD cases ($n = 3$), the degree of masculinization was dictated by the presence of the SRY gene.
Discussion
Testicular DSDs represent a heterogeneous group of disorders. In our cohort, testosterone synthesis defects were the most predominant category, likely due to the high incidence of consanguinity. Unlike larger pediatric series, our cohort primarily included peri-pubertal individuals. Clinical presentation was highly variable but could be guided by static and dynamic hormonal assessments. Molecular analysis has become essential, though sometimes insufficient. Our findings on phenotype-genotype correlations aligned with the literature for CAIS, LH resistance, complete gonadal dysgenesis, 17βHSD3 deficiency, and XX DSD. However, we refuted a previously suggested correlation for the MAP3K1 gene mutation.

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EP1319

JOINT2789

Genotype-phenotype correlation of patients with androgen insensitivity syndrome: a cohort study including 9 families

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Background
Androgen Insensitivity Syndrome(AIS) is an X-linked disorder and the most common cause of disorders/differences of sexual development(DSDs) in individuals with a 46, XY karyotype. AIS is classified into complete(CAIS), partial(PAIS), and mild(MAIS) forms based on clinical and genetic findings. Phenotypic expression varies from normal female external genitalia in complete CAIS, to normal male genitalia with infertility or gynecomastia in MAIS. The phenotype may be variable in PAIS including incomplete virilization. This study aimed to evaluate the clinical and genetic characteristics of AIS.
Materials and Methods
The data about the medical history, and clinical examination were recorded from the patient files. Chromosomal analysis was performed in all. Next-generation sequencing(NGS) was performed using the *SOPHIA*™ Clinical Exome Solution(CES) v3 and Illumina NovaSeq platform, covering 6,300 genes.A custom gene panel targeting 24 genes associated with XY DSD was analyzed using the Sophia DDM platform. The study included 15 patients from 9 families with hemizygous variants in the *AR* gene (NM:000044.6).
Results
Among 15 patients, seven presented with a female external genital phenotype, six showed incomplete virilization, and two siblings had unique presentations(one with undescended testes, the other with oligoasthenospermia). The consanguinity ratio was 27%. Based on molecular genetic analysis,7 patients were classified as PAIS, 6 as CAIS, and 2 as MAIS. Four patients with CAIS presented with primary amenorrhea, and two were diagnosed after testicular tissue was observed during hernia surgery. All were assigned as female, and five of them underwent gonadectomy in the pubertal period. Frameshift variants[c.1625_1629dup, p.(Arg544Leufs20)($n = 2$, novel); c.1890del, p.(Lys631Serfs*2*)($n = 2$)] and nonsense variants [c.1921C>T, p.(Gln641*)($n = 1$, *novel*); c.1605C>G, p.(Tyr535*)($n = 1$)]were identified in the CAIS group. In PAIS, four presented in the neonatal period with incomplete virilization, while three presented with pubertal virilization. Neonatal cases were assigned male gender, while pubertal cases transitioned from female to male. All patients with PAIS had microphallus, undescended testes, and four had hypospadias, and all underwent orchiopexy. Missense variants [c.2134C>G, p.(Gln712Glu)($n = 4$), c.1794C>A, p.(Ser598Arg)($n = 1$,*novel*), c.1789G>A, p.(Ala597Thr) ($n = 1$)] were identified. One of the patients with peviously reported c.2072A>G, p.(Asp691Gly) variant was presented with complete female phenotype. Two siblings had the MAIS phenotype and one of them presented with undescended testes, while the other had oligoasthenospermia. Both patients were reared as male gender.A missense variant [c.1174C>T, p.(Pro392Ser) ($n = 2$)] was detected. Elevated Anti-mullerian hormone concentrations were detected in pubertal patients except the patients with oligoasthenospermia only.
Conclusion
The combined evaluation of genetic and clinical characteristics is critical for diagnosing and managing AIS and underscores the importance of individualized patient care. Our study identified 9 variants, including 3 novel ones, contributing to the understanding of phenotypic variability of the AIS.
Keywords
Androgen insensitivity syndrome,*AR* gene, Disorders/differences of sexual development.

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EP1320

JOINT3432

Impact of gender-affirming hormone therapy on cardiovascular risk in transgender individuals

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Introduction
Transgender people receive hormone treatments of the opposite sex during the transition process. There are many studies showing that the cardiovascular risks of individuals change as a result of this transition process. It is well-known that

transgender individuals have changes in body composition, body fat distribution, and cardiovascular lipid profile.
Methods
Records of 81 female-to-male and 19 male-to-female patients over the age of 18 who applied to the endocrinology and metabolic diseases outpatient clinic of Ankara University Faculty of Medicine between 2018-2024 were reviewed. We aimed to investigate whether there is a change in cardiovascular risk in both transgender men and women during the transition process using some simple laboratory indices. Lipid parameters requested before treatment and at the 3rd, 6th, and 12th months of treatment, as well as during final follow-ups, were analyzed for transgender men receiving testosterone therapy.
Results
Of the 100 patients evaluated, 81 (81%)were transgender male whereas 19 (19%) were transgender female. The average age at first hospital admission was 22.45 years (SD: 4.425), and the average age at which symptoms were first noticed was 10.3 years (SD: 3.65). Based on this data, there was an average delay of 12.1 years between the onset of symptoms and seeking medical help. Among the 81 patients applying for female-to-male transition, 22 (27.1%) reported using a testosterone preparation obtained independently, without medical supervision. Additionally, 16 patients (19.7%) underwent mastectomy before the transition process upon their own decision, and 2 patients (2.49%) had undergone hysterectomy before transitioning. For evaluating cardiovascular risk profiles of the transgender male, Castelli risk index-1 (Total cholestrol/HDL-C), cardiac risk ratio-II (LDL/HDL-C), and triglyceride/HDL ratios were analyzed before treatment and during follow-up. The total cholesterol/HDL ratio was found to have increased significantly ($P = 0.016$), the LDL/HDL ratio also showed a significant increase ($P = 0.03$), while the triglyceride/HDL ratio did not show a statistically significant change ($P = 0.887$).
Conclusion
We found an increase in Castelli 1 Risk Score and CRI-II, but no difference in tg/HDL-C in transgender males after testosterone therapy. It is known that gender-affirming masculinization treatments can lead to elevated blood pressure, changes in lipid profiles, and increased hematocrit levels, thereby raising cardiovascular risks. This suggests that these young individuals who will receive long-term testosterone therapy should be carefully monitored for other cardiovascular risks throughout their lives, and appropriate medical agents should be used if necessary.

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EP1321

JOINT1352

Raised sex hormone binding globulins levels in men: a retrospective observational study

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Introduction
Sex hormone binding globulins (SHBG) are glycoproteins synthesized in liver, which have high specificity and affinity to bind with sex steroids. Raised levels of SHBG are observed in thyrotoxicosis, hepatic disease, anorexia, growth hormone deficiency and rarely due to oestrogen secreting tumours. Aging and medications (e.g. cytochrome P450 enzyme inducers) are also associated with an increase in SHBG levels.
Objectives
We carried out a retrospective analysis of all the raised SHBG test measurements in men (aged $>$ 18 years), recorded and logged in our University teaching hospital over last 10-years (2014-2024). The primary objective of this observational study was to ascertain possible underlying cause of raised SHBG levels in this cohort apart from registering the final clinical outcome.
Methodology
The existing biochemistry data based was searched for all the raised SHBG test results in men (aged $>$ 18-years) over last 10-years irrespective of their serum testosterone levels. A retrospective analysis of case notes and biochemical & radiological investigation results available on clinical portal was carried out.
Results
We retrieved a list of 123 raised SHBG test results over a period of 10-years in men aged 20-83 years. After excluding the duplication of test results, a total of 45 men ($n = 45$) were included in the final analysis. Table 1, sums up the key observations of our retrospective study:.
Conclusion
Hepatic dysfunction, hyperthyroidism, aging and iatrogenic factors remain well known contributory factors for raised SHBG levels. Oestrogen secreting tumours have been described in literature as rare though important pathology which need to be kept in mind while evaluating men with high SHBG levels. Contrary to what has been described in medical literature, we observed anabolic steroid use associated with raised SHBG levels in 5 of our patients (and the SHBG levels normalized after stopping the anabolic steroids).

Table 1: Underlying etiology of increased SHBG.

Underlying Etiology	Number(n)
Hepatic dysfunction	12
Medications (including carbamazepine, phenytoin)	8
Hyperthyroidism	5
Anabolic steroid use	5
Type 1 Diabetes (no other cause)	3
Nutrional deficiencies related to previous gastro-intestinal surgery	2
Transgender man undergoing transition therapy	1
Immunoassay analytical interference	1
An increased age	3
No known etiology	5

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EP1322

JOINT1878

Free testosterone and shbg play independent roles in insulin resistance and metabolic alterations of women with pcos

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Context/Object
The relationship between hyperandrogenemia and metabolic abnormalities in women with polycystic ovary syndrome (PCOS) is still object of study. The biological effects of testosterone are modulated by SHBG, a protein, regulated by several factors, which binds circulating testosterone and regulates its bioavailability. Both the increase of free testosterone (FT) and the reduction of SHBG have been associated with insulin resistance and metabolic alterations. Whether SHBG may play an independent role in this phenomenon is still unclear, and the use of SHBG in FT calculation makes this analysis very difficult. Aim of this study was to investigate potential differences in the relationships of SHBG and FT with the metabolic, hormonal and phenotypic features of PCOS, using a measurement of serum FT independent of SHBG assay.
Study design and Subjects. Cross-sectional study including 280 women with PCOS diagnosed by the Rotterdam criteria.
Methods
FT was measured by equilibrium dialysis with subsequent direct assay of the hormone by LC-MS/MS on the dialysate. Total testosterone and androstenedione were assayed by LC-MS/MS. Insulin sensitivity was measured by the hyperinsulinemic euglycemic clamp.
Results
Both SHBG and FT showed statistically significant and opposite relationships with anthropometric and metabolic parameters. Categorizing women with PCOS on the basis of their SHBG and FT levels (normal SHBG/normal FT, $n = 74$; low SHBG/normal FT, $n = 39$; normal SHBG/high FT, $n = 39$; low SHBG/high FT, $n = 128$), the two subgroups with low SHBG, and either normal or high FT, had worse anthropometric and metabolic profiles than subjects with normal SHBG/normal FT. This phenomenon was especially enhanced in women with low SHBG/high FT. Conversely, the subgroup with normal SHBG/high FT differed from women with normal SHBG and normal FT only for higher fasting insulin. In multivariable analysis, age, fat mass, insulin sensitivity and FT were all independent predictors of SHBG, whereas only insulin sensitivity and SHBG, but not fat mass, were independent predictors of FT. After adjusting data for age and fat mass, both FT and SHBG were independent predictors of insulin sensitivity. Moreover, in logistic analysis, the presence of metabolic syndrome was independently predicted by SHBG, but not by FT.
Conclusions
In women with PCOS, low SHBG and high FT levels are independently associated with insulin resistance, and the coexistence of these features enhances metabolic abnormalities.

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EP1323

JOINT2547

Severe obstructive sleep apnea syndrome and continuous positive airways pressure therapy impact on testosterone levels in male patients with severe obesity

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Background
To date, the relationship between Obstructive Sleep Apnea Syndrome (OSAS) and testosterone levels in males has not yet been fully elucidated. Some studies reported a correlation between severe OSAS and hypogonadism in patients with obesity, regardless of body mass index (BMI). However, few data from longitudinal studies show the effect of continuous positive airways pressure (CPAP) on gonadal function.
Aim
To investigate the factors related to low testosterone levels in a large cohort of males with severe/complicated obesity, the role of the OSAS in the diagnosis and severity of hypogonadism, and the effects of ventilation therapy on hormonal status.
Subjects and methods
210 male inpatients with grade II (BMI $\geq$ 35 Kg/m^2) complicated or grade III (BMI $\geq$ 40 Kg/m^2) obesity were included in this cross-sectional study. Polysomnography or overnight oximetry and blood tests for inflammation indices, metabolic and hormonal profiles were performed during admission. Decompensated OSAS was defined as Apnea/Hypopnea Index (AHI) in newly diagnosed, or Oxygen Desaturation Index (ODI) in treated patients, above 30 events/hour. Univariate analyses were performed to investigate the conditions related to the decrease in testosterone levels (inflammation, diabetes, eating disorders, waist circumference, previous diagnosis of OSAS, decompensated OSAS). A logistic regression and a multiple linear regression were carried out to identify the independent factors associated with hypogonadism (i.e. testosterone $\leq$ 10.4 nmol/l)and to continuous testosterone levels respectively. Lastly, a prospective longitudinal study of 15 newly diagnosed patients was performed to evaluate the effects of CPAP therapy on hormonal control after 3-6 months of treatment.
Results
130 out of 210 patients showed low testosterone levels. Type 2 diabetes mellitus and C-reactive Protein (CRP) were independently associated with hypogonadism (p-value 0.03 and 0.01, respectively). The correlation between decompensated OSAS and hypogonadism was significant in the univariate, but with only a trend to significance in multivariate analysis (p-value 0.02 and 0.06, respectively). Only waist circumference, CRP, and T2DM were significantly associated with the progressive decline in testosteronemia at linear regression. After 3-6 months of CPAP therapy, ODI was significantly associated with the improvement in testosterone levels, independently from BMI, at multivariate regression (p-value 0.04).
Conclusions
decompensated OSAS, rather than its diagnosis, was found to correlate with low testosterone values also in male patients with severe obesity. As expected, our findings confirmed the contribution of T2DM, waist circumference and inflammation to the deflection of gonadal function. In addition, CPAP therapy was shown to improve testosterone levels.

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EP1324

JOINT3829

Alteration of the tryptophan concentrations in women with polycystic ovary syndrome (PCOS)

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Introduction
Polycystic ovary syndrome (PCOS) is one of the most common endocrinological disorders affecting reproductive age women worldwide; it is conventionally linked mostly to childbearing age; however, it has an influence on patients' health throughout their lifespan. Tryptophan (Trp) is one the amino acids classified as an essential, meaning the body can only obtain it through external sources. It serves as a building block for proteins and acts as a substrate for several signaling molecules.
Methods
The study population comprised 326 women: 208 diagnosed with PCOS and 118 healthy individuals. PCOS was diagnosed according to the revised 2003 Rotterdam criteria. Numerous anthropometric, biochemical and hormonal measurements were performed using standard techniques and commercially available methods. Assessment of branched-chain and aromatic amino acids levels was performed with a gas-liquid chromatography combined with tandem mass spectrometry.
Results
Statistical analysis revealed noticeably higher tryptophan levels in PCOS women compared to the control group: 53.66 $\pm$ 11.42 vs. 49.81 $\pm$ 11.18 nmol/ml ($P <$ 0.01) and the significant increase of the tryptophan concentration in the PCOS group was also observed in the subpopulations of women with metabolic disturbances, such as insulin resistance, abdominal obesity or obesity. On the other hand, further analysis conducted in PCOS group, revealed that, in contrary to other aromatic amino acids, there is no difference in tryptophan level between women with and without diagnosed metabolic issues, including obesity (53.03 $\pm$ 9.69 53.88 $\pm$ 11.85; P = 0.53) and insulin resistance (53.70 $\pm$ 11.08 53.68 $\pm$ 11.66; p= 0.80).
Conclusion
Alteration of tryptophan level seems to be independent from metabolic disturbances and further studies of the kynurenine pathway, which is the main metabolic pathway for tryptophan, are needed to assess the role of tryptophan and its metabolites in the PCOS pathogenesis.

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EP1325

JOINT2861

Semen cryopreservation and semen quality in transfeminine adolescents prior to hormone therapy

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Background
Some transgender individuals wish to become biological parents in the future and transfeminine persons may be offered cryopreservation of semen before starting hormone therapy. However, there is a lack of knowledge about semen cryopreservation outcomes among transfeminine adolescents seeking gender-affirming care.
Aim
To investigate transfeminine adolescents who decide for or against semen cryopreservation.
Methods
This is a retrospective observational national cohort study of 58 transfeminine individuals aged <18 years, assessing clinical data, semen parameters, and reproductive hormone levels.

Results
Among the 58 individuals, 23 (39.7%) opted for semen cryopreservation and successfully collected a semen sample. They were older and more advanced in pubertal development compared to those who did not: median age was 16.4 years (range 13.7-19.4) vs 15.8 years (11.7-17.9), Tanner stage G5 (4-5) vs G3 (2-4), and testis volume 20 ml (15-25) vs 8 ml (3-20). Among 17 individuals with no prior hormone therapy, the median sperm concentration was 11.1 $\times$ 10^6/ml (0.02-163), semen volume 1.8 mL (0.2-3.9), total sperm count 17.8 $\times$ 10^6 (0.1-214.2), and percentage of progressively motile spermatozoa 46% (8-74). Reproductive hormones were within normal ranges for age and sex assigned at birth.
Conclusion
The prevalence of adolescents opting for semen cryopreservation was comparable to other countries with a publicly financed national healthcare system. Overall, semen quality was impaired, which may be attributable to young age, intense gender dysphoria, and lifestyle.

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EP1326

JOINT660

Temporal trends in serum testosterone and luteinizing hormone levels indicate an ongoing resetting of hypothalamic-pituitary-gonadal function in healthy men: a systematic review

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Background
Male fertility is progressively impairing over time, probably related to a multifactorial genesis, involving mainly lifestyle and environmental factors. Only few data suggest temporal trends in serum testosterone levels.
Objective and Rationale
The aim of the study was the evaluation if a Temporal trend in serum testosterone levels exists in healthy men.
Search Methods
A systematic search of the literature between 1971 and July 2024 was performed, selecting study groups in which testosterone serum levels were measured for any reason in healthy men. Exclusion criteria were: (i) subjects' age $<$18 years old, (ii) conditions affecting testosterone levels, (iii) subjects' enrolment based on testosterone serum levels and (iv) blood examinations performed in a time-frame interval $>$10 years. As secondary endpoints, luteinising hormone (LH), follicle-stimulating hormone (FSH), sex hormone binding globulin (SHBG) serum levels and body mass index (BMI) were collected when available.
Outcomes
1,256 papers, accounting for 1,504 study groups, were selected, including 1,064,891 subjects (mean age 42.0$\pm$7.0 years). A significant negative linear regression between testosterone serum levels and year of measurement was detected (P = 0.033). The comprehensive decline in testosterone serum levels over the years was confirmed with meta-regression analysis using the number of patients included in each study, subjects' age and body mass index (BMI) to adjust testosterone trend. No temporal trend was observed regarding BMI in this population. LH serum levels showed a significant decline over the years, adjusting for subjects' age, while no trend emerged considering FSH. The decline in testosterone serum levels was confirmed adjusting data according to the assay used for testosterone measurement and after matching with environmental and demographic data.
Wider Implications
This study is the first comprehensive meta-regression analysis suggesting a progressive decrease in serum testosterone and LH levels in healthy men, independent of age and BMI. The observed decline in both testosterone and LH levels could be a consequence of an ongoing resetting of the hypothalamic-pituitary testicular function.

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EP1327

JOINT3375

Circulating gut hormone concentrations in women presenting with menstrual disturbance

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Background
Polycystic Ovary Syndrome (PCOS) and Functional Hypothalamic Amenorrhoea (FHA) are the commonest causes of secondary amenorrhoea. PCOS is typically associated with increased bodyweight, appetite, insulin resistance, and metabolic dysfunction, whereas FHA is typically associated with lower body weight and decreased energy availability. Importantly, there are only limited inconsistent data describing gut hormone levels in these conditions and no direct comparisons. Ghrelin is reported to be reduced in PCOS and increased in FHA. Additionally, administration of ghrelin decreases LH pulsatility in healthy women, consistent with a possible causal role in FHA. GLP-1 is reported to be reduced or unchanged in PCOS. PYY3-36 is reported to be increased in FHA, and reduced or unchanged in PCOS. PYY1-36 is converted to the more active isoform PYY3-36 by the enzyme Dipeptidyl peptidase-4 (DPP4). Here, we provide the first direct comparison of levels of gut hormones in women with metabolically divergent causes of menstrual disturbance.
Methods
Fasting total ghrelin, total glucagon like peptide-1 (GLP-1), and peptide YY isoforms (PYY1-36, PYY3-36) were measured in women aged 18-35 years in the follicular phase who were healthy (n = 47), had PCOS (n = 73), or FHA (n = 44). Ghrelin (Merck Millipore) and GLP-1 (Mercodia) were measured by ELISA, whereas PYY1-36 and PYY3-36 by in-house LC-MS/MS (Acquity UPLC with TQ-S). Groups were compared by the Kruskal-Wallis Test with post hoc Dunn's test.
Results
Mean ($\pm$SD) ghrelin levels were lower in PCOS (1004 $\pm$572 pg/ml) than healthy women (1316 $\pm$616; P = 0.0043), or in FHA (1369 $\pm$570; P = 0.0012) . However, this was predominantly due to higher BMI in PCOS, and levels did not differ in those with lean PCOS (BMI $<$25 kg/m^2; P = 0.39). In PCOS, ghrelin was negatively correlated with the Ferriman-Gallwey score (r=-0.30, P = 0.015) and Free Androgen Index (FAI) (r=-0.6531, P $<$0.0001). PYY1-36 (pmol/l)was reduced in FHA (0.31 $\pm$0.5) compared to PCOS (0.75 $\pm$0.74; P = 0.0001), and even to those with lean PCOS (0.69 $\pm$0.74; P = 0.0068). Neither ghrelin nor PYY1-36 correlated with other reproductive hormones. No changes were observed in PYY1-36 or GLP-1 between the groups.
Conclusion
This is the first study to directly compare gut hormone levels in patients presenting with menstrual disturbance due to PCOS or FHA. Ghrelin levels were lower in women with PCOS (albeit mainly due to bodyweight). However, PYY1-36 levels were higher in PCOS than FHA independent of bodyweight. Taken together, these data inform our understanding of the intricate coupling between reproductive function and metabolism in common reproductive disorders.

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EP1328

JOINT12

Primary amenorrhea secondary to β-thalassemia major: a case report

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Background
Primary amenorrhea can stem from a variety of etiologies, including hypogonadotropic hypogonadism, a condition frequently seen in patients with β-thalassemia major due to iron overload from repeated blood transfusions. This iron toxicity primarily affects endocrine organs, including the anterior pituitary, leading to endocrine complications.

Case Presentation
We report the case of a 17-year-old adolescent, with a history of β-thalassemia major diagnosed at birth, who presented with primary amenorrhea and growth delay. She receives blood transfusions every 21 days and chelation therapy to manage iron overload. Clinical examination revealed a weight of 30 kg and height of 145 cm (BMI = 14 kg/m^2), with pubertal development assessed at Tanner stage S2 (breast) and P3 (pubic hair). Laboratory tests showed low FSH (0.97 mIU/ml) and estradiol levels (<24 pg/ml), with normal TSH. Pelvic MRI indicated uterine hypoplasia and small ovarian volume, while pituitary MRI showed anterior pituitary atrophy, compatible with iron overload. Hormone replacement therapy was considered to correct the endocrine deficiencies and promote pubertal development.
Discussion
β-thalassemia major is frequently associated with endocrine disorders, predominantly due to iron overload impacting the anterior pituitary. This disruption in hormonal secretion leads to hypogonadotropic hypogonadism, which is the primary cause of primary amenorrhea in thalassemic females. In this case, clinical and radiologic findings confirmed central hypogonadism with low FSH and estradiol levels and pituitary atrophy. Hormone replacement therapy is essential for inducing and maintaining secondary sexual characteristics and preventing long-term complications, such as osteoporosis. Despite advancements in transfusion and chelation therapies, endocrine complications remain a significant concern for thalassemic patients, particularly during adolescence.
Conclusion
Primary amenorrhea due to iron overload is a common complication in adolescent females with β-thalassemia major. This case underscores the importance of early detection and appropriate therapeutic intervention, including hormone replacement therapy, to enhance quality of life and prevent long-term complications in these patients.

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EP1329

JOINT2792

Androstenedione method comparison of three automated immunoassays and ID-LC-MS/MS in routine testing and disorders of steroid synthesis

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Introduction
Androstenedione is a steroid hormone produced in the adrenals and gonads, commonly used in the diagnosis and monitoring of hyperandrogenism and congenital adrenal hyperplasia (CAH) in conjunction with other hypothalamic and pituitary hormones. Excess androgens such as androstenedione are also evaluated in conditions including polycystic ovarian syndrome (PCOS) and adrenal tumours. We present here the comparison of three commercially available immunoassays and one isotope dilution liquid chromatography mass-spectrometry method (ID-LC-MS/MS) for androstenedione in frequently investigated patient groups with changes in steroid biosynthesis.
Methods
We evaluated the correlation between the Elecsys Androstenedione (Roche, Mannheim, Germany) and IDS Androstenedione (IDS, Boldon UK) automated immunoassays in a set of 141 remnant routine serum samples (CHU de Liege). The IDS method was additionally compared to the automated Liaison Androstenedione (DiaSorin, Salluggia, Italy) in a set of 119 routine samples (LMU Munich and CHU Liege), and in a set of 94 samples with clinical diagnosis (n = 20 CAH, n = 20PCOS, n = 13 adrenal carcinoma, n = 21 adrenal insufficiency, n = 20 post-menopausal females). Androstenedione levels were also determined with a validated ID-LC-MS/MS (Chromsystems, Gräfelfing, Germany) in the same samples.
Results
The Roche and IDS Androstenedione methods showed excellent correlation (Passing-Bablok regression IDS = 1.05*Roche – 0.11ng/dl, R^2=0.99) with no systematic bias across the range of samples (Bland Altman mean bias 5.5%). Agreement between the IDS and Diasorin assays in general routine samples was acceptable, but results were approximately 33% lower with IDS compared to Diasorin (IDS = 0.67*Diasorin + 3.44ng/dl, R^2=0.97, mean bias -33.5%). The overall difference between the two assays was similar in the samples from specific patient groups where excess androgens commonly occur (IDS = 0.74*Diasorin – 5.4ng/dl, R^2=0.94, mean bias -35.9%). In the same set of samples where values were additionally determined with LC-MS, the IDS had a mean -0.2% bias (IDS =1.18*LC-MS -12.67, R^2=0.79) while mean bias on the Diasorin was 38% (Diasorin = 1.56*LC-MS - 51ng/dl, R^2=0.97).
Conclusion
Our investigation into the performance of three commercially available automated immunoassays for Androstenedione revealed a close alignment between measurements from the IDS and Roche methods, the latter being standardised to ID-LC-MS/MS. While there was a good agreement overall, the Diasorin assay measured 33-38% higher than the IDS and ID-LC-MS/MS in routine samples and samples where androgens can often exist in excess. Values generated by the IDS assay were also closely aligned to ID-LC-MS/MS, indicating adequate clinical specificity in this recently available method.

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EP1330

JOINT1001

The impact of gender dysphoria on mental health of transgender and gender non-conforming patients – 7-year of experience in the first gender unit for youth in poland

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Introduction
The worldwide trend of rising referrals of youths to gender clinics is widely discussed and observed in Poland as well. To our knowledge, there is no data presenting the medical and psychological status of gender dysphoric youth in Central Europe. Similarly, the data about the relation between the Gender Minority Stress (GMS) and health – both mental and somatic – is scant.
Aim
Here, the mental health diagnoses and endocrinological status based on steroid metabolome from 24-hr urinary collection are analysed in the context of minority status-related data.
Methods
This prospective study has examined consecutive series of children and adolescents diagnosed due to gender incongruence/dysphoria in accordance with WPATH SOC-8 in one university center between July/2017 and Sep/2024. Clinical and laboratory data was collected in unified medical records.
Results
The population consists of 269 participants (female: male at birth -230:39) with the mean/median age of diagnosis 15.8/16.1 years and the mean age of gender identity mismatch onset of 12 years. Mental health diagnoses among our patients include: mood disorders - 59.8%, anxiety disorders - 26.0%, adjustment disorders - 3.8%, psychotic disorders - 4.6%, conduct/disruptive disorders – 0.8%, substance use disorders - 2.3%, eating disorders - 12.6%, personality disorders – 9.6%, attention deficit hyperactivity disorder – 9.6%, autism spectrum disorders – 22.6%. Further statistical analyses have revealed that gender dysphoria is a positive predictor of a number of mental health diagnoses (P <0.05) and correlates positively with values of THF+allo-THF/THE (reflects 11ßHSD1 activity), α- and β-cortolone (cortisone metabolites) (P <0.05). Negative association was found between the age of gender incongruence onset and values of F/E (11ßHSD1 activity) and positive between the age of coming out to friends and relatives and values of tetrahydrocortisone (THE), tetrahydrocortisol (THF) and β-cortol (cortisol metabolite) (P <0.05). The results of the intergroup differences analysis have shown that adolescents who have parental acceptance of their minority status report lower intensity of gender dysphoria than those who have no parental support in this respect.
Conclusions
The analyses further indicate the significance of gender dysphoria alleviation for transgender and gender non-conforming adolescents' mental health. Our results show that Gender Minority Stress (including gender dysphoria) influences the glucocorticoids balance, which indicates a need for further investigation.

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EP1331

JOINT2859

Comparison of metabolic outcomes in lean and obese women with polycystic ovary syndrome

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Introduction
Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting up to 20% of women of reproductive age. Characterized by ovarian dysfunction, hormonal imbalances, and metabolic abnormalities, PCOS has traditionally been associated with obesity. However, increasing numbers of lean women are being diagnosed with PCOS. While obesity exacerbates metabolic disturbances, non-obese PCOS women may also present significant metabolic issues. This study compares the metabolic profiles of lean and obese women with PCOS.
Subjects and Methods
This analytical cross-sectional study included 122 women diagnosed with PCOS at the Endocrinology and Diabetology Department of FARHAT HACHED Hospital in Sousse between January and December 2024. Participants were divided into two groups based on BMI: Obese PCOS (O-PCOS; BMI >25 kg/m^2) and Lean PCOS (L-PCOS; BMI <25 kg/m^2). Metabolic parameters assessed included anthropometric data, markers of insulin resistance, and glycemic and lipid profiles.
Results
Of the 122 participants, 38 (31.1%) were lean and 84 (68.9%) were obese. The average age was 23.61 $\pm$ 4.97 years. The mean BMI was 32.26 $\pm$ 5.85 kg/m^2 for O-PCOS and 21.85 $\pm$ 1.98 kg/m^2 for L-PCOS ($\boldsymbol{P < 0.001}$). Android fat distribution was significantly more prevalent in the obese group (72.6% vs. 13.2%; $\boldsymbol{P < 0.001}$), with mean waist circumferences of 90.56 $\pm$ 10.22 cm in O-PCOS and 75.66 $\pm$ 4.59 cm in L-PCOS. Acanthosis Nigricans was significantly more common in O-PCOS (76.2%; $\boldsymbol{P < 0.001}$). In terms of the lipid profile, hypertriglyceridemia was observed in 14.3% of obese and 13.2% of lean women ($\boldsymbol{P = 0.028}$), and hypercholesterolemia was present in 7.1% of the obese and 5.7% of the lean participants ($P = 1.000$). Additionally, the metabolic syndrome was more prevalent in O-PCOS (44% vs. 2.6%; $\boldsymbol{P < 0.001}$). Lastly, impaired fasting glucose was noted in 19% of obese and 5.3% of lean women ($P = 0.055$), and impaired glucose tolerance was detected exclusively in obese participants (22.6%; $\boldsymbol{P = 0.001}$).
Conclusion
Obese women with PCOS exhibited more pronounced metabolic abnormalities, including higher rates of metabolic syndrome, insulin resistance, and glucose intolerance. However, lean women also displayed notable metabolic disturbances. These findings underscore the importance of comprehensive metabolic assessment and individualized management strategies in all PCOS patients, regardless of BMI.

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EP1332

JOINT1395

Evaluation of thyroid hormone sensitivity in polycystic ovary syndrome

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Background
Polycystic ovary syndrome (PCOS) is a complex disorder that is associated with an increased risk of cardiometabolic disorders. The metabolic dysfunction seen in PCOS has been tried to be explained by the presence of hypothyroidism, and it has been emphasized that cardiometabolic dysfunction becomes apparent when TSH is high. However, this relationship could not be demonstrated in euthyroid PCOS patients. In this context, we hypothesized that the metabolic dysfunctions in euthyroid PCOS patients could partly be explained by the presence of acquired mild thyroid hormone resistance (THR). We aimed to evaluate thyroid hormone sensitivity using thyroid hormone sensitivity indices and its relationship with homocysteine and PAI-1 levels in PCOS patients.
Methods
Patients aged 18-50 years with a diagnosis of PCOS were included in the PCOS group. Subgroup analysis of the patients was performed by grouping them as TSH <3.0 μIU/ml and TSH ≥ 3.0 μIU/ml. Euthyroid subjects matched for age and body mass index (BMI) with the patient group, were included in the control group. TSH index (TSHI), thyrotropin thyroxine resistance index (TT4RI), thyroid feedback quarter-based index (TFQI) were calculated using TSH and fT4; TSHI(fT3), thyrotropin triiodothyronine resistance index (TT3RI), TFQI(fT3) were calculated using TSH and fT3; fT3/fT4 ratio was calculated using fT3 and sfT4. Statistical analysis was performed using the IBM SPSS 26.0 program. The level of statistical significance was accepted as $P < 0.05$.
Results
Although no statistically significant difference was found between the PCOS and control groups in terms of central and peripheral thyroid hormone sensitivity indices; fT3 and TFQI(fT3) were statistically signifcant between TSH ≥ 3 PCOS and TSH ≥ 3 control group. Positive correlations were found between TFQI value and HDL and total cholesterol levels and between TSHI, TSHI(fT3), TT3RI and TT4RI and waist circumference in the PCOS group, whereas negative correlations were found between TFQI(fT3) value and fasting glucose and between fT3/fT4 and fasting glucose, LDL and total cholesterol levels.
Conclusions
In our study, we thought that decreased thyroid hormone sensitivity may be one of the factors involved in the increased cardiometabolic risk in PCOS. More multicenter prospective studies with larger sample groups are needed to elucidate this relationship.

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EP1333

JOINT1479

Physical growth of chinese girls' menarche onset

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Objective
We aimed to identify the contributing physical predictors for menarche and further to establish critical weight for menarche onset in Chinese girls.
Methods
This was a retrospective study. The sample was composed of 253 girls who visit within 3 months after menarche. For propensity score matching, data of 253 girls with similar chronological age and mid-parental height who haven't menarche yet were collected. All girls were from Beijing city, China and visit pediatric clinic during 2018 to 2023. Receiver operator characteristic curve was performed to determine cutoff values. Multivariate logistic regression was used to construct a nomogram. The discriminatory ability of the model was determined by calculating the area under the curve (AUC). Moreover, calibration analysis and decision curve analysis (DCA) of the model were performed.
Results
The average age of menarche of the 253 girls was 10.2 ± 1.0 years, with average weight of 42.9 ± 6.8kg, height of 148 ± 5.1cm and BMI of 20.2 ± 2.5kg/m^2, with significant higher compared to pre-menarche girls with similar age and mid-parental height ($P < 0.01$). Among the girls of different menarche age groups, height, weight, BMI, and their standard deviation scores were compared, there was significant difference between groups except weight ($P = 0.088$). Based on receiver operating characteristic (ROC) curve analysis, weight of 36.6kg was significantly related to menarche occuring, and the specificity and sensitivity were 65.2% and 81.7%, respectively. A nomogram was built based on weight, the proportion of height to mid-parental height, and bone age. The predictive model yielded an AUC of 0.818 (95% CI, 0.780, 0.856). The predictive model was well-calibrated, and DCA showed when the threshold probability of menarche below 80%, using the proposed nomogram to predict menarche would obtain more benefit than using weight prediction alone.
Conclusions
Menarche age is highly related to physical development. The optimal critical value of weight has important application value in menarche. Besides, a nomogram was constructed for predicting menarche by physical status. Physical growth, as a simple and easily obtainable information, can be reliable indicators for predicting menarche.

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EP1334

JOINT873

Ovarian suppression using GnRH analog followed by estrogen and progestin for the classic form of lipoid congenital adrenal hyperplasia: A case report and its implications for ovarian morphology

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Background
Lipoid congenital adrenal hyperplasia (LCAH) is caused by pathogenic variants in *STAR*, encoding steroidogenic acute regulatory protein. LCAH is characterized clinically by impaired steroidogenesis and pathologically by cholesterol ester accumulation in the adrenal glands and gonads. Most 46,XX patients with the classic form of LCAH undergo spontaneous puberty but develop premature ovarian failure in later life. In addition, approximately 33% of women with LCAH experienced large ovarian cysts or ovarian torsion requiring cystectomy or ovariectomy, respectively (Ishii T, *et al*. J Clin Endocrinol Metab 2020;105:1870–1879). These ovarian complications are potentially associated with hypergonadotropinemia; however, effective interventions to prevent such complications remain unclear. Here, we report a 46,XX female with LCAH who underwent GnRH analog followed by estrogen and progestin, with detailed monitoring of ovarian morphology.
Case Presentation
The patient was an 18-year-old Japanese female diagnosed with LCAH after presenting primary adrenal insufficiency and adrenal hyperplasia with low CT attenuation in the neonatal period. Genetic analysis of *STAR* identified compound heterozygous pathogenic variants (p.Gln258* and p.Glu218Val). With glucocorticoid and mineralocorticoid replacement, she exhibited breast development at 10 years of age and pubertal response of serum gonadotropins to GnRH stimulation. After thorough discussions with her guardians, subcutaneous injections of leuprorelin acetate were initiated and maintained until the transition to estradiol and norethindrone at 14 years of age. Ovarian morphology, including the maximum cyst diameter and ovarian volume, was regularly assessed using ultrasonography and MRI. Before leuprorelin therapy, the maximum cyst diameter was 13 mm (greater than 9 mm, corresponding to +2.0 SD for her age), which reduced to 6 mm after 6 months of treatment and remained within the reference range. Ovarian volume SD scores decreased from +0.82 and -0.12 before therapy to -0.85 and -0.72 at 12 months, respectively, and stabilized within the normal range. At the most recent follow-up, she had not developed ovarian cysts or hyperplasia under the control of estradiol and norethindrone.
Discussion and Conclusion
This is the first reported case of LCAH who underwent ovarian suppression with GnRH analog followed by estrogen and progestin. Despite the presence of a large ovarian cyst before therapy, no subsequent large ovarian cysts, ovarian hyperplasia, or ovarian torsion were observed during the therapy. These findings suggest that this therapeutic approach may prevent such ovarian complications in patients with the classic form of LCAH. Further clinical studies are warranted to evaluate the efficacy and safety of this intervention.

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EP1335

JOINT3843

Evaluating olfactory and gustatory function in patients with hypogonadotropic hypogonadism

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Introduction
Hypogonadotropic hypogonadism (HH) is a condition marked by deficient secretion of gonadotropin-releasing hormone (GnRH), resulting in impaired sexual development and reproductive function. Olfactory dysfunction, including anosmia and hyposmia, frequently accompanies HH due to the shared embryological development of the olfactory system and the hypothalamic-pituitary axis. Recognizing sensory impairments in smell and taste in boys with HH is critical for early diagnosis and treatment planning.
Aim of the Study
To conduct a standardized evaluation of olfactory and gustatory function in a group of boys with HH and to explore associations between clinical symptoms, sensory dysfunctions, and genetic findings.
Materials and Methods
patients aged 8-17 years with confirmed HH were assessed for olfactory and gustatory function using standardized smell identification tests "Sniffin Sticks KIDS Polska," "Screening 6-odor smell test," and taste recognition using "ODOFIN Sniffin Sticks." A control group consisted of individuals without pubertal disorders. Additional assessments included magnetic resonance imaging (MRI) of the hypothalamic-pituitary region and olfactory bulbs, as well as genetic testing for mutations linked to HH.
Results
Olfactory dysfunction was identified in seven out of eight patients, with one exhibiting normal olfactory function. One patient demonstrated complete taste impairment (hypogeusia), while another exhibited partial taste dysfunction with difficulty recognizing sour and salty flavors. Genetic testing for HH-related mutations revealed three cases of Kallmann syndrome (two patients with KAL1 gene mutations and one with a PROK2 mutation). All three had olfactory impairments, and one also exhibited hypogeusia.
Conclusions
Olfactory and gustatory assessments in patients with HH provide valuable diagnostic insights and can help guide genetic testing. These non-invasive tests offer a practical approach to identifying sensory dysfunctions and refining diagnostic strategies.

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EP1336

JOINT3955

Primary gonadal dysfunction after oncological treatment in a cohort of childhood medulloblastoma survivors

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Background
Medulloblastoma is a cerebellar tumour that is usually diagnosed during childhood. Since the 5-year survival rate has risen, due to new therapeutic approaches, a high proportion of survivors develop late endocrine complications. These endocrinopathies may consist of hypothalamic–pituitary and growth disorders, obesity and metabolic syndrome, but also primary gonadal dysfunction. Gonadal insufficiency and infertility may impact the physical status and quality of life of these young patients. Therefore, we aimed to evaluate primary gonadal insufficiency in 31 subjects diagnosed with medulloblastoma that were treated with cranial and spinal radiotherapy apart from chemotherapy.
Material and Methods
We performed anamnesis, physical examination and hormonal profile in 31 survivors of childhood medulloblastoma that were evaluated in our clinic for long-term endocrine complications, median age at diagnosis 6 years (IQR 10), median follow-up length 31 month (IQR 35). Primary gonadal impairment was defined by any of the following: delayed/arrested puberty, primary/secondary amenorrhea, irregular menses, FSH >25 mIU/ml, low estradiol, low AMH.
Results
Primary gonadal dysfunction was present in 9 patients (29%) and occurred at a median time of 13 months (IQR 40). Our study showed a statistically significant correlation between primary gonadal dysfunction and underweight status ($P = 0.005$) and the age at diagnosis and treatment initiation ($P = 0.038$), respectively. There was no correlation between gonadal impairment and obesity, hypothyroidism, treatment protocol.
Conclusion
Our study demonstrated a high prevalence of primary gonadal insufficiency in survivors of childhood medulloblastoma that usually present with hypothalamic–pituitary damage as a result of radiotherapy. Therefore, we recommend counselling patients with a diagnosis of medulloblastoma with regards to potential damage to the gonads and thereby offer fertility preservation procedures in selected patients.

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EP1337

JOINT1815

A novel de novo mutation of the DHX37 gene in patients with 46,XY DSD

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Introduction
The set of conditions referred to as 46, XY gonadal dysgenesis (GD) is marked by abnormalities in sexual development. As in DHX37, an autosomal gene located on chromosome 1, encodes an RNA helicase that plays a crucial role in essential RNA processes. Mutations in DHX37 are associated with a range of DSD phenotypes, such as atypical genitalia and hormonal disruptions, thus makes it crucial to highlight DHX37 gene importance in sex differentiation and the significance of genetic testing for diagnosing DSD cases.
Objective
To report a novel mutation and to update the literature regarding the manifestation of the case of a De Novo heterozygous variant in DHX37 that causes 46, XY gonadal dysgenesis, which is a rare condition in DSD.
Case Presentation
We report 3 cases in King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, presented with unusual manifestations and subsequently diagnosed with an uncommon disease. Initially presented with ambiguous genitalia, further karyotyping revealed the presence of a positive SRY gene and a 46XY chromosomal pattern.
Conclusion
A total of 3 cases following in pediatric endocrinology clinic having 46 XY Disorder of Sexual Development (DSD). Consequently, a heterozygous missense variant of DHX37 was discovered using whole exome sequencing which was not reported before in our region. One of the cases had a novel Missense variant and we suggest upgrading the variant classification of DHX37:c.1433G>T p.(Gly478Val) to likely pathogenic, according to the evidence found in our patient.
Keywords
DSD, DHX37 gene, 46XY, ambiguous genitalia, Saudi Arabia.
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EP1338

JOINT56

Exercise habits and activity levels in an international sample of people with PCOS

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Background
Polycystic Ovary Syndrome (PCOS), an endocrine disorder affecting 9-18% of reproductive-aged females, can negatively impact health in many ways. Physical activity may be used to promote health in PCOS. This study investigated exercise habits and activity levels in an international sample of people with PCOS.
Methods
Participants were recruited from social media sites from January-February 2024. Eligibility criteria included being $\geq$ 18 years of age and having a prior diagnosis of PCOS. Survey questions included demographics, self-reported height and weight to calculate body mass index (BMI), and the short-form international physical activity questionnaire (IPAQ). Descriptive analyses were performed. Categorical data were analyzed as count and frequency and numerical data as median and standard deviation.
Results
Most participants (n = 101) were between the age of 26-35 (56.4%, n = 57), from North America (69.3%, n = 70), were diagnosed with PCOS more than 10 years ago (39.6%, n = 40), and had a BMI in the obese range (66.3%, n = 63). The median BMI of participants was 33.12 kg/m^2. Approximately 52.5% (n = 53) of respondents reported no days of vigorous activity and 44.6% (n = 45) reported no moderate activity. Median time spent doing vigorous exercise (n = 48) per bout was 60.0$\pm$42.7 minutes, median metabolic equivalents of a task (MET-min/week) minutes of exercise per week of vigorous exercise was 960$\pm$1415.8 and average days of vigorous activity per week was 1.2$\pm$1.7. Median time spent doing moderate exercise (n = 56) per bout was 40.0$\pm$79.0 minutes, median MET-min/week of moderate exercise was 360$\pm$1415.8 and average days of moderate activity per week was 1.5$\pm$1.9. Most participants reported walking regularly with 22.4% (n = 22) walking 1-2 times/week and 66.3% (n = 65) walking 3 or more times/week. Median time spent walking (n = 87) per walking bout was 40.0$\pm$80.5 minutes, median MET-min/week of walking was 693$\pm$1389.3 and average days of walking per week was 4.1$\pm$2.6. Only 14 (13.9%) of the 101 respondents reported no activity each week. Based on total MET-min/week, 35.6% (n = 36) of participants were categorized as achieving low levels of activity each week (including those reporting no activity), 39.6% (n = 40) moderate levels, and 24.8% (n = 25) high levels. Median total MET-min/week was 996$\pm$2414.9.
Conclusions
People with PCOS may predominantly engage in low intensity exercise like walking and less in vigorous and moderate intensity exercise. Most participants did not participate in vigorous intensity exercise which may be most beneficial for PCOS management. Future research should further examine activity levels in people with PCOS and identify optimal exercise intensity for this population.
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EP1339

JOINT530

Ten-year experience of a referral center for transgeneder and gender diverse children and adolescents in north-east of italy

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Background
In 2015, the APEVAGE clinic (Ambulatorio Pediatrico per la Varianza di Genere, Pediatric Clinic for Gender Variance) was established at the Institute for Maternal and Child Health "Burlo Garofolo" in Trieste. It is one of the few Italian centers dedicated to transgender and gender-diverse (TGD) childrens and adolescents. The clinic is run by a multidisciplinary team, including pediatric endocrinologists, psychologists, child psychiatrists, bioethicists, as required by Italian regulations for prescribing and reimbursing triptorelin. Additionally, the clinic provides access to a fertility specialist.
Methods
Data were collected from individuals referred to the clinic from 2015 to 2024.
Results
Eighty individuals have been evaluated, with referrals increasing over time (up to 21 new cases in 2022), showing no differences by assigned sex at birth (P = 0.432). The median age at first visit was 15.3 years (IQR 13.6–16.4; minimum 4.8 years), increasing significantly over the years (P = 0.035). Thirty-one individuals (39%) were diagnosed with gender dysphoria (GD) according to DSM-5 criteria (required by Italian regulations for the prescription and reimbursement of triptorelin). Of these, 14 (45%) were referred directly to adult endocrinologists due to their proximity to 18 years of age. The remaining 15 (48%) started triptorelin at a median age of 16.7 years (IQR 16.0–17.2; minimum 14.5 years), with no significant differences between assigned sex at birth: 8 transitioned to gender-affirming hormone therapy (GAHT) after a median of 6 months (IQR 5–6; minimum 3) on triptorelin in pediatrics, 2 initiated GAHT directly with adult endocrinologists, 5 are still on triptorelin, either due to age below 16 or having started treatment recently. Two individuals recently diagnosed with GD are considering their next steps. Fertility preservation was discussed with 26 individuals with GD (83%), of whom 5 (16%) chose to conserve their gametes (3 assigned female at birth, 2 assigned male at birth).
Conclusions
The APEVAGE clinic provides essential care for TGD minors, reflecting a growing demand for specialized services in Italy. Most individuals with GD began treatment with triptorelin, with many transitioning to GAHT. Fertility preservation discussions were integral, with a subset opting for gamete conservation. These findings highlight the importance of multidisciplinary care and the need for early access to services to support TGD youth effectively.
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EP1340

JOINT3895

Complete androgen insensitivity syndrome (CAIS) management: balancing malignancy risk, hormonal benefits, and patient autonomy

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Objective
This study aims to evaluate the clinical presentation, hormonal profile, genetic characteristics, and management strategies in patients with Complete Androgen Insensitivity Syndrome (CAIS). We explore the necessity of gonadectomy by weighing its benefits—such as reducing malignancy risk—against its drawbacks, including loss of endogenous hormone production and psychological impact. Additionally, we analyze histopathological findings in patients who underwent gonadectomy.
Methods
A retrospective review was conducted on medical records of 16 patients diagnosed with CAIS between 2004 and 2024 at a tertiary care university hospital. All patients, aged between 3 days and 19 years, had a confirmed mutation in the androgen receptor (AR) gene.
Results
Most patients were diagnosed in the prepubertal period due to inguinal hernias. Familial cases were identified in four instances. Hormonal evaluations revealed elevated antimüllerian hormone (AMH) levels in prepubertal patients, reflecting the presence of testicular tissue, and markedly high testosterone levels during puberty. In three cases, gonadal biopsy was performed during inguinal hernia repair due to atypical gonadal appearance inconsistent with the female phenotype. Given the relatively low malignancy risk, 11 patients retained their gonads, while five underwent gonadectomy and subsequently received estrogen replacement therapy. Psychological assessments indicated better well-being in patients who retained their gonads compared to those who underwent early gonadectomy. All patients received regular ultrasound monitoring of the gonads.
Conclusions
Our findings highlight the importance of considering CAIS in females presenting with inguinal hernias or primary amenorrhea. Delaying gonadectomy until after puberty facilitates spontaneous sexual maturation, secondary female characteristic development, and natural growth progression while minimizing psychological distress associated with early surgery. Given the low malignancy risk and benefits of gonadal preservation, a personalized approach that includes delayed or even omitted gonadectomy may be warranted. Furthermore, postponing surgical decisions allows patients to actively participate in their medical management, emphasizing the significance of patient autonomy in healthcare decision-making.
Keywords
Complete androgen insensitivity syndrome, AR gene, primary amenorrhea, inguinal hernia, gonadectomy, gonadal preservation.
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EP1341

JOINT3929

Pregnancy in patients with a history of oncological diagnosis in the childhood-juvenile stage

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Introduction
Advances in cancer treatments have significantly improved the prognosis of pediatric cancers, with 5-year survival rates approaching 75-80%. However, fertility is affected in 8-12% of female survivors. Several studies suggest that cancer survivors have a similar likelihood of maintaining pregnancy beyond 20 weeks, but preterm birth rates are higher, with nearly 9% of babies born to mothers with cancer being premature (<37 weeks) compared to 6% in those without cancer treatment.
Objective
To evaluate the characteristics of pregnancies in patients undergoing oncological treatment in the childhood-juvenile stage.
Population and methods
Patients with a history of oncological disease in the childhood-juvenile stage treated at the Professor Alejandro Posadas National Hospital were studied, evaluated during the period from 11/01/2020 to 10/31/2022 by determining AMH, antral follicle count, and FSH determination. The participants were recruited during the follow-up of the long-term effects of cancer treatment. Descriptive statistics were presented.
Results
71 pubertal and young adult patients were evaluated, 40 had the cancer diagnosis being prepubertal (56.3%) and 31 after having started puberty (43.7%). The median age at the start of cancer treatment was 8.1 years (0.9-17.6) and at the end of treatment was 10.1 years (2.1-20.3). The median of follow-up was 11.8 years (5-25) and at evaluation 19.9 years (10.8-31.9). The diagnosis was ALL in 59.2%, Hodgkin's lymphoma in 11.3%, AML in 7% 53% received only chemotherapy treatment (CMT), 15.5% (CMT + RT); 15.5% (CMT + surgery). All participants who received BMT (8.4%) as part of their treatment had ovarian function and follicular reserve impairment. Thirteen patients had at least one pregnancy prior to evaluation, 3 of which became pregnant twice and 1 had a twin pregnancy. Of the 17 gestational products: 6 were TNB (4 AGA, 2 SGA), 8 PTNB (4 AGA, 4 SGA), 2 spontaneous abortions (9 and 11 weeks), and 1 legal pregnancy interruption (12 weeks). The age of the first pregnancy was 18.8 (15.2-23) years. 18.3% managed to conceive without using assisted reproduction techniques. Two of the patients who subsequently became pregnant had AMH values < 1 ng/ml and none of the patients who achieved pregnancy had FSH values ≥25 IU/L.
Conclusion
In our study, 18.3% of cancer survivors had a recorded pregnancy. Patients would benefit from more frequent obstetric monitoring to reduce the risk of possible gestational complications.
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EP1342

JOINT2691

A rare case of a child with a 46XY disorder of sex development with multiple congenital anomalies

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Introduction
Disorders of sex development (DSDs) are rare conditions involving atypical chromosomal, gonadal, or anatomical sex development. Among these, 46XY DSD is particularly significant due to its association with gonadal dysgenesis and an elevated risk of gonadal malignancy. Early diagnosis and management are critical to prevent complications, but challenges arise when additional congenital anomalies or delayed presentations are present.
Objective
We present a rare case of a child with a 46XY karyotype, presented with a disorder of sex development (DSD). This case highlights the complexity of managing a pediatric patient with 46XY DSD and developmental anomalies.

Case description
A 10 years old female patient, was referred to the endocrinology department for evaluation of short stature. A neurologist first evaluated her at 7–8 months of age following multiple consultations for mild mental retardation, developmental delays, and dysmorphic features, including a flat nose, low-set eyebrows, and small, low-set earlobes. The brain MRI at the time showed no abnormalities. Dysmorphic features and Turner syndrome-like dysembryogenesis symptoms prompted genetic evaluation. Karyotyping revealed a 46XY genotype, confirming the diagnosis of 46XY DSD. Further investigations revealed bifurcated kidneys, left kidney pyelectasis, and anomalies of the coronary vessels. Upon admission to the endocrinology department, a physical examination revealed hypertelorism of the nipples, an enlarged clitoris, a narrow vagina, and hypoplastic internal sex organs. Laboratory investigations demonstrated significantly reduced anti-Müllerian hormone (AMH) levels at 0.012 ng/ml and testosterone at 2.5 ng/dl (both below the normal range). IGF-1 was 68.2 ng/ml (IGF-1 SDS: -2.38), with a bone age of 6 years, reflecting delayed skeletal development. The hCG stimulation test results showed no increase in testosterone levels. Given the high risk of gonadal malignancy associated with 46XY DSD, diagnostic laparoscopy and gonadectomy were planned but postponed due to asymptomatic leukocyturia detected during preoperative testing. The patient now remains under close monitoring and is preparing for the surgery. Considering the presence of gonadal dysgenesis, growth hormone treatment is planned to begin after gonadectomy.
Conclusions
This case underscores the critical importance of timely multidisciplinary evaluation in 46XY DSD patients. Early genetic testing and endocrinological referral are essential for optimizing outcomes and preventing delays in diagnosis and management. This case also highlights the importance of vigilant monitoring for gonadal malignancy, necessitating timely surgical intervention when feasible as there is a high risk of gonadal malignancy.

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EP1343

JOINT911

Polycystic ovary syndrome: what we know about it?

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Introduction and Aim
Approximately 70%of people with PCOS are undiagnosed.
The aim was to study the knowledge of PCOS among medical students.
Materials and Methods
It was a cross-sectional study by questionnaire method. The research involved survey consisting of 15questions, first9 questions were about the definition, symptoms and the diagnostic criteria of PCOS; the second part was about the student's experience and opinion. The sample size was 17 students(14 females and 3males) from international faculty of general medicine (4-5courses) 20-25years old with BMI between 23,5 and 32,5kg/m^2.
Results
In "What is PCOS from your point of view?",58,8%answered that is a disease, the other answered that PCOS is an ultrasound diagnosed symptom. In "What is the correct definition for PCOS?" there were significant debate about the convenient definition:29,4%(5students) chose that it is reproductive disorder, 35,3 ($n = 6$) answered it's a metabolic disorder, and the rest chose none of the above choices. In "What is the most affected age?" most of the students answered18-38. Coming "How can you tell ovulation had happened?" 47,1%(8students) answered that by hormonal changes and ultrasound, 29,4%($n = 5$) chose by mood swings and feelings, however the rest confirmed that test is the one to know if ovulation had happened. There was similar answer in "Gallwey Score is used to test?" most of them had confirmed that they had never heard about it. Majority had answered that dysmenorrhea is the needed criteria to diagnose PCOS, only 17,7%(3students) chose that infertility and psychosexual dysfunction is the needed one. It was a popular opinion the female should be treated from PCOS despite of her planning pregnancy, so 64,7% (11students) chose that any female who has dysmenorrhea should be suspected with PCOS. Question10 was only for females, if they use any application to check their menstrual cycle, however in answering question 4about the normal cycle length all had the same answer21-35. Most the students confirmed that the female should check her hormone levels every3 months. Apparently, most of them think that PCOD(disorder) is different from PCOS(syndrome). There was difference in opinions about who should treat PCOS:58,8%($n = 10$)chose gynecologist,23,5($n = 4$) added their own opinion and the others chose the endocrinologist.
Conclusion
The most of the female students use menstrual calendar, however they didn't know what is the normal cycle length. Although every one of the medical students had different point of view and thoughts about the best treatment for PCOS, but all had confirmed that PCOS is a huge misunderstanding topic.

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EP1344

JOINT2104

Diabetic turner syndrome patients – conclusions from the bulgarian diabetes registry

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Background
The Bulgarian healthcare system requires individual compulsory health insurance administered by the National Health Insurance Fund (NHIF), operating with the health data of 2.75 million Bulgarian women. The Bulgarian Diabetes Register (BDR) collected all pseudonymized NHIF electronic health records of patients with diabetes mellitus type 1 or type 2 (T1DM or T2DM), with the latest dataset being from 2018 (1). BDR includes outpatient NHIF records from all primary care providers and specialists in secondary care nationwide for every visit of a patient suffering from DM.
Methods
The available data about diabetic patients with Turner syndrome (TS) (ICD-10 Q96, ORPHA:881) from the BDR were extracted and analyzed. The collected information included age, type of diabetes, diabetes complications, treatment, concomitant diseases, and a number of medical consultations yearly.
Results
A total of 19 diabetic patients (median 40 [13-69] years) with TS have been found in the BDR database. 84.2% of patients were with DMT2, while 15.8% were with DMT1. Diabetic neuropathy was found in 7 (36.8%) of the patients. The TS patients showed significant co-morbidity and a high number of consultations with general practitioners and/or clinical specialists yearly - an average of 14 (2-29) in 2018.
Conclusions
The lower-than-expected prevalence of diabetic TS patients in the BDR might result from TS or DM underdiagnosis. Diabetic TS patients have a high prevalence of complications and co-morbidities and require high healthcare resources. More efforts should be made by the public health system in the country to ensure the proper diagnosis of TS. Furthermore, regular estimation of carbohydrate metabolism in TS patients is paramount for the early diagnosis of DM in the affected women and the prevention of complications and high medical costs.
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EP1345

JOINT1135

Etiologic distribution of adult-onset male hypogonadism in the modern era: retrospective cohort study from finnish tertiary center

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Although signs and symptoms associated with male hypogonadism are commonly encountered in endocrinology outpatient clinics, their clinical implications are not well characterized. In present study, we aimed to describe the etiologic distribution, as well as the anthropometric and biochemical features of adult-onset male hypogonadism, using electronic health record data of individuals referred for an endocrine evaluation between 2020-2022 due to low testosterone and hypogonadal symptoms. Of the total of 119 individuals referred, 88 patients who had low testosterone (*i.e.*, less than 10 nmol/l)on repeated measurements constituted the study population. Patients were grouped into four categories according to the etiology of hypogonadism: primary hypogonadism ($n=13$), morbid obesity-associated secondary hypogonadism (MOSH) ($n=49$), prior anabolic-androgenic steroid use (AAS) ($n=5$), and hypogonadotropic hypogonadism (HGHG) ($n=21$). The latter group included patients with a specific disease of the pituitary gland ($n=6$), as well as patients with prior and/or current opioid/glucocorticoid use ($n=8$), patients with obstructive sleep apnea without morbid obesity or other sleep disorders ($n=3$) and patients with miscellaneous etiology of HGHG ($n=4$). The median serum testosterone levels were 6.7 [5.0-9.4], 7.3 [5.9-8.6], 6.3 [2.8-8.0] and 6.9 [3.9-8.2] nmol/lin primary, MOSH, AAS and HGHG groups, respectively (NS in Kruskal-Wallis test) and symptoms distribution (NS in chi-square test) were comparable among the groups whereas luteinizing hormone (LH) levels were higher in patients with primary hypogonadism (10.8 [5.0-21.2] U/l)than other groups (4.1 [2.2-5.4], 1.3 [0.0-2.5] and 2.9 [0.3-4.5] U/lin MOSH, AAS and HGHG groups, respectively, $P < 0.001$). Prevalence of hypertension and obstructive sleep apnea (both $P < 0.01$) were higher in MOSH compared to the rest of the groups although glucose and lipid profiles were comparable among the groups. Surprisingly, serum testosterone levels in the MOSH group were inversely correlated with gonadotropin levels (LH: $r=-0.42$, $P<0.01$; FSH: $r=-0.41$, $P<0.01$); this was not observed in HGHG group. In summary, morbid obesity is the leading cause of adult-onset male hypogonadism whereas cases due to specific conditions affecting HPT axis, such as prolactinoma or testicular failure, are rare. Although negative feedback of testosterone on gonadotropins is preserved in hypogonadal men with morbid obesity, gonadotropin secretion is insufficient for maintaining adequate testosterone levels. This is in contrast with hypogonadotropic hypogonadism, which is characterized by a total disruption of HPT axis regulation.

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EP1346

JOINT620

Obstetrical outcomes after oocyte donation in turner syndrome: retrospective study among patients with primary ovarian insufficiency

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Turner syndrome is a chromosomic disease affecting 1 fetus in 2500. In more than 95% of cases, these patients have primary ovarian insufficiency (POI), consisting of premature cessation of ovarian function before the age of 40. When a pregnancy is expected, usually, *in vitro* fertilization (IVF) with oocyte donation is necessary. Current data suggest increased obstetric and perinatal morbidity for these pregnancies, such as hypertensive disorders. A retrospective monocentric cohort study was conducted in the reproduction medicine ward of the University Hospital Center of Lyon. The study population included all patients aged 18 to 40 who had received at least one embryo transfer after IVF with oocyte donation, in POI context, with or without Turner syndrome, from January 1, 2007 to December 31, 2023. 97 patients were included. Live birth rate, obstetrical and perinatal outcomes were compared between the 2 populations. Embryo transfer success (live birth) was conducted by adjusted logistic regression. Several odds-ratio were estimated, depending on the rank of transfer attempt. A purely descriptive analysis of obstetrical and perinatal data was conducted. 29% of the embryo transfers resulted in a live birth among the Turner patients, and 27% among the other POI patients. A statistically significant decrease of live birth rate in the first attempt among the Turner was seen, with an odds ratio at 0,09 (0,01; 0,64) and a p-value at 0,017. No statistical difference was noted for the third transfer and beyond, with a p-value at 0,095. The obstetrical and perinatal morbidity was high, with 70% of cesareans, 18,7% of premature births and 26% of non-cephalic fetal presentations for Turner patients. The retrospective nature of the study is responsible of selection bias. A more precise analysis of the obstetric outcomes would require distinguishing single-fetal pregnancies from multiple pregnancies, having their own morbidity. Live birth rates in our study are high, in line with lower miscarriage rates than usually found in the literature. The optimization of hormonal replacement therapy prior to ART course, and of the artificial cycle during embryo transfer seem to be plausible explanations of the better results. The obstetrical and perinatal morbidity is high, as expected.

Key words

Turner syndrome, primary ovarian insufficiency, oocyte donation, obstetrical outcomes.

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EP1347

JOINT1426

Case report of a newborn child with dsd due to 46,XX/46,XY chimerism

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Background

We present the case of a newborn child with prenatal diagnosis of 46,XY karyotype in non-invasive prenatal testing (NIPT) in two tests in combination with a female internal and external genital phenotype in prenatal ultrasound.

Case Presentation

The child was born at term with a birth weight of 3575g and a length of 50cm. External genitalia were unremarkably female without virilisation or malformations. On postnatal ultrasound, the internal genitalia showed a uterus. However, gonads could not be identified with certainty. The postnatal karyotype from blood lymphocytes showed a 46,XX(2)/46,XY(18) chimerism. A second postnatal karyotype from oral mucosa showed a 46,XY karyotype in all cells analyzed. A plasma steroid analysis obtained at the age of 3 months during the so-called 'mini puberty', analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS), showed testosterone and estradiol levels below the lower limit of detection ($<$ 0.02 nmol/l[reference: 0.1-0.7) and $<$5 pmol/l[10-193], respectively). However, laboratory analysis showed significantly elevated Anti-Müllerian hormone (AMH) and Inhibin B levels for female gender (21 ng/ml [0.08-8.9] and 210 pg/ml [4.8-83], respectively), which could be interpreted as confirmation of the presence of Sertoli cells and thus the presence of male gonadal differentiation.

Conclusions

In a newborn child with undoubtedly female external genitalia, karyotype from peripheral blood showed a chromosomal 46,XX/46,XY chimerism, whereas the karyotype from oral mucosa did not. When interpreting this, we must take into account that cell mosaics may have a different expression in different tissues. Elevated levels of AMH and Inhibin B indicate testicular gonadal differentiation. However, this is currently in contradiction with the presence of a uterus on ultrasound. The absence of testosterone is consistent with female external genital differentiation. As estradiol is not detectable by a highly sensitive LC-MS/MS method, we have no information on possible ovarian differentiation of the gonads. As only 2 out of 20 cells in the peripheral blood showed the 46,XX constellation, we also initiated array-CGH analysis and exome sequencing. Finally, a minimally invasive gonadal biopsy should be performed to assess the presence of ovotestes and the risk of gonadal tumor development. Medical care will be provided throughout childhood and adolescence, including hormone therapy if necessary and counselling on gender identity issues.

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EP1348

JOINT75

RAB5B Gene expression and its association with insulin resistance in women with PCOS

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Polycystic Ovary Syndrome (PCOS) is a complex endocrine, reproductive, and metabolic disorder accompanied by hyperandrogenism and hyperinsulinemia mediated insulin resistance, but the precise molecular mechanism remains unclear. The study aimed to explore the potential link between RAB5B gene expressions and insulin resistant among women with PCOS.A total of age matched 270 subjects were enrolled in this study which included 135 PCOS women and 135 apparently healthy controls. The study participants were subjected to detailed medical history, clinical examination and physical examination. All subjects were further evaluated for biochemical, hormonal and inflammatory. Expression levels of *RAB5B* gene were analyzed using gene-specific primers and the SYBR® Green PCR Kit (Qiagen, Germany) and their qPCR reaction mix, according to the manufacturer's guidelines. Student t-test and ANOVA were used to evaluate the differences in the means of various parameters. The HOMA-IR (2.28 ± 1.4 *vs.* 1.36± 0.73) was significantly elevated among women with PCOS than controls ($p<0.001$). We also found that the QUICKI (0.35±0.04 *vs.* 0.37±0.04), MATSUDA (12.59±4.71 *vs.* 15.47± 4.33) and FGIR (11.56±7.06 *vs.* 14.32±8.66) were higher in controls than women with PCOS ($P<0.001$). Our findings revealed that women with PCOS exhibited significantly higher RAB5B mRNA levels compared to apparently healthy controls. This study highlights a potential link between RAB5B gene expression and insulin resistance, particularly in relation to insulin indices, in women with PCOS.

Keywords
Polycystic ovary syndrome, Insulin Resistance, HOMA-IR.
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EP1349

JOINT1419

The role of triglyceride-glucose index in women with polycystic ovary syndrome: a systematic review and meta-analysis

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Background
Polycystic ovary syndrome (PCOS) is one of the common disorders affecting women of reproductive age. Insulin resistance (IR) plays a pivotal role in its pathogenesis, leading to metabolic complications such as hyperglycemia, dyslipidemia, and increased cardiovascular risk. The triglyceride-glucose (TyG) index, a surrogate marker of IR, has gained attention for its simplicity and diagnostic accuracy across metabolic disorders. This study aims to comprehensively assess the role of the TyG index in PCOS and its utility as a diagnostic and prognostic biomarker.
Methods
A systematic review and meta-analysis were conducted following PRISMA guidelines. PubMed, Scopus, Embase, and Web of Science were searched up to December 2024. Observational studies reporting TyG indices in PCOS and control groups were included. Subgroup and meta-regression analyses explored sources of heterogeneity. Sensitivity analysis and publication bias assessments ensured robustness.
Results
Fifteen studies (7,175 participants) were analyzed. The TyG index was significantly higher in women with PCOS compared to controls (SMD 0.34, 95% CI 0.14–0.54, $I^2 = 70.9\%$). Subgroup analysis revealed a significant association in Chinese studies (SMD 0.42, 95% CI 0.35–0.49, $I^2 = 0\%$) and cross-sectional studies (SMD 0.45, 95% CI 0.32–0.57, $I^2 = 3.2\%$). The TyG index exhibited excellent diagnostic accuracy for distinguishing PCOS from controls (AUC 0.86, 95% CI 0.80–0.94, $I^2 = 80.8\%$). Similarly, the TyG-BMI index showed a significant association with PCOS (SMD 0.34, 95% CI 0.10–0.57, $I^2 = 0\%$) and excellent diagnostic performance (AUC 0.81, 95% CI 0.75–0.88, $I^2 = 0\%$). Meta-regression analysis identified no significant impact of age, BMI, or lipid profiles on heterogeneity.
Conclusion
This meta-analysis uniquely highlights the triglyceride-glucose index as a robust and clinically significant marker for PCOS women. While the homeostatic model assessment of insulin resistance (HOMA-IR) is widely used, its reliance on insulin measurements limits its practicality in routine clinical settings. In contrast, the TyG index, derived from simple triglyceride and fasting glucose measurements, provides a more accessible and cost-effective alternative, facilitating early screening for insulin resistance, particularly for identifying metabolic risks in the PCOS population. Given that PCOS encompasses a heterogeneous spectrum of metabolic, hormonal, and ovarian dysfunctions rather than a single uniform disease, future research should focus on stratifying the TyG index's association with insulin resistance across different PCOS phenotypes. Establishing phenotype-specific thresholds and refining its predictive capabilities for long-term cardiometabolic outcomes will be crucial in optimizing risk assessment and personalized management in this heterogeneous population.

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EP1350

JOINT850

Bone mineral density and trabecular bone score in adolescents and young women with primary ovarian insufficiency

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Background
Primary Ovarian Insufficiency (POI) is associated with osteoporosis and an increased risk of fractures. However, scarce data exists on the trabecular bone score (TBS) in adolescents with POI. We aimed to evaluate bone mineral density (BMD) and TBS in adolescents and young adults with POI.
Methods
This retrospective study included girls aged 10–24 years with POI who underwent at least one dual-energy X-ray absorptiometry (DXA) scan at our institution between 2020 and 2025. POI was defined as irregular menses and follicle-stimulating hormone (FSH) levels >20 IU/lon two occasions at least one month apart. Clinical data, including hormonal levels and POI etiology, were extracted from medical records. Measurements were compared between girls with Turner syndrome (TS) and those without Turner syndrome (non-TS).
Results
Twenty-four girls underwent DXA scans at a mean age of 17.7±2.2 years (range 15.3–21.7). POI was diagnosed at a mean age of 14.8±3.3 years, earlier in TS (11.7±2.6) than in non-TS girls (16.4±2.5). The mean FSH level at diagnosis was 75.3±41.4 IU/l,lower in TS (48.3±23.2) than in non-TS girls (88.7 ± 42.5, $p=0.01$). Most girls presented with amenorrhea (96%, $n=23$): among them, 52% ($n=12$) had primary amenorrhea, 48% ($n=11$) had secondary amenorrhea, and one was diagnosed through fertility counselling. The mean L1-L4 bone mineral density (BMD) Z-score was -1.55±1.24, the total body less skull BMD Z-score was -0.62±0.92, and the L1-L4 TBS Z-score was -0.87±0.78. In three patients with repeated DXA scans, TBS Z-scores increased from 1.37±0.13 to 1.44± 0.07 after an average of 1.7±0.7 years of hormone replacement therapy (HRT). TS girls had higher mean L1-L4 BMD Z-scores (-0.26±1.25 vs. -2.08±0.76, $p=0.007$), total body less skull BMD Z-scores (0.12±0.56 vs. -0.90±0.75, $p=0.01$), and TBS Z-scores (-0.17±0.91 vs. -1.15±0.51, $p=0.03$) compared to non-TS girls. TS girls also had a longer duration of HRT before DXA (3.10±3.34 vs. 0.38±1.42 years, $p=0.07$). The mean age at DXA was similar between TS (17.89±2.75) and non-TS girls (17.61±1.91).
Conclusions
Girls with POI exhibited low L1-L4 BMD and TBS Z-scores, which improved with HRT. TS girls had significantly better bone health metrics than non-TS girls, potentially due to a longer duration of HRT. These findings underscore the critical need for early diagnosis and intervention to optimize bone health in this population.

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EP1351

JOINT2964

Transitioning care in hypogonadism: a retrospective analysis

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Introduction
The transition from pediatric to adult endocrinology care is a critical period for patients with hypogonadism. Effective management during this phase is essential to ensure continuity of care, adherence to treatment, and proper management of associated concerns such as fertility and bone health. This study aims to evaluate the characteristics and clinical outcomes of patients with hypogonadism undergoing transition from pediatric to adult care.
Methods
A retrospective analysis was conducted on all patients who transitioned from pediatric to adult endocrinology care between January 2022 and January 2025, following the establishment of the sexual medicine transition clinic at our centre. Epidemiological and clinical data were collected.
Results
A total of twenty-two individuals ($n = 22$) transitioned to adult endocrinology care over the 3-year observation period, with a median age at transition of 18.9 years (interquartile range (IQR) 18.5-19.7). The cohort comprised 59% females ($n = 13$). The primary diagnosis included Turner syndrome ($n = 7$, 32%), gonadal dysgenesis ($n = 5$, 23%), Klinefelter syndrome ($n = 4$, 18%), Kallmann syndrome ($n = 2$, 9%), androgen insensitivity syndrome ($n = 1$, 4%), mosaic trisomy 22 ($n = 1$, 4%), Triple X syndrome ($n = 1$, 4%), and a single case of hypergonadotropic hypogonadism of unknown etiology. Hypogonadism was diagnosed in 91% ($n = 20$) of patients, with hypergonadotropic hypogonadism being the predominant subtype, accounting for 82% ($n = 18$). Hormone replacement therapy was initiated in 86% ($n = 19$) of patients, with a median age at initiation of 14.1 years (IQR 12.0-15.5). Short stature was observed in 36% ($n = 8$), of whom six received growth hormone therapy, initiated at a median age of 6.8 years (IQR 3.1-10.6) and continued for a median duration of 7.3 years (IQR 5.8-12.4). A multidisciplinary team was involved in 82% of cases ($n = 18$), and no patients were lost to follow-up during the transition period. Bone mineral density assessment was performed in 73% ($n = 16$), while fertility-related discussions were documented in 45% ($n = 10$).
Discussion
This study highlights the diverse etiologies and complexities of hypogonadism in transition care. Despite high rates of hormone therapy initiation and multidisciplinary involvement, gaps remain in fertility discussions and bone health monitoring. Optimizing transition pathways with standardized protocols can enhance continuity of care and patient outcomes. Future efforts should focus on addressing these gaps and exploring patient-reported outcomes to further improve the quality of care for this population.

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EP1352

JOINT2888

Psychosomatic outcomes in adulthood among north african patients with testicular DSD

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Introduction
The long-term outcomes of adults living with disorders of sex development (DSD) remain poorly studied. This study aims to characterize the somatic and psychosocial features of an adult North African population with testicular DSD.
Methods
This was a cross-sectional descriptive study conducted at the DSD reference center in Sfax, Tunisia, including 30 adult patients ($\geq$18 years old) of diverse North African origins diagnosed with testicular DSD. The study assessed sexual development, cardiometabolic profile, bone mineralization, and psychosocial outcomes.
Results
The mean patient age was 23.68 ± 8.8 years. The most common diagnoses were steroidogenesis defects (38%) and gonadal dysgenesis (32%). The average follow-up duration was 8.2 ± 4.7 years. All patients received hormone replacement therapy aligned with their assigned civil gender, resulting in appropriate sexual development (Tanner stage 4.15 ± 1.14). Three cases of de novo hypertension and hypertriglyceridemia were identified. Glucose intolerance tests were negative among all patients. Bone demineralization was found in 9 out of 17 evaluated patients, predominantly and most severely among those with complete androgen insensitivity syndrome. All patients identified as cisgender with a binary heterosexual orientation. Access to mariage and sexual activity was reported only in patients over 30 years old without genital anomalies. The unemployment rate was high (70%).
Discussion
Genetic anomalies and hormone therapy contribute to an unfavorable metabolic and bone profile in testicular DSD. Contrary to literature reports, no cases of gender identity disorders or homosexuality were observed, likely due to socioreligious factors. Access to marital and sexual life was delayed and correlated with the absence of genital anomalies, reflecting feelings of shame and barriers to reproduction. Social integration also appeared to be impaired. These findings highlight the need for larger longitudinal studies for further validation.

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EP1353

JOINT1967

The effect of gender-affirming hormone therapy on the occurrence of axial spondyloarthritis in people with gender dysphoria

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Objective
Axial spondyloarthritis (axSpA), especially radiographic axSpA, is more frequently observed in males, and the role of testosterone in the etiology remains controversial. Our study aims to determine the prevalence of axSpA in people with gender dysphoria (GD) undergoing gender- affirming hormone therapy (GAHT) and to assess whether testosterone therapy increases disease prevalence in female-to-male (FtM) GD.
Materials and Methods
Using a structured questionnaire prepared by the rheumatology department, the medical histories of people receiving GAHT were collected in face-to-face or telephone interviews. HLA-B27 and C-reactive protein (CRP) levels were determined in participants who had been suffering from chronic back pain for more than three months and whose symptoms started before the age of 45, in line with the entrance criteria of The Assessment of SpondyloArthritis International Society (ASAS) classification for axSpA. X-rays of the sacroiliac joints and magnetic resonance imaging (MRI) were also performed.
Results
In the first step, a total of 280 individuals with GD were approached, and 250 (61 male-to female (MtF), 189 FtM) participated in the study. Inflammatory back pain was identified in 6% of participants with GD (13 FtM, 2 MtF). All patients were HLA-B27 negative. The sacroiliac joint radiographs of three FtM GD individuals showed findings suggestive of axSpA, but they did not meet the modified New York criteria for radiographic axSpA. Three FtM GD individuals with suspicious radiologic findings had chronic structural lesions suggestive of chronic sacroiliitis on sacroiliac MRI. In the second step, we also examined 41 FtM GD individuals for chronic back pain before starting GAHT. At baseline, 10 subjects reported chronic back pain, of which only 2 had inflammatory back pain, while the remaining 8 had mechanical back pain. After one year of GAHT only one individual continued to suffer from chronic back pain. Remarkably, this person was one of the two individuals who had reported inflammatory back pain before starting GAHT.
Conclusion
According to the ASAS criteria, the prevalence of inflammatory back pain in this cohort was 6%, similar to the general population. Although none of the patients met the modified New York criteria for radiographic axSpA, three FtM GD had radiographic findings suggestive of sacroiliitis. early-stage axSpA. Although

there is ongoing debate about whether non-radiographic axSpA is an early stage of radiographic axSpA or whether these 2 entities are mutually exclusive, longitudinal follow-up of these individuals to monitor disease progression is warranted.

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EP1355

JOINT3737

Evaluation of test results according to body mass index of patients who had a gnrh stimulation test with a preliminary diagnosis of precocious puberty

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Introduction
The appearance of secondary sex characteristics 2-2.5 standard deviation score (SDS) earlier than the expected age is defined as precocious puberty. Childhood obesity has emerged as an important public health problem in recent years. GnRH stimulation test is considered the gold standard in the diagnosis of precocious puberty. Our study aims to determine possible differences in responses according to body mass index in female patients who underwent GnRH stimulation test with the preliminary diagnosis of precocious puberty.
Materials and Methods
In this retrospective study, female patients aged 6-9.5 years who applied to tertiary Pediatric Endocrinology clinic between September 2022 and December 2023 and underwent GnRH stimulation test with the preliminary diagnosis of precocious puberty were included. Patients were grouped according to their BMI SDS values as normal weight (BMI SDS between -1.5 and +1.5), overweight (BMI SDS between +1.5 and +2) and obese (BMI SDS > +2). Detailed anamnesis of the patients was taken and their demographic data, anthropometric measurements, laboratory results and radiological imaging were evaluated.
Results
Among the 241 girls included in the study, 147 (60.99%) were of normal weight, 46 (19.08%) were overweight, and 48 (19.91%) were obese. The mean chronological age of all cases was 7.8 $\pm$ 0.66 years, the mean bone age was 9.4 $\pm$ 1.2 years, and the mean height age was 8.7 $\pm$ 1.28 years. When comparing the three groups, no significant difference was found in chronological ages. However, there was a difference in bone ages and height ages ($P < 0.05$). While there was no significant difference in basal LH and E2 levels, a difference was found in basal FSH levels ($P < 0.05$). Differences were also observed in peak LH and peak FSH responses ($P < 0.05$).
Discussion
In our study, the test results of patients who underwent GnRH stimulation test with the preliminary diagnosis of precocious puberty were evaluated according to their BMI SDS, and a difference was detected between the groups in peak LH and peak FSH responses. The low peak LH responses in overweight and obese patients as a result of the GnRH stimulation test performed when basal LH levels are not sufficient to make a diagnosis indicate that it may be more appropriate to evaluate the results of the GnRH stimulation test, which is considered the gold standard test in terms of pre-puberty, together with other test results in these patients.

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EP1356

JOINT1019

Multidisciplinary team (MDT) clinics for children and young people with differences in sex development (DSD): evaluation of clinical outcomes and patient/caregivers' experiences

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A multidisciplinary team (MDT) approach is recommended to provide holistic patient-centred care for those affected by Differences in Sex Development (DSD). We evaluated regional DSD services in a large Children's hospital with the aim to investigate 1) clinical outcomes for patients, and 2) patients/caregivers' experiences of the service.
Methods
Electronic records of all patients who attended the DSD MDT clinics over a 5-year period (2019-2023) were reviewed retrospectively for clinical outcomes. Feedback using questionnaires (7 items on 5-point Likert-scale) and semi-qualitative survey (4 items) completed by a subset of patients/caregivers attending 3 clinics during 2024 were analysed.
Results
Fifty-eight patients were reviewed at 98 appointments. Median age at the start of this study was 4.4 years (36 days-17.9 years). Karyotype was 46XY in 30 (51.7%), 46XX in 23 (39.7%) and other in 5 (8.6%) patients. Pathophysiology categorization suggested defects in gonad differentiation in 22 (38%) [19 (33%) gonadal dysgenesis, Mullerian ducts in 3 (5%)], steroid biosynthesis in 22 (38%), androgen action in 11 (19%) and unknown in 3 (5%). A definitive diagnosis was made in the DSD clinic in 33/58 (56.9%). The commonest diagnosis was 21 hydroxylase deficiency congenital adrenal hyperplasia ($n = 15$, 25.9%). Before attending the clinic, gender assigned was male for 21 (36.2 =%) and female for 37 (63.8%) patients. Reconstructive genital surgery had been done in 21/58 (36.2%) patients before they attended the clinic. Specialists in endocrinology, urology, clinical psychology, clinical genetics, nursing and biochemistry were present at each clinic. MDT discussions with patients/caregivers led to complex decisions about gender reassignment from female to male ($n = 3$), prophylactic gonadectomy owing to risk of malignancy (8/19, 42.1% patients with gonadal dysgenesis; 4/9, 44% with androgen insensitivity) and external genital surgery ($n = 10$, 17.2%). All 9 patients/caregivers who attended 3 clinics completed questionnaires; 100% were 'very satisfied' with the clinic and found the MDT 'very helpful', 89% 'felt comfortable asking questions' and over 75% 'understood everything about their complex condition'. Semi-qualitative review suggested that the clinic was meeting the needs of patients/caregivers, and no changes were requested.
Discussion
This MDT clinic contributed to shared decisions for complex interventions, including gender reassignment, prophylactic gonadectomy and reconstructive genital surgery, supported by positive feedback from patients/caregivers. From the feedback responses, the MDT recognizes a need to give patients/caregivers more opportunities and encouragement so that they feel completely comfortable asking questions, and which may contribute to enhancing their understanding about their complex condition.

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EP1357

JOINT2048

Thyroid status of women in preparation for *in vitro* fertilization

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Introduction
Hypothyroidism affects the reproductive function of the female body, leading to infertility. Prolonged disturbance of hormonal status with infertility requires the use of *in vitro* fertilization (IVF) programmes.
Purpose
To evaluate the thyroid gland status of women for preparation for the IVF programme.
Material and Methods
The patients are divided into the following groups: 32 patients with history of female infertility with hypothyroidism conceived by IVF- first group, 22 patients with history of female infertility with hypothyroidism conceived naturally - second group. Out of 54 patients, 37 (68.5%) had primary and 17 (31.5%) had secondary infertility.

Results
Common complaints in women of both groups were ectodermal disorders like dry skin, hair loss, brittle nails which occurred in half of all patients. Hyperprolactinaemia was significantly more frequent in women of the first group (31.3%), increased blood pressure was observed in 5 (16.1%) patients of the first group and in 1 (4.5%) of the second group. On palpation of the thyroid gland and examination of imaging techniques, particularly ultrasound, the following thyroid changes were found. Nodular goitre was found in 9 (16.7%) patients. One patient underwent fine-needle aspiration biopsy (FNAB) of the nodule due to its exceeding its size by more than 10 mm and to confirm its benignity. Hypoplasia of the thyroid was observed in 7 patients, diffuse goitre of the first degree in 21 (38.9%) women. Autoimmune thyroiditis (AIT) with confirmation of hormonal studies was found in 25 (46.3%) patients. To make a final diagnosis, the hormonal profile of the women was investigated, which showed the following results. In women of the first group thyroid hormone (TSH) was higher than normal and hypothyroid state lasted longer, due to this there was an increase in prolactin levels in the blood. The increase of luteinizing and follicle stimulating hormones in the same group indicated pronounced menstrual cycle disorders in the form of menorrhagia in 48%, oligomenorrhoea in 14.8% and increase of anovulatory cycles in 54.8% of cases. Decrease in the number of antral follicles was observed in 40.7% of cases, which is one of the indicators of reduced ovarian reserve.
Conclusion
In conditions of thyroid hormone imbalance, also higher levels of luteinising and follicle stimulating hormones and low levels of progesterone in relation to the second group, manifested more often by menorrhagia and oligomenorrhoea, decreased ovarian reserve necessitates correction of hormonal status for IVF efficiency.

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EP1358

JOINT7

Time is testicular: early cryptorchidism care to avert tumors

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Background
Cryptorchidism, or undescended testis, is a prevalent anomaly of the male genitourinary system and a well-established risk factor for testicular tumors. This case highlights the critical importance of early intervention in cryptorchidism to prevent malignancy.
Case Presentation
We report the case of a 54-year-old male with neglected bilateral cryptorchidism since childhood, presenting with abdominal pain and distension over the past three years. Imaging revealed intra-abdominal masses, leading to surgical resection, which confirmed bilateral testicular tumors. The patient underwent 25 sessions of chemotherapy with positive outcomes.
Investigations
Routine blood tests were normal. Imaging studies, including ultrasonography and contrast-enhanced CT, identified large homogeneous masses in the bilateral lumbar regions. The serum α fetoprotein (AFP) and β human chorionic gonadotropin (HCG) levels were normal, while lactate dehydrogenase (LDH) was elevated.
Outcome and Follow-up
The patient showed a favorable response to chemotherapy and remains under regular follow-up.
Discussion
Testicular tumors, predominantly germ cell tumors (GCTs), are the most common malignancies in men aged 20–40 years, with cryptorchidism increasing the risk by 4–6 times. Early orchidopexy significantly reduces malignancy risk by relocating the testis to the scrotum, thus promoting normal germ cell development. This case underscores the rarity of bilateral synchronous abdominal GCTs in cryptorchidism and highlights the necessity of early detection and intervention.
Conclusion
Prompt management of cryptorchidism is crucial in preventing malignant transformation and ensuring better patient outcomes.

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EP1359

JOINT443

Anti mullerian trends after aGnRH initiation in trans boys adolescents

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Introduction
People identifying as transgender continues to increase year after year, and with it, the healthcare services offered to this community. In 2016 our health system established the care program for this population. Its purpose was to standardize healthcare for transgender minors based on the most reliable and solid information currently available. We know trangender medicine could have an impact on health. The analogues of gonadotropin-releasing hormone (aGnRH) are a commonly used treatment to achieve puberty suppression in adolescents who experience gender dysphoria and desire sex reassignment. However, the effect on fertility that their use may have on transgender adolescents remains unknown.
Objective
The aim is to analyze how gonadotropin-releasing hormone analogues impact on the fertility of transgender adolescents undergoing pubertal suppression.
Study Methodology
The study included transgender male adolescents who attended the Gender Diversity unit at Puerta del Mar University Hospital from January 2015 to December 2024 Who had initiated pubertal suppression (PS) with aGnRH. We register Anti-Müllerian Hormone (AMH) available every 6 months after aGnRH initiation during 18 months. Non-parametric statistical tests were performed.
Results
We recruited 38 adolescents. Median current age 15.4 (14.8-16.3 years old. Median PS age was 13.4 (12.2-14.5) years old. 73%has tanner stage 5. We observed no significant changes in AMH in first 18 months after aGnRH initiation (p-value: 0.347). No differences in AMH were observed when comparing PS in tanner 2-3 vs PS in tanner 4-5 (p-value: 0.431).
Conclusions
In our cohort we could establish no relevant changes in AMH after aGnRH initiation. Studies with larger participants could be performed to better support these results.

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EP1360

JOINT2933

Association between folic acid levels and physiological and developmental indicators in children with developmental delays

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This study investigates the relationship between folic acid levels and various physiological and developmental indicators in children with developmental delays. Folic acid plays a crucial role in human growth and development, particularly in neurological development and metabolism. A total of 110 children with developmental delays were selected for the study, and a range of physiological indicators were collected, including gestational age, birth weight, height, weight, BMI, thyroid function, folic acid, vitamin D, lactate, homocysteine, and free fatty acids. Developmental assessment was conducted using the Gesell Developmental Schedule to evaluate social adaptability, gross motor skills, fine motor skills, language ability, and personal-social competence. The findings reveal that children with folic acid levels above 24 ng/ml scored significantly higher in vitamin D, lactate levels, and the five domains of the Gesell Developmental Schedule (social adaptability, gross motor skills, fine motor skills, language, and personal-social competence) compared to those with folic acid levels below 24 ng/ml. Additionally, children with higher folic acid levels had significantly lower birth weight and homocysteine levels than those with lower folic acid levels, with statistically significant differences. However, no significant differences were observed between the two groups in terms of BMI, gender, age, and thyroid hormone levels. The results suggest that higher folic acid levels may be positively associated with neurological development and metabolic health in children with developmental delays, highlighting the potential importance of folic acid in child growth and development. Future research should explore the long-term effects of folic acid supplementation in children with developmental delays and the underlying mechanisms at play.
Keywords
Developmental delay, Gesell Developmental Schedules, Folic acid.

Disclosure of interest
The authors have not any conflict of interest or competing interest to declare.
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EP1361

JOINT1278

Yoga intervention effects on metabolic profiles in polycystic ovary syndrome: plasma metabolomics analysis

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Introduction
Polycystic ovarian syndrome (PCOS) is a complex endocrinopathy characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. It affects 5–20% of women of reproductive age worldwide. Its pathogenesis involves oxidative stress (OS), mitochondrial dysfunction, and inflammation. It increases risk for dyslipidemia, fatty liver disease, cardiovascular diseases (CVD), and type 2 diabetes (T2DM). Pharmacological treatments often yield inconsistent results with side effects, highlighting the need for alternative approaches. PCOS is a lifestyle disease, that can be best managed by lifestyle modification like Yoga.
Objectives
To explore the effects of Yoga on metabolic profile in women with PCOS.
Methods
This study involved 80 women (40 diagnosed with PCOS, 40 age and BMI matched healthy control women). PCOS women underwent 12-week Yoga practice (5 days/week, 1 hour/day) including physical postures (Asanas), regulated breathing (Pranayama), and meditation (Dhayana) under a trained therapist. Clinical characteristics and laboratory biochemical data were recorded, followed by a metabolome analysis using LCMS. In addition, the depression scale (BDI-II) and quality of life (WHO-BREF-QOL) were assessed.
Results
Post Yoga intervention we have observed significant improvement in clinical parameters of PCOS women. The metabolome analysis showed 20 significant differentially expressed metabolites (DEMs) involved in the tricarboxylic acid (TCA) cycle, antioxidant pathway, pentose phosphate pathway (PPP), pyrimidine, and tryptophan metabolism, bile acid biosynthesis, urea cycle, mitochondrial electron transport chain, and fatty acid biosynthesis that address key factors of pathogenesis in PCOS. Furthermore, also observed a significant reduction in depression severity and improvement in quality of life after the 12 week regular Yoga practice.
Conclusion
Yoga positively targets key pathological pathway involve in OS, mitochondrial dysfunction, and inflammation. It improves endocrine and reproductive health and lowers the risk of dyslipidemia, CVD, and T2DM. Hence, it can be used as an adjunct for PCOS treatment.

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EP1362

JOINT400

Clinical, biochemical, instrumental and genetic evaluation of a group of patients with hypogonadotropic hypogonadism

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Hypogonadotropic hypogonadism is a rare endocrine disorder secondary to congenital or acquired diseases affecting the hypothalamus or pituitary gland. The congenital form is caused by alterations in genes that fuel the development and migration of GnRH-secreting neurons or interfere with the physiology of the hypothalamic-pituitary axis. It can be classified into Kallmann Syndrome (associated with anosmia) or normosmic congenital isolated hypogonadism (associated with normosmia). Congenital forms are characterized by micropenis, cryptorchidism, eunuchoid proportions and delayed puberty in males and by primary amenorrhea in females. Acquired forms may result from numerous functional or organic causes impairing the physiology of the hypothalamic-pituitary region, manifesting as erectile dysfunction, reduced libido and infertility in males and secondary amenorrhea in females. In this prospective study 31 patients (23 females and 8 males) were recruited at the Department of Endocrinology in Pisa for disorders related to hypogonadotropic hypogonadism. For each patient, medical history and clinical characteristics (pubertal development stage, signs or symptoms of estrogen or androgen deficiency) were evaluated. Ultrasound of the pelvis (to assess uterine and ovarian size and structure) and scrotum (to evaluate testicular location and size) was performed. Hormonal profiles, bone densitometry, brain and sella turcica MRI (to check for hypoplasia or absence of olfactory bulbs), olfactory tests (if anosmia was present) and genetic analysis of genes associated with hypogonadotropic hypogonadism were conducted. In 18 female patients (all with secondary amenorrhea) and one male patient, hypothalamic-pituitary axis dysfunction was suspected to have a functional cause (associated with significant weight loss, severe emotional stress or excessive physical exercise). Brain MRI of one female patient with primary amenorrhea revealed a triventricular hydrocephalus, while two patients were found to have an "empty sella." One patient presented with a markedly reduced pituitary gland size. Four patients exhibited anosmic congenital hypogonadism or Kallmann Syndrome, associated with various mutations in the KISS1R gene and hypoplasia or aplasia of the olfactory bulbs. Two patients were found to have normosmic congenital hypogonadism, linked to mutations in the GnRHR gene and the CHD7 gene respectively. Finally, one male patient presented with hypogonadism in the context of Hartsfield Syndrome, associated with a mutation in the FGFR1 gene. Most of our patients showed impaired bone mineral density. In conclusion, hypogonadotropic hypogonadism is a rare endocrine disorder with various clinical manifestations. Its diagnosis requires careful integration of clinical, biochemical, instrumental, and genetic investigations to determine its etiology, enabling appropriate treatment of the condition.

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EP1363

JOINT2290

Differences of sexual development – a portuguese single-center case series of the last 24 years

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Introduction
Differences of Sexual Development (DSD) include a group of congenital disorders associated with atypical development of the chromosomal, gonadal or phenotypic sex. The most frequent clinical manifestations are atypical genitalia at birth or postnatal virilization, delayed/absent puberty, primary amenorrhea and infertility.
Aim
To characterize DSD patients followed in our center in Portugal.
Methods
Paediatric patients diagnosed with a DSD and followed in our paediatric endocrinology unit in the last 24 years (2000-2024). Sex chromosome' DSD were included.
Results
We identified 206 patients, 54% male (assigned at birth) and with a median age at first appointment of 6.5 years (IQR 10.2). In 31% ($n = 64$) the diagnosis was prenatal. The most frequent clinical manifestations were atypical genitalia (28.2%, $n = 58$), including micropenis, cryptorchidism (uni or bilateral), hypospadias, clitoromegaly and posterior fusion of the labia; followed by short stature (19,4%, $n = 40$), neurodevelopment disorder (17%, $n = 35$) and delayed puberty (5,8%, $n = 12$). Associated malformations were found in 24.7% ($n = 51$) patients: cardiac in 13% ($n = 27$), of the urinary tract in 4.3% ($n = 9$), microcephaly/micrognathia in 3.4% ($n = 7$) and orthopaedic in 2,4% ($n = 5$). A karyotype was performed in 87% of the cases ($n = 180$) and a molecular study was carried out in 23% ($n = 48$). In terms of classification, 66% ($n = 136$) belonged to sex chromosome' DSD group, 13.1% ($n = 27$) to XY DSD, 12.1% ($n = 25$) to the XX DSD, 4.4% ($n = 9$) had gonadal development disorders, 3.9% ($n = 8$) isolated hypospadias and 0.5% ($n = 1$) persistent Mullerian duct syndrome. Of the 206 patients, 116 (56.3%) underwent medical treatment: 32.5% ($n = 67$) puberty induction, 20.3% ($n = 42$) somatotropin, 3.9% ($n = 8$) LHRH analogue and 10.2% ($n = 21$) glyco/mineralocorticoid replacement. 17% ($n = 35$) underwent surgical treatment.

Conclusion
DSD are rare conditions, associated with differences in internal and/or external genitalia. Due to its complexity, these patients must be followed in multidisciplinary and specialized teams, throughout their lives.

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EP1364

JOINT2880

Neuroanatomical insights into gender identity: the role of hypothalamic subregions in therapy-naïve transgender individuals

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Background
Gender incongruency potentially has a multifactorial etiology but little is known about specific neuroanatomic regions consistently associated with this condition. We aimed to recognize the potential role of hypothalamic subregions in therapy-naïve transgender population to provide a better understanding on neuroendocrine pathways involved in gender identity.
Methods
Transgender and age-matched cisgender participants were recruited from a national tertiary center and from the local community, respectively, during the same temporal period. All subjects were right-handed. Gender incongruence was diagnosed according to ICD-10-CM criteria following independent psychiatric evaluations. T1-weighted structural data were acquired using a 3T Siemens MAGNETOM Prisma MRI scanner. Automated hypothalamic subunits segmentation was conducted using FreeSurfer v7.3.2. Blood samples were collected to measure anterior pituitary hormone levels. Preliminary statistical analyses were performed in SPSS v28 at a 5% significance level.
Results
From 40 participants, 34 were included in the final sample (9 CisMale, 10 CisFemale, 9 TransMale, 6 TransFemale). Mean age was 24.5 ± 7.38 y in the transgender group and 25.5 ± 5.69 y in the cisgender group. Specifically, the TransFemale group exhibited a significantly larger left inferior tubular (infTub) hypothalamic subunit volume (153.6 ± 15.50 mm^3) compared to TransMale *group* (121.2 ± 18.44 mm^3). No significant differences were found for this region between cisgender and transgender subgroups *(*CisMale 140.7 ± 24.96 mm^3, CisFemale 127.7 ± 16.62 mm^3). No additional significant volumetric differences were found in the right infTub or the other subunits, bilaterally (anterior-inferior, anterior-superior, posterior, superior tubular regions). Exploratory correlation analysis between hypothalamic left infTub volumes and anterior pituitary hormone levels (FSH, LH, total testosterone, TSH, T4I and prolactin) in each transgender group was performed. There was a strong significant negative correlation ($r = -0.872$, $P = 0.024$) between left infTub volumes and total testosterone levels in TransFemale participants. No other significant correlations were found.
Conclusion
Our findings suggest a potential neuroanatomical region of interest in therapy-naïve TransFemale individuals, characterized by increased volume in the left infTub hypothalamic subregion. Interestingly, the hypothalamic hormone kisspeptin, a key regulator of reproductive behavior, is predominantly expressed in the infundibulum. Given the functional association of infTub with the infundibular (arcuate), preoptic, and ventromedial nuclei—critical regulators of metabolic function and sexual behavior—further research is warranted to elucidate its role in gender identity and neuroendocrine regulation.

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EP1365

JOINT2414

Leydig cell ovarian tumor in initially normal sized ovaries - a case report

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Introduction
Hirsutism can be caused by many factors, which can be divided into distinct phenotypes: ovarian, adrenal, other endocrinopathies, iatrogenic and idiopathic. Hyperandrogenism manifests itself through excessive body hair growth in male pattern, balding in the male pattern, acne, menstrual disorders and deeper voice. Ovarian Leydig cell tumors are a rare type of androgen-secreting tumor. They account for less than 0.1 % of all ovarian neoplasms and are predominantly unilateral, benign, and found in the ovarian hilum.
Case presentation
The phenotypic characteristics of a 64-year old female patient showed the presence of features of hyperandrogenism. The hirsutism was evaluated at 18/36 on the Ferriman-Gallwey scale. Male type androgenic alopecia presented as hair loss in front of the scalp. Excessive face hair was removed by laser treatment. The patient reported rare pains in the abdomen, but she indicated that first symptoms of excessive body hair appeared 3 years before being admitted. The gynecological history was regular (normal monthly cycles until menopause at the age of 47, pregnant 2 times). Laboratory tests and imaging examinations were performed. Total testosterone was increased to 12.9 nmol/l(normal range for females up to 1.0 nmol/L), FAI index was high at 40.3, androstendion and DHEAS were normal. Erythrocytosis was also present, (4.93 g/dl; normal range for females up to 4.0 g/dl). Cushing syndrome, PCOS and other causes of hirsutism were excluded. Initial transvaginal ultrasound was normal. Abdominal computer tomography (CT) showed intraductal papillary mucinous neoplasm, ovaries were described as normal. Control abdominal ultrasound showed slightly enlarged right ovary, high total testosterone and erythrocytosis were persistently showing in laboratory tests. Patient was referred to gynecologist for bilateral adnexectomy. One year later the removal of adnexa on both sides was performed. Histopathologic examination revealed a 1 cm Leydig cell tumor in hilum of the enlarged right ovary.
Conclusion
A case of unilateral Leydig cell tumor in an initially normal sized ovary under abdominal ultrasound and CT in postmenopausal female is described. Our case highlights the importance of thorough pelvic examination as well as consideration of steroid cell tumors causing androgen excess even if ovaries appear normal in size. Radiological studies alone are not enough to diagnose ovarian pathology, as often any such lesions will be small and the affected ovary within the expected normal size. Excess androgens and erythrocytosis combined with hirsutism in the absence of other endocrinopathies should raise the suspicion of a Leydig cell ovarian tumor.

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EP1366

JOINT761

Primary amenorrhea in adolescents: a deep dive into the causes and characteristics

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Introduction
Primary amenorrhea is a failure to menstruate by the age of 15 in the presence or absence of pubertal development or by the age of 13 without signs of puberty. Pathologiesvin any of functional and structural components of the hypothalamus, the pituitary, the ovaries and the genital out flow tract, other endocrine problems can lead to amenorrhea. To date, only a few studies have attempted to characterize the causes of pediatric patients with primary amenorrhea. This study aimed to identify the causes and clinical characteristics of adolescents presenting with primary amenorrhea.
Methods
Medical records of adolescents with primary amenorrhea between 2010 and 2025 years were retrospectively reviewed. Data were abstracted on patient's medical history, etiology of primary amenorrhea, laboratory evaluation, imaging results and genetic analyzes.
Results
The study included 53 children who met the criteria for primary amenorrhea. Hypergonadotropic hypogonadism, hypogonadotropic hypogonadism, congenital mullerian defects and other endocrine disorders were diagnosed in 27(51%) ,6(11.3%),9(17%) and 11(20.8%) of the patients respectively. Among the patients diagnosed with hypergonadotropic hypogonadism and POI; 16 (30.19%) had normal 46XX karyotype. MRPS22, MCM9, CLPP, FMR1 premutation, FSHR variations were detected in 5(9.43%) patients with normal 46,XX karyotype. Gonadal dysgenesis was determined ın 11(20.75%) patients. Systemic other endocrine causes of primer amenorrhea (adrenal disease, prolactinoma, malnutrition, 5 alpha reductase deficiency, androgen insensitivity syndrome,

Table 1: Etiology of primary amenorrhea.

Hypergonadotropic Hypogonadism $n = 27(51\%)$	Hypogonadotropic Hypogonadism $n = 6(11.3\%)$	Congenital Mullerian Defects $n = 9(17\%)$	Other Endocrine Disorders $n = 11(20.8\%)$
Normal 46 XX karyotype $n = 16(30.19\%)$ cytotoxic chemotherapy $n = 3(5.66\%)$, galactosemia $n = 1(1.89\%)$, mucopolysacharodsois $n = 1(1.89\%)$ MRPS22, MCM9, CLPP, FMR1 premutation, FSHR variations $n = 5(9.43\%)$ Idiopathic $n = 6(11.32\%)$ **Gonadal dysgenesis** $n = 11(20.75\%)$ 45,X0 $n = 5(9.43\%)$, 46XX/45X $n = 1(1.89\%)$, 46XY/45X0 $n = 2(3.77\%)$, 46 XY $n = 3$ (5.66%).	FGFR1 mutation $n = 1(1.89\%)$, PNPLA6 gene $n = 1(1.89\%)$, Pituatary adenom $n = 1(1.89\%)$ Idiopathic $n = 3(5.66\%)$,		Adrenal disease $n = 1(1.89\%)$ Prolactinoma $n = 1(1.89\%)$ Malnutrition $n = 3(5.66\%)$ 5 alpha reductase deficiency $n = 2(3.77\%)$ Androgen insensitivity syndrome $n = 3(5.66\%)$ 46 XY ovotesticuler syndrome $n = 1(1.89\%)$

46XY ovotesticuler syndrome) were diagnosed in 11(20.8%) patients. Müllerian agenesis with normal female sexual characteristics was found in 9(16.98%) patients. Etiology of primary amenorrhea is summarized in table 1.

Conclusions

In our study, we found that the most common cause of primary amenorrhea is POI with normal karyotype, followed by systemic endocrine diseases. Chromomosamal abnormalities were the most cause of POI in adult studies. This study shows that in adolescent patients with POI other systemic and genetic factors should also be sought.

Keywords

Primary amenorrhea, Primary ovarian insufficiency(POI).

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EP1367

JOINT394

Bridging endocrinology and genetics: uncovering familial partial lipodystrophy type 2 in an adolescent with primary amenorrhea

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Introduction

Familial partial lipodystrophy, Dunnigan type (FPLD2), is a rare genetic disorder characterized by the loss of subcutaneous adipose tissue from the trunk, buttocks, and limbs. Its prevalence is estimated to be less than 1/100,000 in Europe. FPLD2 is commonly associated with metabolic complications, elevated androgen levels and consequently disruptions in the hypothalamic-pituitary-ovarian axis.

Case Presentation

A 14-year-old patient presented with primary amenorrhea and significant hirsutism that developed over the past two years. Clinically, she had a BMI of +1.6SD, full moon facies, acanthosis nigricans, hirsutism, and muscular hypertrophy. Laboratory findings revealed dyslipidemia, marked insulin resistance, and hormonal hyperandrogenism. Pelvic ultrasound showed ovaries with a predominantly stromal appearance. Progestin therapy was recommended to induce menstruation, with follow-up planned for further investigation. At 19 years, the patient returned with a diagnosis of high blood pressure. Menarche occurred at 15 under progestin therapy, but bradymenorrhea persisted. Her BMI was 28 kg/m^2, with absence of adipose tissue in the limbs, chest, abdomen, but accumulation in the facial, cervical, axillary, and inguinal regions, giving a Cushingoid appearance with muscular hypertrophy and phlebomegaly. Hirsutism and acanthosis nigricans worsened. Clinical examination revealed normal external genitalia, and the breasts had a tubular appearance with sparse adipose tissue. Biochemical analysis showed severe mixed dyslipidemia, significant insulin resistance (HOMA-IR = 13), and evolving ovarian hyperandrogenism (FAI=10.8%). Pelvic ultrasound revealed micro-polycystic ovaries. Cardiac examination indicated grade III hypertension without structural heart changes. Further investigations with FIBROMAX revealed a NashTest-Score of 0.5 (N1). Next-generation sequencing (NGS) identified a heterozygous mutation in the LMNA gene (chr1-156106775 C>T, NM_170707.4 c.1444C>T), confirming the diagnosis of FPLD2. We resumed the anamnesis and found that the patient's paternal grandmother had a similar phenotype and died from complications of type 2 diabetes. The father also exhibits suggestive traits and will undergo evaluation.

Conclusion

This case highlights the importance of a multidisciplinary approach integrating endocrinologic, genetic and metabolic assessments in evaluating adolescent girls with primary amenorrhea. Understanding the connection between metabolic disturbances, hormonal imbalances, and reproductive dysfunction is crucial. Early diagnosis and management of FPLD2 are essential for preventing long-term reproductive issues and mitigating the risks of severe insulin resistance, dyslipidemia, and cardiovascular disease.

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EP1368

JOINT2594

Biochemical hyperandrogenism: a diagnostic pitfall

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Introduction

Biochemical hyperandrogenism, defined by an elevated serum testosterone level, is a frequent reason for endocrine consultation. However, the absence of clinical signs of hyperandrogenism challenges the diagnosis and requires thorough investigation to identify potential physiological, pathological, or analytical interferences.

Observation

We report the case of a 34-year-old woman referred for the evaluation of isolated biochemical hyperandrogenism, with elevated total testosterone levels (up to 3.76 ng/ml) but no clinical signs of hyperandrogenism or virilization. The patient had a history of cyclic metrorrhagia treated with norethisterone (Primolut Nor). Comprehensive hormonal and imaging assessments, including adrenal and ovarian MRI, ruled out tumoral and non-tumoral endocrine causes. Notably, after discontinuation of Primolut Nor, serum testosterone levels gradually normalized (0.24 ng/ml at two months and 0.21 ng/ml at three months post-withdrawal).

Discussion and Conclusions

This case illustrates the pitfall of analytical interference in the assessment of biochemical hyperandrogenism. Norethisterone, a synthetic progestin, is structurally similar to anabolic steroids and has been reported to cross-react with certain immunoassays for testosterone measurement, leading to falsely elevated results. This highlights the importance of considering drug-induced analytical interference in cases of discordance between biochemical and clinical findings. Confirmatory methods such as liquid chromatography-mass spectrometry (LC-MS) should be considered in doubtful cases to avoid unnecessaryinvestigations and misdiagnosis.

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EP1369

JOINT3390

Sociodemographic and metabolic profiling of transgender and gender diverse treatment-naïve adolescents – seven-year experience in the first gender unit dedicated to youth in poland

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EP1369.

	Variables	all (n = 269)	RFAB (n = 230)	RMAB (n = 39)
BMI (centiles)	>97[n/%]	61/22.7	56/24.3	5/12.8
	90-97 [n/%]	33/12.3	29/12.6	4/10.3
	10-90[n/%]	150/55.8	126/54.8	24/61.5
	3-10	15/5.6	13/5.7	2/5.1
	<3	10 /3.7	6/2.6	4/10.3
	z-score BMI (IOTF) [median, mean+/-SD]	0.660.72+/-1.2	0.74 0.79+/-1.2	0.27 0.35+/-1.3
Fasting blood	glucose = or >100 mg/dl	16/5.9	14/6.1	2/5.1
	HOMA-IR >2.5	94/34.9	80/34.8	14/35.9
	triglycerides >150 mg/dl	20/7.4	20/8.7	0/0.0
	HDL-cholesterol <40 mg/dl	26/9.7	18/7.8	8/20.5
	morning cortisol > 25mg/dl	4/1.5	4/1.7	0/0.0
	midnight cortisol >5.7mg/dl	17/6.3	15/6.5	2/5.1

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Introduction
The rise in referrals of transgender and gender diverse children and adolescents to clinical diagnosis is a widely discussed topic around the word. Similarly to adult population they are at risk for weight-related problems resulting from pathological eating behaviors, which in turn negatively influence the individual's metabolic health.
Aim
We assess the basic sociodemographic and metabolic profile of the youth population in the first clinical unit dedicated to transgender youth in our country.
Methods
This prospective study has examined a consecutive series of transgender and gender diverse children and adolescents (TGDC&A) based on WPATH SOC-8 between July/2017 and Sep/2024. Clinical and laboratory data was collected in unified medical records. Sociodemographic and TGDC&A history has been analysed alongside anthropometric and metabolic parameters. The population has been divided into registered female (RFAB) or male at birth (RMAB) groups.
Results
The population consists of 269 participants (230 RFAB, 39 RMAB), with increasing number of diagnosis in subsequent years 2017 (July-Dec) - 2/0, 2018 - 9/0 2019-16/3, 2020-18/4, 2021- 52/3, 2022- 68/22, 2023- 51/4, 2024 (Jan-Sep) 14/3 (RFAB/RMAB, respectively), with the mean/median age of diagnosis 15.8/16.1 years and the mean age of gender identity mismatch onset of 12 years. BMI distribution, fasting components of the metabolic syndrome and cortisol in circadian rhythm are presented in table.
Conclusions
Sociodemographic fluctuations in the proportion of RFAB/RMAB are visible, however difficult to explain now. The increased risk of abnormal BMI, mostly elevated in RFAB and decreased in RMAB, and higher risk of metabolic syndrome/complications are key issues to consider when preparing patients with GI/GD for medical transition.

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EP1370

JOINT2062

Cabergoline treatment reduces androgen levels and restores menstrual cycles in women with hyperprolactinemic polycystic ovary syndrome

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Purpose
Cabergoline is widely used to treat hyperprolactinemia, but its effects on polycystic ovary syndrome (PCOS) remain unclear. Since hyperprolactinemia is present in nearly 30% of PCOS cases, this study aims to assess the impact of cabergoline on androgen levels and clinical outcomes in hyperprolactinemic PCOS (hPCOS)cases, discussing these findings with the results in prolactinoma cases.
Methods
A total of 66 women aged 18 to 40 were included in this retrospective cohort study, with 36 in the PCOS group(median 24.0(22.0-27.5) years) and 30 in the prolactinoma group(median 28.0(23.7-33.0) years). Only patients who had been started on cabergoline treatment and had available follow-up data were included. Hormonal profiles and clinical findings, including hirsutism and menstrual cycle regularity, were assessed before and after cabergoline treatment.
Results
After cabergoline treatment, significant reductions in prolactin and total testosterone levels were observed in both hPCOS and prolactinoma groups. In the hPCOS group, total testosterone decreased from 0.65 to 0.49 ng/ml ($p<0.001$) and dehydroepiandrosterone-sulphate levels from 407.5 to 301.0 µg/dl ($p<0.001$)(Table-1). In the prolactinoma group, total testosterone decreased from 0.39 to 0.29 ng/ml ($p<0.001$) (Table-2). Menstrual irregularities improved markedly in both groups, with prevalence decreasing from 83.3% to 5.6% in hPCOS group and from 80.0% to 10.0% in the prolactinoma group($p<0.001$). Furthermore, in hPCOS group, the prevalence of hirsutism was decreased from 86.1% to 61.1%($p=0.007$).
Conclusion
Cabergoline is effective in lowering prolactin and androgen levels while improving menstrual regularity in both hPCOS and prolactinoma patients, highlighting its potential as a valuable therapeutic option for PCOS.

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EP1371

JOINT2390

Circulating anti-müllerian hormone and inhibin b levels in reproductive disorders causing oligo/amenorrhoea

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EP1370

Table 1. Comparison of clinical and laboratory parameters in PCOS cases before and after cabergoline.

	Before treatment (n = 36)	After treatment (n = 36)	P-value
DHEA-S(ug/dl), median (IQR)	407.5(247.5-534.2)	301.0(210.7-405.7)	**<0.001**
Total Testosteron(ng/ml), median (IQR)	0.65(0.54-0.85)	0.49(0.32-0.58)	**<0.001**
Estradiol(pg/ml), median (IQR)	55.0(45.0-90.0)	67.5(45.7-113.2)	0.15
FSH(mIU/ml), median (IQR)	6.3(5.5-7.4)	5.3(4.1-6.5)	0.06
LH(mIU/ml), median (IQR)	10.6(7.2-16.0)	10.6(7.2-18.0)	0.66
TSH(uIU/ml), median (IQR)	2.6(1.9-3.1)	2.1(1.2-2.8)	0.05
Prolactin(ng/ml), median (IQR)	40.0(28.2-61.5)	1.1(0.4-11.2)	**<0.001**
Insulin(uIU/ml), median (IQR)	10.7(8.1-14.0)	11.5(8.3-12.8)	0.60
Glucose(mg/dl), median (IQR)	87.0(82.7-93.0)	89.0(84.0-93.5)	0.39
HOMA-IR, median(IQR)	2.49 1.67-3.01)	2.49(1.48-2.83)	0.90
Hirsutism, n(%)	31(86.1)	22(61.1)	**0.007**
Menstrual irregularity, n(%)	30(83.3)	2(5.6)	**<0.001**
Acne, n(%)	8(22.2)	7(19.4)	0.56

EP1370

Table 2. Comparison of clinical and laboratory parameters in prolactinoma cases before and after cabergoline.

	Before treatment (n = 30)	After treatment (n = 30)	P-value*
DHEA-S(ug/dl), median(IQR)	227.0(206.0-400.5)	249.5(136.5-344.2)	0.19
Total Testosteron(ng/ml), median(IQR)	0.39(0.22-0.50)	0.29(0.20-0.36)	**<0.001**
Estradiol(pg/ml), median(IQR)	61.0(37.5-135.5)	93.5(62.0-144.2)	0.12
FSH(mIU/ml), median(IQR)	6.1(3.8-8.4)	5.1(4.1-8.7)	0.65
LH(mIU/ml), median(IQR)	8.7(5.6-10.8)	9.6(6.7-14.6)	0.07
TSH(uIU/ml), median(IQR)	2.7(1.47-3.1)	2.6(1.67-3.2)	0.45
Prolactin(ng/ml), median(IQR)	57.0(39.0-99.5)	10.0(2.0-17.5)	**<0.001**
Insulin(uIU/ml), median(IQR)	14.0(4.8-19.4)	10.3(8.0-20.7)	0.18
Glucose (mg/dl), median(IQR)	94.0(91.0-96.0)	93.0(86.2-101.0)	0.18
HOMA-IR, median(IQR)	3.20(1.08-4.74)	2.30(1.65-4.76)	0.18
Hirsutism, n(%)	5(16.7)	3(10.0)	0.16
Menstrual irregularity, n(%)	24(80.0)	3(10.0)	**<0.001**

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Background
Anti-Müllerian Hormone (AMH) and Inhibin B (INB) are key glycoprotein hormones produced by granulosa cells that serve as key markers of ovarian reserve. INB modulates FSH secretion at the pituitary gland, whilst AMH stimulates hypothalamic GnRH neuronal pulsatility *in vitro*. Anovulatory menstrual disturbance results from reproductive disorders including polycystic ovary syndrome (PCOS), functional hypothalamic amenorrhea (FHA), and congenital hypogonadotropic hypogonadism (CHH). The prevalence of polycystic ovarian morphology on ultrasound is increased in FHA and PCOS. However, there is limited data directly comparing AMH and INB in women with PCOS, FHA, and CHH.
Methods
We investigated levels of AMH and INB in women aged 18-35yrs classified as: healthy controls (n = 46), PCOS (n = 73), FHA (n = 44), or CHH (n = 8). Groups were compared by Kruskal Wallis test with *post hoc* Dunn's test and continuous variables by correlation.
Results
Median (IQR) AMH (pmol/l)was higher in PCOS 42.9 (27.75–56.95) than in healthy controls 22.1 (14.0–26.85; P <0.0001), FHA 25.8 (14.0–30.44; P = 0.0018), and CHH 4.3 (8.4–21.45; P = 0.0001). AMH differentiated PCOS from FHA, with an area under the ROC curve (auROC) of 0.705; P = 0.0002, whereas for lean PCOS (BMI <25kg/m^2) vs FHA, auROC was 0.762; P <0.0001. AMH was positively correlated with LH in PCOS (P = 0.003, r = 0.34), but negatively in FHA (P = 0.017, r=-0.21). Additionally, AMH negatively correlated with FSH in FHA (P = 0.001, r=-0.49) and healthy controls (P = 0.005, r=-0.41). Among women with PCOS, higher BMI was associated with lower AMH levels (P = 0.0139, r=-0.287). Median INB levels (ng/l)were similar in PCOS (77) and healthy controls (79), but lower in FHA (58, P = 0.0421) and markedly reduced in CHH (7, P = 0.0001). INB reliably differentiated CHH from FHA (auROC 0.98; P <0.0001). Women with PCOS and obesity (BMI >30kg/m^2) had lower INB levels than their non-obese counterparts (67 vs. 87-90; P = 0.015) with a negative correlation between INB and BMI (P = 0.0108, r=-0.297). INB positively correlated with LH (P = 0.002, r = 0.46), and FSH (P = 0.002, r = 0.45) in FHA, as well as with FSH in healthy controls (P = 0.029, r = 0.32).
Conclusion
Although AMH was slightly higher in FHA than healthy women, it was markedly elevated in women with PCOS. INB levels were lower in FHA but markedly reduced in CHH. Both AMH and INB decreased with increasing BMI. Despite its established role in inhibiting FSH secretion, INB positively correlated with FSH in both FHA and healthy women. These data suggest that AMH and INB are valuable biomarkers in the evaluation of anovulatory menstrual disturbances.

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EP1372

JOINT3655

Beyond genetics: exploring the challenges of diagnosis and management in 46xy disorders of sex development

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Background
Disorders of sex development in individuals with a 46XY karyotype pose significant diagnostic and therapeutic challenges due to heterogeneous etiologies and overlapping clinical features. Despite advances in genetic testing, many cases lack a definitive molecular diagnosis, complicating management. The differential diagnosis includes androgen insensitivity syndrome, gonadal dysgenesis, enzymatic defects in androgen biosynthesis, and other endocrine or receptor-related abnormalities. While stimulation tests are widely used, they are costly, time-consuming, and may yield inconclusive results. Whole-exome sequencing has improved diagnostic precision but does not always identify causative mutations, emphasizing the need for a broader approach.
Case Presentation
A male infant with a 46XY karyotype presented at birth with ambiguous genitalia, including penoscrotal hypospadias and bilateral undescended testes. The External Masculinization Score was 3. Laparoscopy confirmed the absence of Mullerian structures, and testicular biopsy revealed normal testicular parenchyma. A comprehensive diagnostic evaluation included genetic and biochemical assessments. Partial androgen insensitivity syndrome was ruled out through androgen receptor gene sequencing. Initial hormonal testing suggested 5-alpha-reductase type 2 deficiency, with a testosterone-to-dihydrotestosterone ratio of 30.8 following human chorionic gonadotropin stimulation. However, repeat testing two years later showed a ratio of 12, challenging this diagnosis. Whole-exome sequencing failed to identify pathogenic variants in SRD5A2 or other relevant genes, further complicating classification.
Management and Follow-up
Due to significant undervirilization, testosterone therapy was initiated before surgical interventions. The patient later underwent bilateral orchidopexy, penile elongation and staged urethroplasty. Ongoing multidisciplinary follow-up, involving endocrinology, urology, and psychological support, remains essential to monitor pubertal development and long-term well-being.
Discussion and Conclusion
This case highlights the complexities of diagnosing and managing 46XY disorders of sex development when biochemical markers suggest an enzymatic defect, yet genetic confirmation is absent. The variability in testosterone-to-dihydrotestosterone ratios underscores the limitations of hormonal assays and the need for functional enzyme activity testing. Stimulation tests, though commonly used, require careful interpretation as they do not always yield definitive results. Whole-exome sequencing has enhanced diagnostic accuracy, yet unexplained cases persist, underscoring gaps in the understanding of sexual differentiation. A standardized, multidisciplinary approach integrating endocrinology, genetics, pediatric urology, and psychological support is crucial for optimizing patient outcomes. Advances in molecular diagnostics and functional assays will be pivotal in refining diagnostic pathways and guiding individualized management.

Keywords
46XY disorders of sex development, differential diagnosis, 5-alpha-reductase type 2 deficiency, whole-exome sequencing, endocrine-disrupting chemicals.
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EP1373

JOINT3019

Mutations in MSH5 in primary ovarian insufficiency in adolesent: a case report

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Background
Primary ovarian insufficiency (POI) is characterized by 4 to 6 months of amenorrhea and elevated serum FSH and LH in females less than 40 years. Ovarian insufficiency is uncommon in pediatrics and typically results from a chromosomal abnormality or treatment for malignancy. Idiopathic POI in which no apparent precipitant is identified is even rarer.
Case report
The 17- year- old girl was diagnosed with primary amenorreha. She was born from a normal pregnancy, delivery in 40hbd, in good general condition, weight 2350g, length 52cm. The neonatal period was complicated by hypoglycemia, needing 10% intravenous glucose. Due to delayed puberty, the girl was consulted by a gynecologist, who diagnosed hypergonadotropic hypogonadism (FSH-166.5; LH- 49.43). MRI scan excluded pathological changes in the pituitary gland. The uterus and ovaries were identified on an ultrasound. The girl was confirmed to have a normal female karyotype (46,XX). Genetic testing found a pathogenic variant in both alleles of the MSH5 gene. Disorders of the MSH5 gene are associated with primary ovarian insufficiency, a disease inherited in an autosomal recessive manner. A girl is given estrogen and progesterone as treatment.
Results
1. Primary ovarian insufficiency should be considered in the diagnosis of primary amenorrhea. 2. Recognizing POI in teens who present with amenorrhea is essential in order to provide appropriate endocrine, and gynecologic care and counseling. 3. In patients with primary ovarian insufficiency, the risk of comorbidities and the possibility of genetic inheritance of the condition should be determined.

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EP1374

JOINT1075

Case report and literature review: a 46,xx infant with atypical genitalia diagnosed with primary ovarian insufficiency (POI) caused by hfm1 gene variants

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Introduction
Primary Ovarian Insufficiency (POI) due to single gene variant is classified as a 46,XX difference of sexual development. Variants in the *Helicase Family Member 1* (*HFM1*) gene are associated with POI in females and non-obstructive azoospermia in males.
Case Report
We described a case of POI with unique genital characteristics, including clitoromegaly, fusion of the labia majora, an opening of the urethral meatus at the perineum, and the absence of the vaginal opening. Hormonal analysis revealed hypergonadotropic hypogonadism. Genetic testing identified two variants in the *HFM1* gene: c.1978-2A>C and c.2681-3T>A. A comprehensive analysis of published cases with *HFM1* gene variations was conducted to summarize the range of variants and phenotypes associated with *HFM1* gene mutations.
Discussion
This study connects *HFM1* gene variants to external genital malformations, expanding the spectrum of phenotypes related to *HFM1* mutations. Clinicians should consider the possibility of POI in 46 XX female infants with atypical genitalia and perform genetic testing for *HFM1* to avoid overlooking the diagnosis.

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EP1375

JOINT963

Efficacy of oral testosterone undecanoate in children with androgen insensitivity syndrome

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Objective
To investigate the efficacy and safety of oral testosterone therapy in individuals diagnosed with androgen insensitivity syndrome (AIS).
Methods
A self-controlled study design was utilized, focusing on individuals with AIS who were genetically diagnosed at the Department of Endocrinology, Genetics, and Metabolism of Beijing Children′s Hospital. These patients underwent treatment involving the administration of testosterone. The primary observed indexes include the measurement of penis length, which should meet the minimal surgical standard or greater than or lower limit of normal. Secondary observed indexes include penile length standard deviation score (PL-SDS), an increase in penis longitude (ΔPL), medication dosage, the course of therapy, and safety indicators, among others. There were four courses of treatment. After each course, patients were evaluated to determine whether termination of treatment was appropriate. Patients who exhibited inadequate post-treatment penile length growth were advised to continue with further treatment. The statistical methodology included t-test, and a Wilcoxon rank sum test to describe efficacy and safety.
Results
Both penile length and PL-SDS interventions showed statistically significant gains when compared to the baseline performance of the 4 courses. The study involved the longitudinal monitoring of patients with the highest recorded age being 13.7 years. The weight, height, body mass index, bone age/age, cholesterol, hemoglobin and so on were all within the normal range. All patients were no changes in precocious puberty, pubic hair growth, aggressive behavior, vulvar skin darkening, diarrhea or other conditions.
Conclusions
The initial course of treatment for patients with PAIS demonstrates observable enhancements in penile length and PL-SDS. For patients with inadequate penile length growth, continued treatment in subsequent courses (such as the second, third, and fourth courses) is recommended toenhance outcomes gradually. Testosterone undecanoate was safe and effective for the majority of individuals with PAIS patients, with few adverse effects and good treatment tolerance.

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EP1376

JOINT2910

Clinical profile and biomolecular assessment of a group of patients suspected 46 xy dsd in an african setting

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Introduction
Aetiological diagnosis of patients with abnormal genitalia remains a big challenge in African context. Despite a proposed algorithm, difficulties related to arrival out of mini puberty (gonadotrophic axis then difficult to explore), unavailability of AMH dosage are some limiting factors for diagnosis of those suspected 46 XY DSD according to Hughes *et al* classification. We aim to explore clinical and biomolecular profile of this group f patients to better understand their aetiology in our context.
Methods
We did a retrospective observational study on a period of 11 years in the endocrinology and diabetology unit of the Mother and child center in Yaounde. We included all patients with a suspected 46 XY DSD according classification of Hughes *et al*. With limited resources, all patients with a least one palpable gonad was considered as "suspected 46 XY patient" (operational definition). Those with diagnosis of ovotesticular DSD after morphological exam were excluded from our analysis. We then explore their clinical profile, hormonal assay and when available biomolecular findings.
Results
We found 64 patients with our operational definition, ovotestis excluded. There were 3 missing files and we included 61 patients in our analysis. All the patients

were born at term. Two was reported to have acute foetal distress at birth. Most of the patients had a unique orifice 97.7%. The localisation of the orifice was penoscrotal in two third of patients realising a severe hypospadias. Both right and left gonads were reported palpable by hands of clinicians in 70% of patients. The localisation was mostly inguinal (incompletely descended). In two patients, a mullerian structure was found despite a clear description of two homogenous gonads by 3 senior radiologists. The karyotype was available for 27 patients from which, a clear anomaly was found in 9 (33%): 4 had PAIS, 3 mixed gonadal dysgenesis, one with 5alpha reductase mutation, one with SF1 mutation. For two third of patients, further analysis might be necessary.
Conclusions
Suspected 46 XY patients presents with severe hypospadias, with mostly 2 palpable gonads in the inguinal region. When biomolecular are performed, an aetiology is found in one third of the patients.

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EP1377

JOINT2847

Demographic and psychosocial characterisation of transgender and gender-diverse youngsters referred to the danish gender identity service

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Background and aims
A considerable increase in referrals of adolescents to the Danish Gender Identity Service has been seen in recent years. Prior studies have suggested an elevated risk of internalising problems, a higher level of psychiatric morbidity along with higher suicidality rates among transgender and gender-diverse adolescents compared to cisgender peers. Therefore, it is important to understand the characteristics of youngsters experiencing gender incongruence to optimise the current assessment and treatment protocol and improve personalised care. We aim to describe the psychosocial profile of youngsters referred for evaluation of gender incongruence. We will describe the demographic characteristics, the history and development of gender identity and incongruence, as well as the development of sexuality. We will also examine the prevalence of psychiatric disorders, substance abuse, self-harm, and suicidal ideation.
Methods
This is a retrospective, observational study of a national cohort consisting of all children and adolescents under 18 years of age referred to the Danish Gender Identity Service from 2016 through 2022 (approximately 1200 individuals). We will use existing data from medical records obtained at routine visits from first assessment through repeated visits at the clinic. Data will be examined in subgroups according to sex assigned at birth, age of onset of gender incongruence, and treatment trajectory. Group comparisons will be performed using Student's T-test and Mann-Whitney/Wilcoxon tests as appropriate. The statistical software R will be applied for analysis and data representation.
Perspective
The evidence base for the current assessment and treatment protocol is sparse, although treatment options have existed for more than two decades in some countries. Large-scale population-based studies are needed to further improve healthcare for youngsters with gender incongruence. Thus, this study intends to provide better evidence for future assessment and treatment protocols to improve the well-being of transgender and gender-diverse youngsters.

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EP1378

JOINT3529

5α-reductase type 2 deficiency- are there early predictors for gender identity outcome?

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Background
5α-reductase type 2 deficiency (5αRD2) is a rare cause for 46, XY DSD. The enzyme catalyzes the conversion of testosterone (T) into dihydrotestosterone (DHT). In the fetus, T is responsible for the masculinization of the internal genitalia while DHT is needed for the masculinization of the external genitalia. During puberty, T facilitates changes in psychosocial behaviour, deepening of the voice, increase of muscular mass and the further masculinization of the external genitalia. Individuals with 5αRD2 present at birth with a wide clinical spectrum ranging from total female appearance to a nearly complete male phenotype with mild symptoms depending on the resting enzyme activity. During puberty, they often virilize both physically and psychologically. The first 5αRD2 studies describe a population in the Dominican Republic where affected individuals often changed gender identity after puberty from female to male, which resulted in a general recommendation for male gender identity. 5α-reductase 2 is encoded by the *SRD5A2* gene on chromosome 2. More than 100 different pathogenic variants of *SRD5A2* have been described, with no strong genotype-phenotype correlation. However, recent studies have suggested that the location of the mutation in the protein plays a role in the severity of the phenotype.
Methods
A cohort of 18 patients followed at pediatric endocrinology, endocrine gynecology and andrology departments is described according to their phenotype at diagnosis, genetics, hormonal profile and gender identity. The external genitalia score (EGS) was used to describe the genitalia phenotype.
Results
A wide range of phenotypes with 12 females and 6 males was observed. Treatment ranged from hypospadias operation and early treatment with DHT to treatment with estrogen or oral contraceptives. In some cases gonadectomy was performed in early puberty to prevent further masculinization. The genetic investigation showed different pathogenic variants, both homo- and heterozygous. The majority of the patients had a non-caucasian background. Late diagnosis, which could be caused by more female-looking genitalia (*i.e.* a more severe phenotype), seemed to more often lead to a female gender identity also after puberty.
Conclusions
The variation in gender outcome in the described cohort underlines the importance of patient-centered care, individual counseling for families with children born with 5αRD2 where the initial phenotype and genetics, including information about the expected enzyme activity, may provide guidance in clinical decisions.

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EP1379

JOINT612

Epidemiological, clinical and etiological aspects of acne in adult women

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Introduction and Objective
Traditionally considered as an inflammatory skin disorder of adolescence, acne can also affect adults, especially women. This study aims to analyze the epidemiological and clinical data of acne in adult women and to screen for hormonal imbalances in this population.
Materials and Method
We conducted a retrospective study (January 2022 - December 2023), enrolling all women aged 25 years or older who presented with acne. The diagnosis of polycystic ovary syndrome (PCOS) was made according to the revised Rotterdam criteria (2003).
Results
We included 107 women, with a mean age of 29 years. The acne either persisted since adolescence (18.7%) or appeared after the age of 25, either de novo (68.2%) or as a recurrence (13.1%). It was inflammatory (40.2%), comedonal (18.7%), or mixed (41.1%). The lesions were located on the face (96.3%), neck (8%), chest

(2.8%), and/or back (2.8%). Acne occurred in the context of hormonal imbalances in 31.8% of cases, including PCOS, which was suspected in 23 patients and confirmed in 16 cases (15%), hyperprolactinemia in 4 cases (3.7%), and hormonal contraception in 3 cases (2.8%) (hormonal intrauterine device, oral levonorgestrel, progestin implant). Acne was triggered or worsened by pregnancy in 3 cases and linked to the menstrual cycle in 1 case. Iatrogenic acne (8.4%) was induced by systemic ($n = 2$) or topical ($n = 3$) corticosteroids, azathioprine ($n = 1$), erlotinib ($n = 1$), teriflunomide ($n = 1$), and interferon beta ($n = 1$). Exogenous acne (40.2%) was induced by cosmetic products (20.6%), mask-wearing (maskne) (15.9%), and/or waxing (3.7%).

Conclusions

Our results are consistent with those of a Colombian study revealing a peak in late-onset acne among women aged 25 to 29 years. However, the prevalence of PCOS in our series is about half that of a Moroccan study (39% vs 15%). A lower demand for hormonal testing may explain this disparity. According to Dréno *et al*., adult female acne is predominantly mixed, but the involvement of the trunk is significantly less frequent in our study (48.4% vs 2.8%). Pregnancy can trigger or worsen acne due to global hypertestosteronemia. This condition may be attributed to an increase in Testosterone-Binding Globulin (TeBG) synthesis and elevated androstendione levels during pregnancy. Paroxysmal acneiform eruptions can be caused by glucocorticoids, androgens, halogens, lithium salts, vitamin B12, certain antidepressants, antiepileptics, immunosuppressants, and also epidermal growth factor receptor (EGFR) inhibitors. Comedogenic cosmetic products increases pore obstruction and bacterial proliferation.

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EP1380

JOINT3274

A case report of aromatase deficiency

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Objective

This study describes the clinical characteristics of a child with aromatase deficiency.

Methods

Clinical data of a child with aromatase deficiency were collected, including physical examination, gonadal axis hormone levels, genetic testing results, and surgical treatment.

Results

The patient, socially identified as male, was admitted with the chief complaint of "abnormal external genitalia for 5 months." Physical examination revealed clear consciousness, no significant abnormalities in the heart or lungs, soft abdomen, and ambiguous external genitalia with clitoral hypertrophy resembling a penis, urethral opening at the scrotum, bifid scrotum resembling labia, and no visible vaginal opening. Auxiliary examinations showed a karyotype of 46,XX, negative SRY gene, anti-Müllerian hormone (AMH) 0.717 ng/ml, inhibin B 104 pg/ml, testosterone 8.6 ng/dl, estradiol 36.7 pg/ml, prolactin 16.00 ng/ml, luteinizing hormone (LH) 0.33 IU/l,human chorionic gonadotropin (hCG) <1.00 mIU/ml, follicle-stimulating hormone (FSH) 3.65 IU/l,dehydroepiandrosterone sulfate (DHEA-S) <15.0 µg/dl, and normal levels of cortisol, androstenedione, and adrenocorticotropic hormone (ACTH). Color Doppler ultrasound revealed a pelvic cyst measuring approximately 43.62.3 cm (likely ovarian in origin). The patient underwent laparoscopic gonadal exploration and biopsy, left ovarian cystectomy, cystoscopy, clitoral reduction, and vulvoplasty. Whole-exome sequencing identified compound heterozygous variants in the CYP19A1 gene (c.1352T>C and c.1304G>A), confirming the diagnosis of "aromatase deficiency." Postoperative pathology reported: (left ovary) serous cystadenoma; (right ovary) ovarian stroma and immature oocytes, consistent with benign malformation; (ovarian cyst) serous cystadenoma with a small amount of ovarian follicular cells.

Conclusion

This study reports a case of aromatase deficiency in a child presenting with an ovarian cyst. Surgical removal of the cyst revealed a serous cystadenoma on pathology.

Keywords

aromatase deficiency, CYP19A1 gene, ovarian cyst, serous cystadenoma, ambiguous genitalia.

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EP1381

JOINT820

When hyperandrogenism hides more: a sertoli-leydig cell tumor in a 16-year-old girl

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Introduction

The evaluation of secondary amenorrhea and progressive virilization in adolescent females requires a comprehensive approach to identify underlying causes of hyperandrogenism, from functional conditions to tumor-related causes, including adrenal and ovarian pathology. We present the clinical progression, diagnostic workup and successful management of a young patient with virilizing ovarian tumor, highlighting the importance of timely recognition and intervention.

Case Presentation

A 16-year-old, primigesta, primipara, known with nodular goiter, but no other significant personal or hereditary medical history, presented to our Endocrinology Department for secondary amenorrhea and progressive virilization over the previous year. Clinical examination revealed moderately severe hirsutism, widening of the biacromial diameter with an androgynous pattern of muscular hypertrophy, deepened voice, clitoromegaly and abdominal pain. Baseline and dynamic testing confirmed ovarian hyperandrogenism: baseline testosterone levels exceeding 5 times the upper limit of normal range [ULN], normal baseline DHEAS and 17-OH-progesterone levels, appropriate inhibition of cortisol, DHEAS and 17-OH-progesterone, but paradoxical increase in serum testosterone (7 x ULN) after the long Dexamethasone suppression test (0.5 mg every 6 hours, 5 days) which further increased (8X ULN) together with 17-OH-progesterone (5x ULN) after continuing with the short-acting GnRh analogue stimulation test. Abdominopelvic magnetic resonance imaging (MRI) revealed the right ovary replaced by a nodular mass measuring 43/29/44 mm, displaying heterogeneous tissue signal with an internal cystic component of 8 mm, diffusion restriction and heterogeneous gadolinium enhancement. A four-fold increase in alpha-fetoprotein (AFP), with normal levels of CA125, CEA and CA19-9, led to the diagnosis of virilizing ovarian tumor. Laparoscopic right adnexectomy was performed and histopathology confirmed a moderately-differentiated ovarian Sertoli-Leydig cell tumor (SLCT). Prompt diagnosis and surgical excision lead to an outstanding response, with restoration of menstrual cycles within weeks and clinical and biochemical resolution of hyperandrogenism within two months post-surgery. AFP returned to normal levels, with no ultrasonographic signs of residual disease.

Conclusions

Accounting for less than 0.5% of ovarian tumors, SLCTs do not usually associate with positive tumor markers, but may rarely produce AFP. When this occurs, they are the most common non-germ cell ovarian tumors associated with AFP secretion. Despite polycystic ovarian syndrome being the most common cause, a structured and thorough diagnostic approach in the evaluation of hyperandrogenism in adolescents is needed, especially when presenting with secondary amenorrhea and progressive virilization.

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EP1382

JOINT3505

The importance of the NR5A1 gene in sexual differentiation

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Introduction

The NR5A1 gene plays a crucial role in gonadal development, sexual differentiation, and steroidogenesis. In the bipotential gonad, its interaction with SRY activates SOX9, promoting testicular differentiation and the formation of Sertoli cells, which activate the AMH gene, responsible for Müllerian duct regression. Sertoli cells induce the differentiation of Leydig cells, where NR5A1 activates the LH receptor (LHCGR) and INSL3, stimulating the production of testosterone and dihydrotestosterone - both essential for Wolffian ducts

differentiation and development of male external genitalia. Mutations in NR5A1 gene can result in a spectrum of phenotypes related to sexual differentiation (e.g., partial or complete gonadal dysgenesis, primary ovarian insufficiency, male infertility – oligo-azoospermia), reflecting its interaction with other key genes, such as GATA4, AMH, WT1, CBX2, and WNT4, affecting the regulatory network of gonadal development.
Case Report
A two-month-old infant was referred to the Endocrinology Clinic due to atypical external genitalia and micropenis. The child was born after an uneventful monitored pregnancy. Prenatal ultrasounds showed no abnormalities, and the fetus was designated as female. Delivery occurred by caesarean section at 42 weeks, with good neonatal adaptation. Due to atypical external genitalia, karyotyping revealed 46,XY and pelvic ultrasound identified testes near the scrotal sacs with no Müllerian structures. Male gender was assigned. At the two-month Endocrinology Clinic visit, the infant presented with penoscrotal hypospadias, micropenis, and testes located in the scrotum. Biochemical assessment excluded congenital adrenal hyperplasia and hormone levels were consistent with mini-puberty. The patient remained under follow-up, with serial ultrasounds consistently showing small testes with hyperechoic foci. At five years of age, molecular testing for androgen insensitivity was performed, but no mutations were identified. At 8 years, testosterone treatment (25 mg monthly for three months) was administered for micropenis, however no response was observed. Due to persistently low gonadotropin and testosterone levels, puberty induction with testosterone was initiated at 12 years, resulting in the development of pubic and axillary hair, penile growth, and the onset of acne. At 16 years, genetic testing identified a likely pathogenic variant, c.442_456del, p.(Glu148Glyfs*44), in heterozygosity, in exon 4 of the NR5A1 gene.
Conclusion
Testing for NR5A1 gene mutations should always be performed in cases of disorders of sexual differentiation, given the broad spectrum of associated phenotypes. Genetic diagnosis in these conditions enables optimised therapeutic management, clearer prognosis assessment, and genetic counselling for family members.

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EP1383

JOINT2197

Increased alpha-glucosidase levels in sertoli cell-only syndrome: a report of three cases

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Background
Sertoli cell-only syndrome (SCOS) is one of the most common causes of non-obstructive azoospermia in infertile men. The definitive test for diagnosing SCOS is the testis biopsy. In this work, we present 3 cases of SCOS in which the alpha-glucosidase (α-GLUC) level was remarkably elevated.
Clinical Cases
Case 1: A 35-year-old male presented with primary infertility and secondary erectile dysfunction. Laboratory investigations revealed hypergonadotropic hypogonadism and total azoospermia. Testicular atrophy was confirmed on ultrasound and testicular biopsy confirmed the diagnosis of SCOS. α-GLUC levels was elevated. Genetic testing identified a partial AZFc microduplication on the Y chromosome. The karyotype was normal. **Case 2:** A 43-year-old male presented with severe osteoporosis, pathological fractures, bilateral gynecomastia, and infertility without erectile dysfunction. Azoospermia was confirmed, along with hypergonadotropic hypogonadism and bilateral testicular atrophy. Genetic screening was negative for Y-chromosome microdeletions. The karyotype was normal. A testicular biopsy revealed SCOS. α-GLUC levels was also elevated. **Case 3:** A 49-year-old male presented with primary infertility and normal erectile function. Laboratory investigations showed hyperprolactinemia without an identifiable cause, hypergonadotropic hypogonadism, and azoospermia. Testicular ultrasound confirmed bilateral testicular atrophy. A testicular biopsy confirmed the diagnosis of SCOS. The karyotype was normal. Genetic testing revealed a partial AZFc microdeletion on the Y chromosome. MRI of the hypothalamic-pituitary axis was normal. α-GLUC levels was elevated.
Discussion
SCOS also known as germ cell aplasia is characterized by azoospermia in which the seminiferous tubules of testicular biopsy are lined only with Sertoli cells. The exact diagnosis of SCOS is based on diagnostic testicular biopsy and histopathological examination. Seminal α-GLUC levels reflect the epididymal function. The diagnosis of SCOS was retained in these 3 patients thanks to the testicular biopsy. These 3 patients had an elevated α-GLUC level suggesting a possible relationship in the pathophysiology of SCOS that should be investigated by large-scale studies. Would this marker be useful in the diagnosis of SCOS in the future?.

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EP1384

JOINT1480

Endocrine factors in the development of recurrent pregnancy loss clinical case

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Introduction
Recurrent pregnancy loss (RPL) is a polyetiological complication of pregnancy, primarily caused by dysfunction of the reproductive system. Endocrine factors play a significant role in the etiology of spontaneous miscarriages. The prevalence of endocrine factors in recurrent pregnancy loss is approximately 17%. The most common hormonal disorders contributing to RPL include ovarian hypofunction, hyperandrogenism of various origins, thyroid hypofunction, hyperprolactinemia, and thyroid pathology.
Objective
Present a clinical case with RPL.
Materials and methods
The primary documentation has been reviewed: medical history, results of clinical, laboratory, and ultrasound examinations.
Results
In January 2023, a 28-year-old woman consulted an endocrinologist to identify possible endocrine causes of RPL. Medical history revealed an irregular menstrual cycle (2537 days). She had experienced four pregnancies: the first ended in preterm delivery at 30 weeks due to placental insufficiency, while the others resulted in spontaneous miscarriages at 9, 10, and 8 weeks. Complaints included fatigue, irritability, emotional instability, headaches, and menstrual irregularities. Hormonal studies were recommended. Test results obtained the following day revealed elevated prolactin levels (63.5 ng/ml) and TSH (8 mU/L), with T4 and T3 levels within the normal range. An MRI of the brain was subsequently recommended to rule out a prolactinoma. After thorough examinations, the patient was diagnosed with idiopathic hyperprolactinemia and subclinical hypothyroidism. Dopamine agonists and hormone replacement therapy were prescribed. Four months later, the patient became pregnant, and all medications were discontinued. However, signs of a threatened miscarriage appeared at 8 weeks. Hormonal analysis revealed elevated prolactin (200 ng/ml) and TSH (6 mU/l)levels, with a decrease in inhibin A (420 pg/ml). Treatment was resumed based on these findings. The patient was closely monitored throughout the pregnancy, with periodic assessments of prolactin, TSH, and inhibin A levels. Treatment was adjusted according to hormone levels. In 2024, the pregnancy concluded with a full-term delivery at 39 weeks without complications.
Conclusion
Elevated prolactin and TSH levels are associated with decreased inhibin A, indicating an increased risk of pregnancy loss. Inhibin A may be used as a predictor of RPL development linked to endocrine factors (e.g., hyperprolactinemia and hypothyroidism).

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EP1385

JOINT2361

The relationship between indicators of leptin and anti-Muller hormone in women suffering from infertility and obesity

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Relevance
In women of reproductive age with obesity, the interval from planning pregnancy to conception increases and as BMI increases, the fertility rate decreases. Obesity can have a significant impact on the reproductive function of women, since adipose tissue produces a large number of biologically active substances, and endocrine-metabolic and hormonal changes associated with excess fat play an undoubted role in dysfunction of the reproductive system. The purpose of the study: to study the relationship between leptin and anti-Muller hormone (AMH) in women of reproductive age suffering from infertility and obesity.
Materials and methods
The study included 55 women of reproductive age with obesity and infertility. The average age of the patients was 30.8 ± 5.9. The body mass index was examined and the baseline levels of the hormones AMH and leptin were determined.
Results
According to the results of the study, 35 women had class 1 obesity (30-34.9 kg/m^2) and 20 women had class 2 obesity (35-39.9 kg/m^2). The results showed a decrease in AMH levels of 1.03 ± 0.5 ($P = 0.004$) in patients with class 2 obesity. There was a significant moderate correlation between Leptin and body mass index ($r = 0.466$, $P < 0.0001$) and a significant moderate negative correlation between leptin and AMH ($r = -0.386$, $p = 0.004$) in the entire cohort of patients.
Conclusion
As a result of the study, it was revealed that the indicators of leptin and AMH reflect the relationship between reproductive disorders and obesity. The results obtained prove that with an increase in leptin levels, there is a decrease in AMH, which is the cause of endocrine infertility in women.

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EP1386

JOINT2495

Unusual pulmonary embolism under testosterone replacement therapy in male hypogonadism: a case report

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Background
Testosterone replacement therapy (TRT) is a well-established treatment for symptomatic hypogonadal men to maintain secondary sex characteristics and alleviate symptoms associated with testosterone deficiency. However, evidence regarding the potential risk of pulmonary embolism (PE) in hypogonadal male patients undergoing TRT remains scarce and controversial. We present a case of male patient with primary hypogonadism diagnosed with unusual bilateral pulmonary embolism (PE) during TRT.
Case report
A 50-year-old male with primary hypogonadism was referred to our endocrinology outpatient clinic for evaluation of unexplained fatigue and persistent exercise intolerance despite ongoing TRT. According to medical history, the patient attributed these symptoms to suboptimal testosterone levels and had increased the TRT dosage without consulting his doctor. Initial laboratory workup revealed significantly elevated hemoglobin and hematocrit levels alongside supraphysiological serum total testosterone concentrations. On physical examination, the patient was tachycardic but normotensive, with a normal respiratory rate and oxygen saturation on room air. Given his clinical presentation, Wells' criteria for pulmonary embolism stratified the patient as moderate risk. A D-dimer assay was markedly elevated, prompting an urgent computed tomography pulmonary angiogram (CTPA), which confirmed bilateral massive PE. Further investigations, including echocardiography, electrocardiography, and Doppler ultrasound of the lower extremities, were unremarkable. Accordingly, the patient was promptly initiated on a direct oral anticoagulant (DOAC) and transferred to a high-dependency unit for close monitoring.
Discussion and conclusion
The exact pathophysiological link between TRT and vascular events remains not fully elucidated. However, increasing body of evidence suggests that testosterone exerts erythropoietic stimulatory effects, leading to polycythemia, which may predispose patients to thromboembolic events. PE is a life-threatening condition, and its occurrence in males with hypogonadism under TRT represents a critical diagnostic challenge. This case highlights the need for awareness to early diagnosis of PE in hypogonadal men receiving TRT, particularly when unexplained symptoms such as fatigue and exercise intolerance arise. Further, we gave an evidence that PE in this patient population may mimic symptoms of testosterone deficiency and potentially leading to unwarranted dosage escalation and an increased risk of adverse vascular events. Therefore, regular clinical monitoring with individualized risk assessment are crucial in hypogonadal patients undergoing TRT to mitigate the risk of thrombotic complications.

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EP1387

JOINT2232

A case of 46, xy dsd: pubertal virilization and gender identity in 17ßhsd3 deficiency

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Background
Inherited 17βhydroxysteroid dehydrogenase type 3 (17βHSD3) deficiency causes 46, XY disorders of sexual development (DSD) with extremely variable clinical presentation: from female genitalia appearance to ambiguous genitalia (AG). 17βHSD3 enzyme is primarily expressed in the Leydig cells where it catalyses the conversion of 4-androstenedione (δ4) into testosterone (T). The 17βHSD enzyme family includes 14 isoforms which are active in multiple tissues controlling final steps of androgen and estrogen biosynthesis. T/δ4 ratio and genetic testing are necessary for early diagnosis.
Case Report
A 16-year-old *girl* was referred to our clinic due to primary amenorrhea. Her mother was from Poland and her father from Italy. In her past medical story, no relevant information was reported. No prenatal investigations were performed during her gestation. At her physical examination AG were observed: a 5.0- cm phallus, palpable gonads were found in both inguinal canals and a single perineal urethral opening with a short vagina. She exhibited facial hair and pubertal development corresponding to Tanner stage B1 and PH5. Virilization had occurred during puberty. Weight was 74.8 kg and height 172.3 cm. Laboratory tests showed: total basal T 268 ng/dl, basal δ4 911 ng/dl, basal T/δ4 0.29 (similar after HCG stimulation), normal DHEAS, 19OHP and slightly increased FSH, LH, 17β-estradiol, DHT levels. Karyotype: 46XY in all metaphases. Abdominal MRI revealed gonads located in the inguinal canals, cavernous body and seminal vesicles; no uterus or ovaries were identified. *HSD17B3* gene sequencing showed the $c.277+4A>T$ homozygous mutation within intron 3 resulting in a splicing defect. She identified herself as female and after psychological evaluation, according to her parents, she decided to maintain the female gender. Bilateral gonadectomy, feminizing genitoplasty, vaginal dilatation, additive mammoplasty and facial sculpture were performed. She is now on hormonal replacement therapy with estrogens.
Conclusion
The clinical manifestations of our patient emerged during puberty and sex assignment was guided by her self-determination. Previous data reported that female-to-male gender assignment occurs in 39-64% if diagnosis is made after virilization. However, diagnosis during puberty has become rarer: 10% of cases according to a French study. Over the time, the initial decision regarding sex rearing has shifted to male gender assignment. Nonetheless, data remain inconsistent: early orchiectomy seems may allow retention of a female gender identity. The process of sex assignment, recognizing predictors of gender identity development, and determining the optimal timing for surgery remain challenging in these patients.

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EP1388

JOINT1808

Clinical profile of turner syndrome patients in a tertiary endocrine center in Nepal

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In Nepal, we have limited data regarding patients with Turner Syndrome, which is a rare chromosomal abnormality seen in females. We reviewed 16 cases of Turner Syndrome attending our endocrine center from July 2013 and Oct 2024. The mean

age was 7.06 ± 5.82 (range 8 - 30) years, weight was 38.12 ± 13.42(range 18-61) kg, height 131.21 cm ± 14.65 (range 104 - 153) cm and BMI was 20.96 ± 4.38 (range 16 - 30.4)kg/m^2. All patients presented with shunted growth. Primary amenorrhea was seen in 8 patients (50%), secondary amenorrhea in 3 patients (18.75%), delayed puberty in 13 patients (81.25%). 2 patients were 8 years old and 1 patient 11 years old. Only one was married and she was infertile. Webbed neck feature was noted in 10 patients (62.5%) and low set ear in 5 patients (31.25%). Madelung deformity was found in 2 patients (12.5%), cubitus valgus 12 patients (75%), kyphosis in 1 patient (6.25%) and broad chest in 8(50%) patients. One patient (6.25%) had hearing impairment and one (6.25%) had ear infection. Left renal agenesis was seen in 1(6.25%). Hypothyroidism was present in 7 patients (43.75%), hyperthyroidism in 1 patient (6.25%) and lymphedema in 1 patient (6.25%). Diabetes was not present in our patients while 1 patient (6.25%) had hypertension. None of our patients had cardiac problems. Mean FSH at presentation was 83.65 mIU/ml. Karyotyping was 45X0 in 10 patients (62.5%) and Mosaic in 6 patients (37.5%). Ultrasonography showed hypoplastic uterus in all patients. Growth hormone treatment was done in 4(25%) patients for the duration ranging from 6 months to 2 years. Hormone replacement therapy was initiated with estrogen only in 8(50%) patients and a combined estrogen & progesterone sequential regime in 8 (50%) patients. All estrogen were conjugated estrogen and progesterone was Medroxyprogesterone acetate. Combined oral contraceptive (COC) was not used in our patients.

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EP1389

JOINT2218

Star protein deficiency in clinical practice: "a case series review"

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Background

Steroidogenic Acute Regulatory (StAR) protein deficiency is a rare autosomal recessive disorder disrupting steroid hormone production, leading to congenital adrenal hyperplasia (CAH) and variations in sexual development. Clinical presentations of StAR deficiency include electrolyte imbalances, ambiguous genitalia, adrenal and gonadal dysfunctions. Understanding the clinical and genetic spectrum of StAR deficiency is vital for accurate diagnosis, effective management, and genetic counselling.

Objectives

This case series provides detailed insights into the clinical presentation and genetic characteristics of StAR deficiency among seven patients diagnosed at King Faisal Specialist Hospital and Research Center (KFSH&RC) in Riyadh, Saudi Arabia.

Case presentation

Total of seven patients were born to consanguineous parents, predominantly first cousins. Patients were having 46, XY karyotype. And all patients exhibited congenital adrenal hyperplasia (CAH), The clinical presentations varied, with some patients showing bilateral inguinal gonads that were morphologically testicular, while others had completely feminized external genitalia or ambiguous genitalia. Most of the patients experienced symptoms of CAH like electrolyte imbalances and chronic salt-wasting. These symptoms were effectively managed using hydrocortisone and fludrocortisone. A notable finding they were having 46, XY karyotype with the StAR gene mutation, and all patients were phenotypically females.

Conclusions

These findings emphasize the importance of genetic counselling in consanguineous populations and highlight the need for continued research to address the complexities of StAR deficiency.

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EP1390

JOINT2078

Italian survey on the endocrinological clinical approach to polycystic ovary syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-aged women, characterized by a range of clinical phenotypes that include reproductive, endocrine, and metabolic alterations.

Materials and Methods

We surveyed Italian Association of Clinical Endocrinologists members to examine PCOS diagnosis and management practices. The questionnaire included 4 demographic questions and 21 PCOS-related questions. Responses were collected anonymously via Lime Survey, preventing duplicate submissions. A total of 2412 members received an email with a link to the survey. Statistical analyses were performed using R software (version 3.4.3) with the EZR extension.

Results

503 out of 2412 physicians filled in the questionnaire, but 52 did not complete it fully. Thus, 451 participants (response rate 18.7%) were included in the analysis. Most respondents were female (62.5%) and over 55 years old (45.2%), Most endocrinologists (72.9%) see fewer than 5 patients per week with menstrual cycle issues, infertility, or hirsutism, while only 4% see more than 10 weekly. Patients with PCOS are 32.6% adolescents, 47.7% women of childbearing age, and 19% women of all ages, with no perimenopausal women. PCOS is confirmed in less than one-third of cases. 74.5% of respondents indicated that both endocrinologists and gynecologists had the expertise to manage PCOS, and most (56.3%) stated that they personally manage this condition from diagnosis to therapy 96.1% of respondents include pelvic US in diagnosing PCOS, mostly referring patients to gynecologists (78.5%) or radiologists (13.5%), with only 3.1% performing it themselves. All endocrinologists assess glucose metabolism: 30.2% using OGTT for all patients, 35.5% for at-risk patients, 30.4% considering fasting blood glucose and insulin, and 4.0% only fasting glucose. 61.0% believe diagnosing PCOS in adolescents is crucial if they show symptoms, 27.9% base it on symptom severity, and 11.1% say diagnosis can wait. Also, 67.2% consider patients' pregnancy desires critical in therapy decisions, with 28.8% referring to gynecologists for reproductive health (17.7%) or contraceptive counseling (11.1%). As for the concomitant presence of overweight/obesity, most manage this condition on their own (27.3%) or in collaboration with a dietitian (63.6%), whereas only a few (8.6%) refer the patient to another specialist.

Conclusions

The variability in PCOS diagnosis and management underscores the need for specialized, individualized care from a multidisciplinary healthcare team. A major pitfall identified in this survey is the assessment of IR during OGTT by most respondents, which is critical for prescribing metformin to about 40% of women with PCOS.

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EP1391

JOINT1346

Gynecomastia as a potential late effect of testicular lymphoma treatment: a case report

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Introduction

Gynecomastia, the benign proliferation of male breast tissue, is often associated with hormonal imbalances. This report describes a 72-year-old man who developed gynecomastia after being treated for an aggressive type of testicular B-cell non-Hodgkin lymphoma. It shows how cancer treatments can sometimes lead to hormone-related side effects.

Case Description

The patient presented with a six-month history of painful bilateral breast enlargement. His medical history included unilateral orchiectomy for testicular lymphoma, four cycles of R-CHOP chemotherapy, and one cycle of immunotherapy. He also underwent radiotherapy to the contralateral testis, thereby achieving complete remission. Tests showed low levels of LH, FSH, and testosterone, pointing to hypogonadotropic hypogonadism. There were no signs of high prolactin levels. Imaging studies ruled out testicular or adrenal masses.

Discussion

The patient's gynecomastia is likely a consequence of treatment-induced hypogonadotropic hypogonadism. Chemotherapy, immunotherapy, and radiotherapy can significantly disrupt hormonal balance. This case underscores the importance of

monitoring endocrine function in patients treated for testicular lymphoma, as gynecomastia may represent a rare but significant late effect of therapy.
Conclusion
Gynecomastia in this patient is attributed to treatment-induced hypogonadism following aggressive therapy for testicular lymphoma. There is a need for further research into the endocrine side effects of oncological treatments and long-term endocrine follow-up in cancer survivors.

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EP1392

JOINT51

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: a case report

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Introduction
Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a genetic disorder that impairs adrenal steroid synthesis, presenting with a spectrum of clinical manifestations and significant psychosocial challenges. The severity of the condition can vary widely, and its management involves not only addressing the hormonal imbalances but also the emotional and social difficulties faced by affected individuals, particularly during adolescence.
Case Presentation
We report the case of a 14-year-old female presenting with severe hirsutism, abnormal sexual development (PRADER stage 4), and metabolic risks. Diagnostic evaluation revealed classic 21-hydroxylase deficiency, confirmed by elevated 17 OH progesterone levels and bilateral adrenal hyperplasia. The patient was started on hydrocortisone therapy (20 mg/day), with a treatment plan that included both pediatric psychiatry and endocrinology support to address the psychosocial aspects of the condition.
Discussion
The management of CAH in adolescents requires a comprehensive approach that balances medical treatment with psychological care. Our case highlights the importance of individualized care plans that address both the physical and emotional aspects of CAH. The patient's family history of CAH further underscores the hereditary nature of the disorder, which can amplify psychosocial challenges. Early intervention, combined with multidisciplinary support, contributes significantly to managing symptoms and improving adherence to therapy.
Conclusion
This case illustrates that effective management of CAH in adolescents requires a holistic approach that includes pharmacological treatment alongside psychological and social support. Personalized care and close follow-up are essential to improving both the physiological and psychosocial aspects of this condition. Early diagnosis and a multidisciplinary approach are crucial in optimizing outcomes for patients with CAH.

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EP1393

JOINT1894

Pure gonadal dysgenesis (46 XX type): 2 cases report

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Introduction
Pure gonadal dysgenesis is defined by the complete or nearly complete absence of ovarian tissue in phenotypic females. We report 2 cases of 2 young girls with a 46, XX karyotype associated with gonadal dysgenesis and no other associated organic abnormalities.
Case presentation
Case 2: 16-year-old girl with no significant medical history reffered for investigated of primary amenorrhea and delayed sexual development. Her height and BMI were within normal range, Tanner stage S1P1with external genitalia appearing normal for a child, without any sexual ambiguity or signs of hyperandrogenism. Hormonal tests showed a high follicle-stimulating hormone level (FSH: 52,58 mIU/ml), a low 17β-estradiol level (7 pg/ml) and normal levels of testosterone, prolactin, thyroid-stimulating hormone were reported, and bone age at 15 years. Her karyotype was 46, XX. At imaging (magnetic resonance imaging) the absence of individualisation of the 2 ovaries with major hypoplasia of the uterus measuring 20*8 mm were revealed. she had been commenced on hormone replacement therapy. **Case 1:** 17-year-old girl, without consanguinity, was admitted for primary amenorrhea with underdeveloped secondary sex characteristics Her height and BMI were normal, tanner stage S1P1, with normal childlike external genitalia, no sexual ambiguity, and no signs of hyperandrogenism. Hormonal testing revealed: FSH at 62 UI/ml, 17β-estradiol at 5 ng/ml, normal prolactin and thyroid-stimulating hormone, bone age were between 13 and 14 years. Pelvic MRI showed a hypoplastic uterus measuring 18.7 $\times$ 7.5 mm, with no individualization of the ovaries and no other malformations. A karyotype revealed two normal X chromosomes in all observed mitoses, and AMH $<$ 0.015 ng/ml. The patient was started on 17-beta estradiol treatment.
Discussion/conclusion
46, XX gonadal dysgenesis without the phenotype of Turner's syndrome is described as "pure" and it's an infrequent cause for primary amenorrhoea. Patients are born as phenotypic female. Pure gonadal dysgenesis (PGD) follows an autosomal recessive inheritance pattern, so genetic counseling is recommended. Management is based on hormone replacement therapy (HRT) to induce female pubertal development, promote uterine growth, and maintain bone health. Regarding fertility, the recommended option is the implantation of embryos fertilized with a donated oocyte.

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EP1394

JOINT299

Complexities of complete androgen insensitivity syndrome

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Complete androgen insensitivity syndrome (CAIS) presents significant challenges in the accurate diagnosis and personalized management of individuals with a 46, XY karyotype who exhibit a female phenotype due to complete insensitivity to androgens. This retrospective case report analyzes the clinical data, genetic testing, hormonal profiling, and imaging studies of a patient who was initially misdiagnosed during hernioplasty and later misidentified as having Mayer-Rokitansky-Küster-Hauser syndrome. The report details the establishment of the correct diagnosis and implementation of a personalized management strategy that postponed gonadectomy until post-puberty. This approach included continuous monitoring and tailored estrogen replacement therapy, which facilitated informed patient decisions and comprehensive feminization while preventing the long-term consequences of estrogen deficiency. Supported by a literature review, this case report emphasizes the necessity of a multidisciplinary approach to managing CAIS, highlighting the importance of heightened awareness, accurate diagnostics, and personalized therapeutic plans to ensure holistic, patient-centered care.

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JOINT2671

Experiences in setting up a transitional care process in patients with differences in sex development and congenital adrenal hyperplasia in a tertiary care centre of a low-middle-income country

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Introduction
Congenital adrenal hyperplasia (CAH) and differences in sex development (DSD) are complex medical conditions requiring lifelong care involving multiple

medical specialties at various stages of life. Transitional care refers to the smooth coordinated transfer of health care from more family-centered paediatric services to more individual-centred adult-care services, and involves meetings between paediatric and adult health care providers, patients and parents. Age of transition can vary from 14-21 years, based on the setting, health care services and socio-cultural aspects.
Method
This cross-sectional study assessed the recently established transitional process for patients above 16 years with CAH and DSD at an university pediatric endocrine unit. The transition process is currently coordinated by clinical-staff, and patients have been educated about its importance by the primary-clinician. Patient data were obtained from the unit-based patient registry (ethics-approval-EC–18-092), and follow-up phone call. Descriptive analyses were performed to determine patient characteristics and outcomes.
Results
The study involved 38 patients aged 16-26 years, with DSD ($n = 15$,39.4%) and CAH ($n = 23$, 60.6%), of whom 21(55.6%) were females, and 17(44.7%) were males. The majority ($n = 32$,84.21%) resided outside the district where the centre was located. Currently, 15 patients (39.5%, mean age:22.2years) have been transferred to adult-care while 17 (44.7%, mean age:17.2y) are currently undergoing the transitional process, and 6 (15.8 %, mean age:17y) are yet to start the transitional process. Among the 15 transferred to adult care, three(20%) hadn't yet engaged with adult-care services due to personal reasons and anticipatory anxiety, while another three(20%), who requested transfer to local hospitals (without specialized endocrine services) have returned due to lack of medication. Among those undergoing transition($n = 17$), seven-patients(41.2%) didn't initially turn up for their scheduled transition meetings citing personal reasons, leading to difficulties in rescheduling. Most patients undergoing transitional process or yet to start the process have requested to remain under paediatric care till completion of major school exams.
Conclusion
Patients appear to be experiencing anxiety/reluctance about transitioning to adult care, despite its importance. The process is also hindered by logistical issues with rescheduling and coordination of joint care meetings in low resource settings, and absence of specialized services and medicine in local hospitals. However, ways of overcoming the challenges identified are important for successful transition which is crucial for optimizing long-term patient care.

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JOINT2914

Clinical hyperandrogenism in obese and non-obese women with polycystic ovary syndrome

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Introduction
Polycystic ovary syndrome (PCOS) is a multifaceted endocrinopathy characterized by a combination of reproductive, metabolic, and dermatological aspects. Among its defining features, clinical hyperandrogenism stands out as a hallmark manifestation, presenting with hirsutism, acne, and alopecia. While hyperandrogenism is observed in both obese and non-obese phenotypes of PCOS, the severity and presentation may vary between these groups. This study compares clinical hyperandrogenism in obese and non-obese PCOS women.
Subjects and Methods
This analytical cross-sectional study was conducted on 122 patients diagnosed with PCOS at the Endocrinology and Diabetology Department of FARHAT HACHED Hospital in Sousse from January to December 2024. Two groups were formed based on body mass index (BMI): the Obese PCOS (O-PCOS) group with a BMI above 25 kg/m^2 and the Lean PCOS (L-PCOS) group with a BMI below 25 kg/m^2. The study focused on various aspects of clinical hyperandrogenism. The severity of acne, hirsutism, and alopecia was assessed using the Global Acne Evaluation Scale, the modified Ferriman-Gallwey score, and Ludwig's classification of female hair loss.
Results
Among participants, 38 were classified as lean (31.14%), while 84 were categorized as obese (68.85%). The average age was 23.61 ± 4.97 years. Clinical hyperandrogenism was present in 89.3% of participants. Acne was the most frequent aspect, with a prevalence of 93.4%, followed by hirsutism (90.1%) and alopecia (35.2%). The mean ages of onset for these aspects were similar between O-PCOS and O-PCOS groups: 14.67 ± 4.99 years vs 13.45 ± 3.21 years for acne; 13.73 ± 2.85 years vs 12.96 ± 2.39 years for hirsutism; and 13.77 ± 2.48 years vs 12.54 ± 3.52 years for alopecia. Regarding severity, a higher prevalence of mild (31.6%) and severe cases (13.2%) of acne was observed in the L-PCOS group compared to O-PCOS ($P = 0.369$, $P = 0.135$ respectively). Mild and moderate cases of hirsutism were nearly equally distributed across both groups: fifty percent in each of the L-PCOS and O-PCOS patients exhibited mild hirsutism ($\boldsymbol{P < 10^{-3}}$), with 31.6% of the lean participants vs 35.7% of the obese showing moderate cases ($P = 0.198$). Alopecia presented similarly in both groups, with most cases classified as Grade 1 ($\boldsymbol{P = 0.041}$).
Conclusion
In conclusion, clinical hyperandrogenism is common in both lean and obese women with PCOS, with similar patterns of acne, hirsutism, and alopecia severity observed across these groups. These findings highlight the importance of comprehensive management of hyperandrogenism in all PCOS phenotypes, regardless of body weight.

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EP1397

JOINT2907

Syndromic gonadal dysgenesis: a rare case of image syndrome

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Introduction
Gonadal dysgenesis (GD) is the leading cause of disorders of sex development (DSDs) in Western societies. However, syndromic forms of GD are extremely rare and challenging to diagnose. We report a rare etiology of syndromic GD: IMAGE syndrome.
Case report
A newborn with a 46,XY karyotype, born to non-consanguineous parents, presented with a salt-wasting crisis at day 7 of life, associated with severe intrauterine growth retardation (IUGR) and a birth weight of 1760 g. Clinical examination revealed a dysmorphic syndrome characterized by scaphocephaly, midface hypoplasia, and external genital anomalies (Quigley stage II/Prader stage IV, distal hypospadias, micropenis, and left testicular ectopia). Hormonal investigations showed peripheral adrenal insufficiency (both glucocorticoid and mineralocorticoid deficiency), partial hypergonadotropic hypogonadism with normal AMH levels, and bilateral adrenal hypoplasia on abdominal CT scan. Genetic analysis did not identify any mutations in the implicated genes (NR0B1, NR5A1, HSD3B2, POR). At 3 years of age, severe growth failure (-3 SD) prompted a stimulation test, which revealed complete growth hormone deficiency (GH peak = 0.29 ng/ml), despite a normal pituitary MRI. The combination of IUGR, adrenal hypoplasia, genital anomalies, and GH deficiency strongly suggested the diagnosis of "Intrauterine growth retardation, Metaphyseal dysplasia, Adrenal hypoplasia congenita, and Genital anomalies" (IMAGE) syndrome. Under hormone replacement therapy (hydrocortisone, fludrocortisone, and recombinant growth hormone), the evolution over 14 years was favorable: improved growth (-0.5 SD), spontaneous pubertal onset, no adrenal crisis, and good academic and social integration.
Discussion
IMAGe syndrome is a very rare condition caused by a mutation in the *Cyclin-Dependent Kinase Inhibitor 1C* (*CDKN1C*) gene. This ubiquitously expressed protein plays a fundamental role in the early stages of testicular development within the genital ridges. The clinical spectrum of IMAGe syndrome is broad and involves multiple organ systems. The dysmorphic syndrome includes facial and skeletal anomalies such as epiphyseal and metaphyseal dysplasia. Genital anomalies are generally mild, often limited to bilateral cryptorchidism and micropenis, as observed in our patient. Since *CDKN1C* is also expressed in the pituitary gland, IMAGe syndrome patients may present with varying degrees of pituitary hormone deficiencies, particularly affecting the somatotropic and gonadotropic axes. This could explain the complete GH deficiency and the moderately elevated gonadotropin levels observed in our patient.

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JOINT3971

From ovary to testis: a case of 46,XX ovotesticular DSD

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Introduction

46,XX ovotesticular disorder of sexual development (DSD) is a rare condition characterized by abnormal gonadal differentiation, with both testicular and ovarian tissue coexisting in the same individual. Typically, the testicular tissue is dysgenetic, while the ovarian tissue is normal.

Methods

We report the case of a 1-year-and-5-month-old child referred to our Pediatric Department A at Hedi Chaker University Hospital in Sfax for evaluation of DSD.

Results

The infant, assigned male at birth, presented with posterior hypospadias and left testicular ectopia. Born to non-consanguineous parents, the child was delivered at term with a birth weight of 3700 g, length of 48 cm, and head circumference of 34 cm. Psychomotor development was normal. On clinical examination, the child weighed 9 kg (−1.5 SD) and measured 79 cm (average height), with no dysmorphic features or limb abnormalities. The genital tubercle measured 2 cm, with penoscrotal hypospadias and a well-developed scrotum. A palpable right gonad (15 mm) was noted, while no gonad was identified on the left side. Hormonal testing at 18 months showed FSH at 1.8 mIU/ml, LH at 0.1 mIU/ml, testosterone at 0.03 ng/ml, DHT at 0.09 ng/ml, and low AMH at 16 ng/ml. Karyotyping revealed a 46,XX chromosomal pattern, and PCR analysis of the SRY gene was inconclusive, requiring FISH for further clarification. Abdominal ultrasound revealed a Müllerian cavity, a right testis in the distal inguinal canal, and no left gonad. Pelvic MRI confirmed the Müllerian cavity, a right testis, and a left oval structure suggestive of either an ovary or a polycystic testis. Surgical intervention included excision of the left gonad and Müllerian structures, along with a biopsy of the right gonad. Histopathological analysis confirmed the presence of an ovary on the left and a testis on the right. Following discussions with the parents, the child was raised as male. Androtardyl® treatment was initiated, with two injections showing a good response, followed by hypospadias repair. At 4 years and 9 months, the child was eutrophic, with a 5 cm phallus, a slightly posterior urethral meatus, a right testis in place, and an empty left scrotum.

Conclusion

46,XX ovotesticular DSD is a rare condition. Sex assignment can be challenging, and management requires a multidisciplinary approach.

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EP1399

JOINT3855

Unilateral drug induced gynecomastia secondary to antiretroviral therapy in an HIV infected patient

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Introduction

Gynecomastia has been described in HIV-infected men undergoing highly active antiretroviral therapy. However, data on the relationship between gynecomastia and a specific antiretroviral drug or hormonal abnormality are insufficient.

Observation

Patient aged 60 years with pulmonary tuberculosis treated 04 months ago. The patient has been treated for HIV infection for 06 months and is on combination antiretroviral therapy containing Efavirenz600mg/Emtricitabine200mg/Tenofovir disoproxil fumarate 245mg daily. Referred to our training for exploration of a left Gynecomastia with palpation of an indurated and nodular mass on the left side without axillary adenopathy with a normal contralateral examination as well as the External Genitalia with right and left testicle size measuring 3*4cm and penis size at 10cm. Mammary ultrasound showed glandular infiltration of the left breast with no individualized mass or collection, complemented by mammography finding a benign-looking left gynecomastia. Liver, kidney and thyroid tests were normal. Hormonal profile: Prolactin 4.7ng/ml Testosterone =4.78ng/ml Oestradiol=22.59pg/ml FSH =11.90mui/ml LH=8.79mui/ml Tumor markers AFP and BhCG negative Testicular ultrasound was normal except for a slight reduction in left testicular volume (38*16*29mm) compared with right (43*19*28mm). In view of the patient's severe discomfort, a local hormone treatment based on androstanolone gel 2.5% with daily cutaneous application was prescribed and the patient will be evaluated after 3 months.

Discussion

Gynecomastia is not uncommon in HIV-infected men on antiretroviral therapy, and is generally transient. Treatment with efavirenz and didanosine is associated with the development of gynecomastia. Underlying hypoandrogenism appears to contribute to the development of this disorder in these patients. Gynecomastia is initially unilateral, but progresses to bilateral but asymmetric disease in more than half of patients. In patients with persistent gynecomastia, testosterone has proved effective and safe when administered transdermally or intramuscularly over several weeks or months. Most cases developed within the first two years of treatment. Discontinuation of efavirenz had positive results, with most cases achieving complete resolution. Active screening and early discontinuation of efavirenz in patients who develop gynecomastia are recommended to improve quality of life and promote adherence to antiretroviral therapy.

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EP1400

JOINT2358

Primary amennorhea caused by hyperandrogenism due to porto-systemic shunting

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Introduction

The liver plays a vital role in the endocrine system. In patients with portosystemic shunting, such as congenital portosystemic shunts or acquired portosystemic shunting because of collateral formation after portal vein thrombosis, several endocrine disturbances can occur. We present a case of a girl with primary amenorrhea after portal vein thrombosis.

Case report

A female,16 year of age, presented with primary amenorrhea and mild hirsutism. Height was 157 cm (-2,0 SD) and BMI 22,8 kg/m^2 (+0,7 SD). Her biochemistry showed hyperandrogenism with an androstenedione level of 19 nmol/l(1.35 – 7.82 nmol/l)and a testosterone level of 6.5 nmol/l(0.100 – 1.70 nmol/L), along with an LH to FSH ratio of 2.2 (LH 14,4 U/land FSH 6,6 U/l; PCOS-like fenotype). Her medical history included hematemesis at the age of 9 years due to esophageal varices, revealing an idiopathic portal vein thrombosis with porto-systemic shunting. She was also known to have mild primary hypothyroidism. In addition to hyperandrogenism, her biochemistry showed increased ammonia (176 µmol/l(15 - 45 µmol/L)), thrombocytopenia and mildly elevated bile salts. A retrograde portogram showed an intact portal bifurcation, after which a MesoRex bypass was performed successfully. This surgical procedure restored the portal flow from the mesentery to the liver, reconstituting the first pass mechanism. During follow-up, androstenedione and testosterone levels normalized (1.1 nmol/land 5.1 nmol/l,respectively), as did the LH to FSH ratio (LH 4,6 U/land FSH 6,2 U/l). Three months postoperatively, menarche occurred and her menses have remained regular since.

Conclusion

Loss of the liver's first pass metabolism due to a diverted portal flow can lead to several endocrine abnormalities, as illustrated in this case. Clinicians should be aware that porto-systemic shunting can mimic polycystic ovary syndrome (PCOS). More information on congenital portosystemic shunts can be found on the website from the International Registry of Congenital Porto-Systemic Shunts: https://ircpss.com.

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EP1401

JOINT2484

From prolactinoma suspicion to fmr1 premutation: a case of overlapping endocrine disorders

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Introduction
Secondary amenorrhea is a relatively common health issue during reproductive years. Besides pregnancy, most common causes include polycystic ovary syndrome, premature ovarian insufficiency (POI), and hyperprolactinemia. POI affects approximately one in 100 females. Although most cases are idiopathic, FMR1 gene mutations should be sought in these patients due to the risk of X-fragile syndrome in future generations.
Case report
A 41-year-old female patient was initially referred to the Endocrinology Department at the age of 33 years due to bilateral galactorrhoea and elevated prolactin, which began two years postpartum (at 30 years), associated with oligomenorrhea. She was evaluated at a private consult and a short cycle of bromocriptine was done, with clinical resolution of the galactorrhoea. No analytical work-up from that period was available. At 31 years, she became pregnant again, but galactorrhoea returned one year postpartum. Testing showed a prolactin level of 95.45 ng/ml, but interpretation of the hypothalamic–pituitary–gonadal axis was limited by ongoing combined oral contraceptive (COC) use. Pituitary magnetic resonance (MRI) revealed a 5 mm lesion, suggesting a microadenoma. Upon referral, the patient was on COC and reported resolved galactorrhoea. She maintained clinical, analytical and imagiological vigilance. Stable imaging and no prolactin rise (maximum: 79.22 ng/ml) were seen during follow-up. At 38 years, after stopping COC, she developed secondary amenorrhea and hot flashes. Testing confirmed hypergonadotropic hypogonadism, with normal prolactin and thyroid function. Negative adrenal and thyroid autoantibodies, along with a normal karyotype, prompted FMR1 gene analysis, revealing a premutation with 70 CGG repeats—consistent with Fragile X-associated POI. The patient is currently on COC for contraceptive efficacy and awaits genetic counseling.
Conclusion
POI is a pathologic condition associated with health risks and negative impact on quality of life. Early diagnosis and systemic hormone therapy is imperative to treat hypoestrogenism symptoms and mitigate long-term health risks as osteoporosis and cardiovascular disease.

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EP1402

JOINT1412

Impact on fertility and bone mass of triptorelin and estradiol therapy in trans girls

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International guidelines recommend puberty blocking with GnRH analogs followed by Estradiol treatment (E2) for trans* girls who request medical therapy. There are still uncertainties about possible side effects, is recommended to consider fertility preservation before starting medication, and to periodically assess their bone mineral density (BMD). Besides genetic and hormonal factors, environmental influences on bone mass are crucial, particularly diet, calcium intake, weight, vitamin D levels and sports activity.
Objective
To study the impact of dual therapy on trans* girls in relation to inhibin B levels and BMD. To find out the proportion of minors participate in sports and its potential influence on bone mass acquisition.
Subjects and methodology
Retrospective study of 19 minors who started Triptorelin at an average age of 13.1 ± 1.6 years (65% Tanner III-IV) and E2 at 14.9 ± 1.08. Included variables: inhibin B, weight (SDS for age and gender identity), BMD in g/cm^2 and in SDS for gender identity and vitamin D levels. Scheduled sports activity data were collected (minimum of 2 hours/week). Variables before and during treatment were studied: Triptorelin (medium dose of 60 µg/k/28 days, started 29.1 ± 6 months prior) and transdermal E2 patches (75 mg/week received for 22.6 ± 9.5 months). SPSS V25 was used for statistical analysis. Non-parametric Wilcoxon test for related samples and Chi-Square for proportions.
Results
Initial data: Inhibin B 204 ± 49 pg/ml, Weight-SDS 0.07 ± 1.6, BMD L1L4 0.89 ± 0.16 g/cm^2 (SDS –1.1 ± 0.89), total body BMD 0.9 ± 0.11 g/cm^2 (SDS -0.23 ± 1.1) and vitamin D 21.9 ± 8.5 ng/ml. 23% (5/19) practice sports and 16% (3/19) visited the fertility clinic to request preservation. Inhibin B levels decreased with therapy. In a subgroup of 6 minors who had been on E2 treatment for 36 months, the decrease was even greater (196 ± 47 vs 87 ± 9.5 26). The weight-SDS increased slightly throughout the treatment. During the 2.5 years of combined therapy, BMD increased, the BMD-SDS values for gender in the lumbar spine showed no changes, and in the body, they decreased. Most of the minors did not engage in scheduled sports, and we could not associate this practice with the other variables studied.
Conclusions
Over the first 2.5 years of treatment with Triptorelin and Estradiol in trans* girls, there is a progressive decrease in Inhibin B levels that may compromise their fertility; however, only a minority seeks to preserve it. Most of them do not participate in sports and have low levels of vitamin D, factors that may negatively impact their bone health.

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EP1403

JOINT3514

Premature ovarian insufficiency in a 26-year-old patient treated with hydroxyurea for sickle cell disease

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Introduction
Reproductive function in women with sickle cell disease can be compromised by various mechanisms, including the direct impact of vaso-occlusive crises on the ovaries, endocrine dysfunction due to iron overload in chronically transfused patients, and iatrogenic factors such as hydroxyurea treatment. Several studies suggest that hydroxyurea may contribute to a decline in ovarian reserve. In this context, we report a case of premature ovarian insufficiency(POI) in a 26-year-old woman treated with hydroxyurea.
Case presentation
A 26-year-old female patient was referred to our department for secondary amenorrhea. The patient has a family history of homozygous sickle cell anemia in one sister and peripheral hypothyroidism in another. She has been treated for sickle cell disease since age 4 and has been on Hydroxyurea for several years, with infrequent need for transfusions and rare vaso-occlusive crises. Her menarche occurred at age 14, followed by 10 years of oligomenorrhea. Over the past year, she developed secondary amenorrhea, unresponsive to dydrogesterone, which had previously been effective. At presentation, she was receiving 500mg of Hydroxyurea twice daily and her hemoglobin was 9.8 g/dl. Hormonal tests revealed elevated FSH (144.34 mUI/ml), LH (80 mUI/ml), and low estradiol (24 ng/L), while thyroid hormones, prolactin, and testosterone were normal. AMH was < 0.05 ng/ml, confirming POI. Genetic testing showed a normal 46XX karyotype. Autoimmune screening showed a slightly positive TPO antibodies but negative anti-21 hydroxylase antibodies, making autoimmune ovaritis less likely given the strong suspicion of iatrogenic cause. Bone mineral density (BMD) tests revealed spinal and femoral osteopenia as a complication of hypogonadism. The patient was started on hormone replacement therapy, and her hematologist was consulted to explore alternative treatments to hydroxyurea in the hope of reversing ovarian function, although it seems very unlikely.
Discussion
Although several studies have reported a decline in ovarian function associated with hydroxyurea, its impact remains controversial. It is still unclear whether this decline can lead to ovarian insufficiency as severe as in our case or whether it is reversible after discontinuation of treatment. Further research is needed to clarify these effects. Meanwhile, these findings highlight the importance of considering fertility preservation for women of childbearing age before initiating hydroxyurea therapy.

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EP1404

JOINT1035

The Puzzle Of 45,X/46,XY mosaicism (MGD): insights from an adult male case report

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Background
Mixed Gonadal Dysgenesis (MGD) describes individuals with a chromosomal mosaicism and underdeveloped gonads, often accompanied by impaired puberty,

fertility challenges and short stature. 45,X/46,XY mosaicism MGD has an estimated incidence of 5.6 per 100,000 liveborn males and median age at diagnosis is 29.1. MGD is associated with an increase in all-cause mortality and heightened risk of gonadal malignancy.
Case presentation
A 53-year-old biological male was referred to secondary endocrinology services with bilateral gynaecomastia and small testes, present since adolescence. Despite these findings, he reported normal libido, successful conception with three children, and no history of testicular infection, trauma, or steroid use. Historical sperm analysis suggested oligospermia. His past medical history includes ankylosing spondylitis (on etanercept), COPD, and benign prostatic hyperplasia. Clinical examination showed a weight of 92.6 kg, height 180 cm and BP 150/91 mmHg. He was well-virilized with male phenotypic features, bilateral gynecomastia, and small, lump-free testes. His blood tests revealed free testosterone of 134 pmol/l(163–473), total testosterone 12.2 nmol/l(6.68–25.7), LH 7.2 IU/l(1.7–8.6), FSH 13.5 IU/l(1.5–12.4), oestradiol 57 pmol/l(41–159), prolactin 167 mIU/l(86–324), cortisol 534 nmol/l(133–537), beta-HCG <0.1 IU/l,and alpha-fetoprotein 2.9 kU/L. Thyroid, renal, liver, and full blood count were unremarkable. Testicular ultrasound revealed bilateral small testes which were normal in shape and reflectivity with no visible mass or cysts. Serum PCR analysis confirmed a male sex chromosome complement with the SRY sequence on chromosome Y, excluding Klinefelter Syndrome. SNP array analysis revealed 27% monosomy X cells and 73% normal male cells, consistent with his clinical presentation of mosaicism, gonadal dysgenesis, and oligospermia. The patient has been referred for genetic counselling. A CT scan of the abdomen and pelvis is pending to evaluate for persistent Mullerian structures. He will undergo annual malignancy screenings, including testicular ultrasounds, due to the increased risk of gonadoblastoma (strongly linked to the presence of a Y chromosome).
Conclusion
This case underscores the rarity of late MGD diagnoses in older males and highlights the need for early investigations in disorders of sexual development. Awareness among paediatricians and general practitioners of MGD signs enables timely referral to specialists. While no standardized management pathway exists, early diagnosis reduces malignancy risks and addresses growth and sexual impairments. Management requires a multidisciplinary approach, including gender assignment, surgical interventions, hormone therapy, fertility considerations, and psychosocial support.

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EP1405

JOINT2045

Gender affirmation and hormonal health: the role of testosterone therapy in a non-binary cis woman with primary ovarian insufficiency

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Introduction
Primary ovarian insufficiency (POI) complicates gender-affirming hormone therapy in non-binary individuals. Testosterone therapy, while effective for masculinization, may exacerbate POI-associated risks such as osteoporosis, cardiovascular disease, and endometrial hyperplasia. This case explores the challenges of testosterone therapy in a non-binary individual with cervical cancer and radiotherapy-induced POI.
Case Report
A 28-year-old non-binary individual (preferred pronouns: they/them) presented with severe hypothyroidism (Free T4 $<$ 2.0 pmol/l,TSH $>$ 100 mu/l)due to Hashimoto's thyroiditis, alongside fatigue, cognitive slowing, and paresthesia. Levothyroxine improved symptoms. The patient had a history of cervical cancer (FIGO Stage III) treated with surgery, chemotherapy, and radiotherapy, likely inducing POI (FSH 113.2 iu/l,LH 68.1 iu/l,Oestradiol $<$ 100 pmol/L). They had previously used testosterone for gender dysphoria but discontinued it due to cancer treatment. The patient had mental health conditions, including bipolar disorder, anxiety, and depression, aggravated by past trauma. They were uncertain about restarting testosterone therapy due to long-term health concerns. Options included testosterone for masculinisation or estrogen/progesterone for symptoms and bone protection. The patient decided to address thyroid health first and was referred to a London gender reassignment clinic.
Discussion
Testosterone therapy in non-binary individuals with POI presents a clinical dilemma. While it alleviates gender dysphoria and induces masculinization, POI increases risks of osteoporosis and cardiovascular disease due to estrogen deficiency. Testosterone may not provide equivalent skeletal or cardiovascular protection, and endometrial hyperplasia remains a concern in individuals with an intact uterus. This case highlights the need for individualized, multidisciplinary care. Shared decision-making is critical, particularly in the context of prior malignancy and complex mental health histories. Further research is needed to establish guidelines for testosterone use in non-binary individuals with POI.
Conclusion
Testosterone therapy in non-binary individuals with POI requires careful consideration of risks and benefits. While beneficial for gender affirmation, its potential harms in POI must be weighed against the individual's health status and goals. This case underscores the need for evidence-based guidelines to optimize care for this population.
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EP1406

JOINT3830

Challenges in managing persistent hypercalcemia during pregnancy after failed surgical intervention: a multidisciplinary approach?

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Introduction
Hypercalcemia in pregnancy is a rare but significant condition with potential maternal and fetal complications, including nephrolithiasis, preeclampsia, and intrauterine growth restriction. Primary hyperparathyroidism, often caused by a parathyroid adenoma, is the most common etiology. However, its management is challenging due to imaging limitations and concerns about fetal safety. While parathyroidectomy is the definitive treatment, surgical timing must be carefully considered. Cinacalcet is an alternative, though its safety and efficacy in pregnancy remain uncertain. This case highlights the challaenges of managing refractory hypercalcemia in pregnancy, emphasizing the role of a multi-disciplinary team (MDT).
Case
A 42-year-old female was referred at 20 weeks of pregnancy due to cognitive impairment, chronic bone pain, fatigue, nausea, polyuria, and polydipsia. She had a history of hypercalcemia (corrected calcium 2.72–2.84 mmol/l)for 1–2 years, with investigations confirming primary hyperparathyroidism. Ultrasound revealed a 2.4 cm left parathyroid mass. She was started on cinacalcet but discontinued due to intolerance. Following MDT discussions, she underwent parathyroidectomy at 28 weeks, but postoperative calcium remained elevated (2.79 mmol/l)with unsuppressed PTH, indicating persistent disease. During pregnancy, from 32 weeks onward, she received weekly IV fluids and had regular calcium levels monitoring. She delivered via caesarean section, with the baby being small for gestational age. Postpartum imaging raised concerns about residual parathyroid tissue. Histology confirmed parathyroid tissue but lacked definitive evidence of an adenoma. A Sestamibi scan later suggested a large left inferior adenoma, though ultrasound findings were inconclusive. Cinacalcet was poorly tolerated, leading to gastrointestinal complications for which extensive investigations were done, which ruled out sinister pathology. Following MDT discussions, she was re-referred for surgical consideration and currently remains under endocrine team for follow-up of persistent hypercalcemia.
Discussion
Limited imaging options during pregnancy and incomplete surgical resection led to persistent disease. Medical therapy with cinacalcet was ineffective due to intolerance. Despite the attempted medical management and emergency parathyroidectomy, persistent hypercalcemia required ongoing MDT discussions. This case emphasizes the importance of individualized treatment plans and the complexities of managing refractory hyperparathyroidism in pregnancy.
Conclusion
This patient did not achieve normocalcemia and remained in borderline high calcium level despite the surgical intervention and was subsequently managed conservatively with medical therapy and close monitoring. MDT approach was required for further management and follow up to assess biochemical stability and to prevent further complications. The case highlights the need for careful MDT coordination to balance medical vs surgical management.

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EP1407

JOINT1270

Type 2 diabetes and hypogonadism: unveiling werner syndrome in a young adult

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Introduction
Werner syndrome (WS), also known as adult progeroid syndrome, is a rare autosomal recessive disorder caused by a mutation in the WRN gene. It manifests as premature aging. Major clinical features include: Cutaneous aging characterized by thin, atrophic skin with chronic ulcerations, and early graying of hair and bilateral cataracts, often presenting at a young age. These manifestations are frequently associated with additional complications, such as type 2 diabetes mellitus (DM), hypogonadism, early-onset osteoporosis, premature atherosclerosis, and an increased risk of developing neoplasms (1).
Case presentation
We report the case of a 40-year-old male followed for type 2 DM and hypogonadism, which ultimately led to the diagnosis of WS, with a history of peripheral hypogonadism, diagnosed due to primary infertility, testicular hypotrophy on ultrasound and low testosterone levels. The patient has a history of surgery for bilateral cataracts at the age of 33. On examination, he exhibited a characteristic facial appearance, including a thin face with atrophic cheeks and a pointed nose, but without cutaneous ulcerations. He has gray hair since the age of 34. Given the association of these signs, we suspected WS despite the absence of a family history of premature aging and proceeded with genetic testing for the WRN gene mutation.
Discussion and Conclusion
Werner syndrome is associated with premature aging during the early third decade of life, and can be firstly recognized by a lack of growth spurt during adolescence leading to short stature in adulthood. Aging-related disorders like DM, osteoporosis, peripheral hypogonadism, atherosclerosis, and malignancies like thyroid carcinomas and melanomas, are common. Deep skin ulcers around Achilles tendons and elbows are rarer but pathognomonic. Hypogonadism is secondary to testicular atrophy. Treatment should be tailored to each patient's needs, with potential therapies including hormone replacement for hypogonadism and appropriate management of diabetes. Early diagnosis and multidisciplinary care are crucial to improving the quality of life and preventing further complications in these patients. The main cause of premature mortality in these patients are myocardial infarction and cancer (2).
(1) He *et al*. Diabetes mellitus coexisted with progeria: a case report of atypical Werner syndrome with novel LMNA mutations and literature review. Endocrine Journal. 2019, 66 (11), 961-969 (2) Ageing Res Rev. 2017 January; 33: 105–114. doi:10.1016/j.arr.2016.03.002.

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EP1408

JOINT4028

Mixed gonadal dysgenesis: a case report and management approach

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Introduction
Disorders of sex development (DSD) encompass a wide range of congenital conditions involving atypical chromosomal, gonadal, or anatomical sex development. Mixed gonadal dysgenesis (MGD) is a rare form of DSD characterized by a mosaic karyotype and asymmetrical gonadal development. We report a case of a neonate diagnosed with MGD, detailing the clinical, hormonal, and imaging findings, as well as the management approach and follow-up.
Methods
We present the case of a neonate admitted to the Department of Pediatrics A at Hedi Chaker University Hospital for evaluation of a suspected disorder of sex development.
Results
A 3-day-old neonate was admitted for DSD evaluation. The pregnancy was uneventful. The neonate was born at term with a normal adaptation to extra-uterine life. Birth parameters were within normal limits: weight 3530g, height 49cm, and head circumference 34cm. There was no parental consanguinity. Examination of the external genitalia revealed pseudo-scrotal genital pads with transverse striation and a single orifice at the base of the bud. No palpable gonads were detected, and there were no signs of hyperpigmentation. Hormonal assays showed normal cortisol levels and normal 17-OHP, anti-mullerian hormone (AMH) was 17.3 ng/ml (normal range for males: 16.8-138) and Blood testosterone was 2.46 ng/ml. Blood karyotype revealed mixed gonadal dysgenesis: 45X [26]/46XY [7]. An abdominopelvic ultrasound revealed the presence of a uterus. Pelvic MRI confirmed a uterine structure without ovarian structures, an inguinal right testicle with an associated vaginal hydrocele, and a smaller left testicle. The biopsy of the gonads revealed the presence of testicular tissue. During follow-up, the patient demonstrated normal growth and psychomotor development. Management included feminizing urogenital surgery with endoscopic revision for bilateral orchiectomy, as the parents opted for a female gender assignment.
Conclusion
This case highlights the complexity of diagnosing and managing mixed gonadal dysgenesis. Early recognition through clinical, hormonal, and imaging evaluations is essential for appropriate gender assignment and surgical management. A multidisciplinary approach, including endocrinologists, pediatric surgeons, geneticists, and psychologists, is crucial to ensure the best long-term outcomes for affected individuals.

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EP1409

JOINT3992

Molecular analysis of AMH and AMHR2 genes in four cases of persistent müllerian duct syndrome (PMDS)

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Introduction
Persistent Müllerian Duct Syndrome (PMDS) is a form of 46,XY disorder of sex development (DSD) characterized by the presence of Müllerian derivatives (uterus, fallopian tubes) in individuals with a 46,XY karyotype. It can result from mutations in the AMH gene, responsible for Müllerian duct regression, or the AMHR2 gene, encoding its receptor.
Methods
The mixed retrospective-prospective study included 46,XY DSD children with PMDS, followed at CHU Hédi Chaker in Sfax between 2008 and 2022. The clinical evaluation involved a review of medical history, hormonal assessment, and imaging of internal genital organs. Genetic analysis focused on the AMH and AMHR2 genes, with DNA extraction, PCR amplification, Sanger sequencing and next generation sequencing.
Results
We studied four children with genital development anomalies in whom ultrasound or surgical examination revealed the presence of Müllerian structures. All patients had a 46,XY karyotype. In two patients, specific mutations in the AMH and AMHR2 genes were found, confirming the diagnosis of PMDS. In a third patient, no mutations were detected, suggesting the possibility of an alteration in an unexplored region of the studied genes. In the fourth patient, genetic variations were also found, requiring further functional studies.
Conclusion
This study highlights the genetic diversity of PMDS and underscores the need for additional analyses to better understand the molecular mechanisms involved. We plan to further investigate the functional impact of the identified variants and expand our cohort to better characterize mutations within our population.

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EP1410

JOINT837

Morbid obesity in a patient with a Y chromosome microdeletion

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Background
Y chromosome microdeletions, specifically those occurring on the long arm (Yq) and within the AZF region, are a rare genetic cause of male infertility. These deletions typically result in the loss of one or more genes crucial for sperm production. While infertility is the primary consequence, an intriguing association with obesity has been observed in some cases.
Case report
A 29-year-old male with a family history of obesity was admitted to the Endocrinology department for morbid obesity. Physical examination revealed a blood pressure of 10/5 cmHg, faciotruncal obesity with a BMI of 61 kg/m^2, capillary fragility, and striae. Notably, the patient had an absent beard but preserved morning erections and libido. Genital examination showed testes measuring 3.2 and 3.4 cm in length with micropenis. No dysmorphic features were present. Laboratory results showed low testosterone levels at 0.51 ng/ml, LH and FSH levels at 4.8 mIU/ml and 12.3 mIU/ml respectively, and a normal prolactin level. Karyotyping revealed a deletion of the long arm of the Y chromosome.
Conclusion
Partial microdeletions of Yq may have side effects such as hypogonadism and obesity. These findings highlight the phenotypic variability associated with Yq microdeletions and emphasize the importance of comprehensive clinical evaluation in affected individuals.

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EP1411

JOINT2669
Adoloscent girl with secondary amenorrhoea due to adult granulosa cell tumour - A rare presentation
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Introduction
Granulosa cell tumors (GCTs) are rare ovarian malignancies. In adolescents it is often missed or diagnosis is delayed due to their nonspecific presentation. This case report highlights the significance of a high index of suspicion and the role of tumor markers in identifying rare causes of secondary amenorrhea.
Case History
A 16-year-old female, previously healthy, presented with a two-year history of secondary amenorrhea. She had no abdominal pain or other associated symptoms her physical examination was unremarkable. Initial laboratory investigations revealed low follicle-stimulating hormone (FSH) levels with elevated inhibin B, raising suspicion of an ovarian tumor. Initial ultra sound pelvis was normal, however follow up ultrasound imaging confirmed the presence of a left-sided ovarian mass. The patient underwent a left-sided salpingo-oophorectomy. Histopathological examination confirmed the diagnosis of an adult-type granulosa cell tumor with a Ki-67 proliferation index of 67%, and tumor staging revealed pT1aN0Mx. Postoperative tumor markers, including inhibin A and inhibin B, normalized, along with normalization of luteinizing hormone (LH) and FSH levels. She resumed regular menstruation following surgery. The patient was subsequently treated with adjuvant chemotherapy to address the high recurrence risk associated with adult-type granulosa cell tumors.
Conclusion
This case highlights the importance of considering granulosa cell tumor in the differential diagnosis of adolescent girls presenting with secondary amenorrhea, especially when initial findings deviate from common conditions such as polycystic ovary syndrome (PCOS). Early identification of granulosa cell tumors is critical, as adult-type tumors are associated with a significant risk of recurrence and require comprehensive treatment, including surgery and chemotherapy. Clinicians should maintain a high index of suspicion and utilize tumor markers, including inhibin A and B, to identify rare underlying etiologies of amenorrhea. This case highlights the need for timely diagnosis and management of granulosa cell tumors to improve outcomes and the importance of long-term follow-up in these patients.

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EP1412

JOINT1952
Unusual case of hirsuitism following isotretinoin therapy for acne
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Introduction
Hirsutism is the presence of terminal hair growth in females with a male distribution pattern. It is usually manifestation of hyperandrogenism in 80 % of the cases. Every effort should be taken to exclude polycystic ovary syndrome, endocrinopathies and rare causes before labelling it as idiopathic.
Case Report
42-year-old female was referred by dermatologist for investigation of hirsuitism. At age 40 years, during covid pandemic, she developed localised papulopustular acne which she felt was triggered by constant mask wearing. This was treated with isotretinoin between 2021 and early 2022. After stopping this therapy, she noticed localised excessive hair growth especially affecting her upper lip and chin area impacting her quality of life. She denied other symptoms of virilization, including change of voice or growth of hair in other locations. She was otherwise healthy with no significant past medical history. Her menstrual cycles have been regular, has 3 children (no concern related to fertility). She was not on any medication or oral contraceptive pill. On examination, her BMI 21.7 with evidence of significant localised hirsuitism affecting upper lip and chin area, with some pigmentation and bumps on skin due to regular plucking. Clinically she was euthyroid, no features of Cushing's or acromegaly. Investigations 9 am pituitary hormone profile, fasting blood glucose, HbA1c, Testosterone (Mass Spec) 1.04 (<1.89 nmol/l)Free Androgen Index (Mass Spec) 4.40 (0.73 - 6.16), DHEAS 2.93 (1.65 - 9.15 umol/l)Androstenedione 6.3 (0.9 - 7.5 nmol/L), SHBG 23.7 (20 - 155 nmol/l)were normal suggesting Isotretinoin exposure as a cause for hirsuitism.
Discussion
Isotretinoin is a synthetic vitamin A derivative used to treat nodulocystic resistant acne unresponsive to conventional treatments. While the exact mechanism of action is unknown, isotretinoin inhibits sebaceous gland function and keratinization. Most of its side effects of are self-limiting, treatable, and dose-dependent. Handful cases reported development of hirsuitism with menstrual irregularity following Isotretinoin therapy. However, to my knowledge this is the only case of isolated hirsuitism without menstrual irregularity. Studies examining the effects of oral isotretinoin on pituitary and adrenal hormones have yielded different results. It is hypothesised that isotretinoin may cause a decrease in SHBG levels and an increase in free androgens, thus leading to hirsutism and menstrual irregularity. This case highlights unusual cause of hirsuitism without menstrual irregularity. Further investigations are required to prove the mechanisms by which oral isotretinoin exerts its variable effects on the menstrual cycle, hirsutism, and hormones.

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EP1413

JOINT2680
Clinical and diagnostic aspects of diminished ovarian reserve in women with thyroid hypofunction
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Introduction
The relevance of the problem, the relationship between reproductive function disorders and thyroid pathology is actively discussed in the scientific literature since thyroid diseases are one of the most common endocrinopathies in women of reproductive age.
Materials and Methods
we used medical databases on the Internet: Medline/PubMed, EMBASE, EBSCO, the Cochrane Library.
The results: The problem of the relationship between reproductive function disorders and thyroid pathology has become increasingly significant in recent years. This problem in women of reproductive age is currently of great theoretical and practical interest. In recent years, to examine the reproductive potential of women, the "ovarian reserve" has been assessed using certain indicators. According to Grigoryan O.R. *et al*.(2019), the vast majority of ovarian reserve indicators characterize the hormone-dependent stage of follicle growth. But discussions about the set and quantitative values of certain markers continue. Researchers from the Southwestern University of the Luzhou Clinic of China, who studied the relationship between ovarian reserve and thyroid function in women with infertility, conducted a retrospective analysis of data from 495 infertility patients who visited the clinic between January 2019 and December 2020. In this study, there was no significant correlation between ovarian reserve and thyroid function in women. A similar result was shown by a study conducted at the Center for Reproductive Medicine at the University Hospital of Brussels in 2015. The authors are Nikolaos P. *et al*. noted that this cross-sectional analysis could not demonstrate the relationship between autoimmune thyroiditis(AIT) and

ovarian reserve. Other researchers Michalakisetal., (2011) revealed results that contradict previous studies. The research showed that women with DOR had higher TSH levels compared to women with normal ovarian reserve, and suggest that thyroid disorders may be associated with ovarian reserve. This study demonstrated a very strong positive correlation between serum autoantibody levels and autoantibody levels in follicular fluid, prompted several researchers to suggest that thyroid diseases can indeed affect ovarian reserve. It should be emphasized that numerous works with similar results are presented in the world literature.

Conclusions

Thus, a review of the literature showed that this problem remains controversial and there are many unresolved issues. To solve them, further researches and presence of scholars of various profiles are needed.

Key words

ovarian reserve, thyroid hypofunction, infertility.

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EP1414

JOINT2628

Should all women with PCOS be treated for insulin resistance? absolutely, but we should know what PCOS is

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The question was the title of a paper published in 2012*, a debate between pro: John C. Marshall and con: Andrea Dunaif reflecting the division in this important topic (not only in therapy). The polycystic ovary syndrome has a wrong and misleading name. It is the most common female endocrine disorder lasting throughout life, a combination of hyperandrogenism and ovarian dysfunction, with detectable insulin resistance in most cases (if we disregard the anovulation – polycystic ovary phenotype of the Rotterdam criteria). Further arbitrary phenotypes were formed with different therapy advice despite the symptoms change from time to time but the patient remains the same. The lack of a comprehensive view and the fragmented treatment options fail to achieve overall improvement of the patients. However, if we join the AES concept (a syndrome combining hyperandrogenism with ovarian dysfunction), this increases the homogeneity of the patients giving more chance to find a common treatment. The authors have been using metformin since the discovery of insulin resistance in PCOS, thus replacing the controversial combined contraceptive pill that reduces hyperandrogenism but maintains anovulation, the other fundamental problem in the syndrome. The metformin monotherapy era was followed by the combination of metformin + life-style changes, and most recently, vitamin D3 was added to the uniform treatment. All these metformin-based therapy variants have improved almost all symptoms including infertility. The metformin + life-style changes was better than metformin monotherapy but the recent addition of vitamin D doesn't seem more advantageous (detailed results will be presented during the congress). The authors' answer is yes: all women with PCOS should be treated for insulin resistance, and probably the 'male equivalents', too.

*J.C. Marshall and Andrea Dunaif: Fertility and Sterility Vol. 97, No.1, January 2012.

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EP1415

JOINT715

Isolated fsh deficiency in man with lujan-fryns syndrome (LFS)

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Lujan-Fryns Syndrome (LFS) is a rare neuro-rheumatological X-linked disorders with mild-moderate mental retardation, psychiatric disorders, marfanoid habitus, hypotonia, tall stature, craniofacial dysmorphism, hypernasal speech, normal sexual development and testis size.

Clinical case

Due to the finding of macrocrania, craniofacial dysmorphisms, normal stature growth, and mild learning and speech disorders an 8-year-old boy came to genetic counselling where a diagnosis of Lujan-Fryns syndrome with normal karyotype (46 XY) and exclusion of X-fragile syndrome in patient with pachydermioperiostosis and Raynaud's syndrome was made. At 21 years of age, she was also diagnosed with hypothyroidism from Hashimoto's thyroiditis (maternal family of thyroidopathy) and for which she is on L-Tyroxine therapy (with fluctuating dosage). Over the years, the patient has been followed for LFS by Geneticists and Endocrinologists with reported normal stature and pubertal growth and bone maturation, thyroid ultrasound picture compatible with autoimmune thyroiditis, testicular ultrasound in the normal range, brain and pituitary MRI also normal. as well as serum levels of prolactin, GH and IGF-I In March 2024, at the age of 33 years old, the patient was admitted to our department for the first time for group B Salmonella gastroenteritis. GH (0.61 ng/ml- reference limit (RF) 0.00-5.00), IGF-I (84 mg/dl -RF. 82-244), 8 o'clock Cortisol (15.8 mg/dl-RF 6.0-18.4), 8 o'clock ACTH (10.2 pg/ml-RF 0. 0-46); LH (0.3 mUI/ml-RF 1.3-8.6), total testosterone (1.15 ng/ml-RF 2.2-10.5), FSH (0.8 mUI/L-RF 12.4) were below normal and substantially confirmed 6 months later (LH 3.1 mUI/l,FSH 1.0 mUI/L), with normal serum levels of total and free testosterone (2.4 ng/ml -RF 2.2-10.5 and 7.6 pg/ml-RF 1.8-21.4, respectively). An LH-RH test (100 mg ev) was then performed, which revealed a normal LH response (baseline: 5.0 mUI/l,peak at 30': 17.7 mUI/l)and isolated FSH deficiency (baseline: 1.3 mUI/l,peak at 90': 2.2 mUI/L). Inhibin B assay was then performed, which was found to be normal (304.4 ng/L-RF 10-357). A spermiogram was not performed due to lack of parental consent.

Conclusions

1) to our knowledge this is the first described case of isolated FSH deficiency in LFS; 2) even with normal pubertal development and normal testicular volume in LFS it is useful in follow-up to evaluate the pituitary-gonadal axis.

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EP1416

JOINT636

Swyer syndrome in a young adult with type 1 diabetes presenting with primary amenorrhea: a case report

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Introduction

Primary amenorrhea signifies underlying genetic or endocrine abnormalities, with Swyer Syndrome, or 46, XY Complete Gonadal Dysgenesis, being a rare cause. Characterized by a female phenotype and male karyotype, it results from failed gonadal differentiation, leading to streak gonads, hypoestrogenism, and increased malignancy risk. This case exhibits a rare presentation of Swyer Syndrome in a young adult with Type 1 Diabetes Mellitus.

Case Presentation

A 31-year-old Filipino female presented to our Outpatient Clinic with primary amenorrhea. She denied family history of infertility, delayed puberty, or atypical genitalia. Patient's medical history revealed a diagnosis of Type 1 Diabetes Mellitus at the age of 22. During that time, laboratory findings demonstrated significant metabolic dysregulation, with a fasting blood sugar (FBS) of 279 mg/dl, indicative of marked hyperglycemia, and an HbA1C of 12.5%, reflecting prolonged poor glycemic control over preceding months. Additionally, serum C-peptide level of 0.11 nmol/lconfirmed severe insulin deficiency, characteristic of Type 1 Diabetes. Insulin therapy was promptly undertaken, and regular follow-up visits were done. Amenorrhea was unreported earlier due to stigma, cultural beliefs, financial constraints, and limited healthcare access. Physical examination revealed a female phenotype with normal external genitalia. Breast development and pubic hair growth corresponded to Tanner stage 2, but axillary hair was absent. These findings suggested significant delays in secondary sexual characteristics, prompting further investigation. Laboratory results showed hypergonadotropic hypogonadism, evidenced by elevated FSH (33.90 mIU/ml) and LH (12.93 mIU/ml), alongside a low estradiol level (10.57 pg/ml), pointing to ovarian insufficiency. Pelvic ultrasound demonstrated a hypoplastic uterus (4.6 × 2.3 × 1.6 cm), thin endometrium (0.2 cm), and a diminutive cervix (1.4 × 1.2 cm), without focal abnormalities. Bilateral ovaries were not visualized, indicating underdeveloped reproductive structures and necessitating further advanced imaging. Pelvic MRI corroborated ultrasound findings, revealing small uterus (2.2 × 3 × 0.7 cm), streak gonads, and a rudimentary vaginal canal. Chromosomal analysis confirmed the diagnosis of Complete Gonadal Dysgenesis or Swyer Syndrome with a 46, XY karyotype. The patient was advised to undergo prophylactic gonadectomy and hormonal replacement therapy but expressed reluctance due to cultural beliefs.

Conclusion

This case highlights the complexities of diagnosing and managing Swyer Syndrome, compounded by Type 1 Diabetes Mellitus. Early detection of primary amenorrhea and delayed puberty is essential for prompt intervention. A multidisciplinary approach is crucial for early recognition and priorities include reducing malignancy risk, and improving quality of life with hormonal therapy and psychosocial support.

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EP1417
Table 1.

Steroid metabolites (origin)	*N-norms*	*All (n = 232)*	*RFAB (n = 194)*	*RMAB (n = 38)*
AN (DHEA, androstenedione and testosterone, C19)	<N	2.6%	2.1%	5.3%
	>**N**	**10.3%**	**10.8%**	**7.9%**
DHA (DHEA-sulfate)	<N	1.3%	1.0%	2.6%
	>**N**	**34.5%**	**38.1%**	**15.8%**
5-AND (DHEA)	<N	0.0%	0.0%	0.0%
	>**N**	**40.5%**	**44.8%**	**18.4%**
16a-OHDHA (DHEA-sulfate)	<N	0.4%	0.0%	2.6%
	>**N**	**47.4%**	**53.6%**	**15.8%**
5-PT (17-hydroxyprogesterone)	<N	0.0%	0.0%	0.0%
	>**N**	**19.0%**	**22.2%**	**2.6%**
17-OHPN (5beta) (17-hydroxyprogesterone)	<N	1.3%	0.0%	7.9%
	>**N**	**26.7%**	**31.4%**	**2.6%**
PT (17-hydroxyprogesterone)	<N	0.0%	0.0%	0.0%
	>**N**	**25.4%**	**29.9%**	**2.6%**
PD (progesterone)	<N	1.3%	0.0%	7.9%
	>**N**	**12.1%**	**13.9%**	**2.6%**
F/E	<**N**	**16.8%**	**19.6%**	**2.6%**
	>N	0.0%	0.0%	0.0%

EP1417

JOINT3424
Steroid metabolome signature of transgender and gender diverse treatment-naïve adolescents – 7-year experience in the first gender unit dedicated to youth in Poland

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Introduction
There are many doubts around the etiology of gender incongruence and the increasing number of transgender and gender diverse children and adolescents (TGDC&A) seeking endocrine treatment.
Aim
We assume that based on urinary steroidal gas chromatography-mass spectrometry (GC-MS), we can look deeply at steroidogenesis in TGDC&A following the concept of delineating "steroid metabolomic signature".
Methods
This prospective study has examined consecutive series of 269 TGDC&A with mean/median age of 15.8/16.1 yrs diagnosed in accordance with WPATH SOC-8 in one university center between July/2017 and Sep/2024. Clinical and laboratory data was collected in unified medical records. Steroid metabolites in 24-h-urine samples were analyzed by quantitative targeted GC-MS.
Results
Urinary samples from 232 TGDC&A (194 RFAB-registered female at birth, 38 RMAB – registered male at birth) were analysed. The values of metabolites were assessed according to age/sex specific norms and presented as % of samples which are above or below norms (table present selected metabolites with important findings). RFAB patients with earlier gender dysphoria presented significantly lower concentration of androsterone and etiocholanolone (metabolites of DHEA, androstenedione and testosterone).
Conclusion
Transgender and gender diverse children and adolescents, mainly whose registered female at birth, present unique steroid metabolome signature. This needs further studies to explain whether these findings are useful, in some way, to explain etiology.

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EP1418

JOINT3648
From diagnosis to adulthood: navigating the complexities of a 46,XX SRY-positive male with DSD

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46,XX SRY-positive males are a rare DSD subset where individuals with a 46,XX karyotype develop a male phenotype due to SRY gene translocation, typically from the Y chromosome to the X chromosome. The SRY gene drives testicular development, but these individuals often exhibit mild genital ambiguity and are infertile due to missing Y-chromosomal genes needed for spermatogenesis. This case report describes the clinical management and long-term follow-up of an 18-year-old 46,XX SRY-positive male who has been under care at our clinic since the age of two. The patient initially presented with atypical external genitalia, including a mild hypospadias, a slightly bifid scrotum with an accentuated perineal raphe, and a normal penile length of approximately 4 cm. Firm gonads, each measuring around 1.5 ml, were palpable in the scrotal sacs but exhibited a tendency to ascend into the inguinal canal. No vaginal opening, excessive hair growth, or other abnormalities were observed. Genetic analysis revealed a 46,XX karyotype with a translocation of the SRY gene from the Y chromosome to the short arm of one X chromosome, confirmed via fluorescence in situ hybridization (FISH). Functional assessment of the gonads via an hCG stimulation test showed a rise in testosterone from baseline nondetectable levels to the low-normal range, confirming functional testicular tissue. In order to promote testicular descent and scrotal development, the patient was treated with hCG, resulting in favorable outcomes. Given the predominantly male phenotype and male psychosocial development, the decision to maintain male sex assignment was made. Over the years, the patient underwent priming with low-dose testosterone to support pubertal development and ensure the proper growth of secondary sexual characteristics, alongside regular hormonal monitoring and testicular ultrasounds to assess gonadal anatomy and exclude ovotestis. At age 16, testosterone therapy was discontinued while the patient was in a hypergonadotropic state. Despite normal external genitalia development to adult size, a spermogram revealed azoospermia, consistent with the expected infertility in 46,XX SRY-positive males. This case highlights the importance of a multidisciplinary approach in the diagnosis, treatment, and long-term management of individuals with DSD, emphasizing the role of genetic, endocrine, and psychosocial factors in guiding clinical decisions.

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EP1419

JOINT2515
Primary amenorrhoea revealing prader-willi syndrome: a case report

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Background
Prader-Willi syndrome (PWS) is a complex genetic disorder characterized by obesity, developmental delay, and hypogonadism. This case describes an adolescent with primary amenorrhea and a genetic profile compatible with PWS, but without SNRPN microdeletion.
Case Presentation
An 18-year, 9-month-old female was referred for primary amenorrhea. She had a history of morbid obesity since infancy, neonatal hypotonia, and delayed motor milestones (walking at 3 years). She was born at term with a birth weight of 3.25 kg, and obesity became evident at 1 year of age. Early hyperphagia and inappropriate feeding practices were noted. In the physical examination, the body mass index was 46 kg/m^{2}and the pubertal development according to the Tanner stage was S4P4. Pelvic ultrasound showed normal internal genitalia. Hormonal investigations revealed normal gonadotropins (FSH 4.41 mIU/ml, LH 5 mIU/ml), normal testosterone (0.14 ng/ml), normal thyroid function (TSH 0.8 mIU/ml, free T4 15 pmol/L), and prolactin 17 ng/ml. A progestogen challenge test was

negative. Genetic analysis revealed a profile consistent with PWS, although no microdeletion of the SNRPN locus was detected. She was started on estradiol and medroxyprogesterone to induce menstrual cycle and prevent complications such as osteoporosis. Follow-up is focused on optimizing endocrine and metabolic outcomes.

Conclusion

This case highlights the importance of considering PWS in patients with early-onset obesity, hypotonia, and endocrine abnormalities, even in the absence of classic genetic findings. Multidisciplinary care, including hormone replacement and nutritional management, is essential for managing the wide range of complications and improving long-term outcomes.

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EP1420

JOINT1937

Impact of hysterectomy on ovarian function and woman health

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Introduction

Hysterectomy is the most common non–obstetric surgery performed on women in late reproductive age in most countries of the world for the treatment of uterine cancer and various non-cancerous uterine conditions. Our aim to investigate the impact of hysterectomy on ovarian function, with a focus on hormonal changes and ovarian reserve by the data from the literature.

Material and Methods

For preparing our investigation we used data regarding clinical and lab data after hysterectomy from internet sourses such as PubMed, Web of Science, MedLine, Medscape, Scopus, Google Scholar.

Results

Elective bilateral salpingo-oophorectomy (BSO) in women under 50 is linked to a higher risk of coronary heart disease (CHD) and sexual dysfunction, and not recommended for women after 50. In contrast, for postmenopausal women, BSO can lower the risk of ovarian cancer without negatively affecting CHD, sexual function, hip fractures, or cognitive abilities. Taiwan National Health Insurance database indicated no significant difference in stroke risk between women who underwent hysterectomy. Whereas women who had hysterectomies before 45 showed a significantly increased risk of stroke. The same results were finds by a study from the Swedish Inpatient Registry. In the other prospective research on ovarian function study, premenopausal women who had a hysterectomy without bilateral oophorectomy faced nearly double the risk of ovarian failure compared to those who did not have a hysterectomy. After four years, 14.8% of women in the hysterectomy group experienced ovarian failure, reported a history of uterine fibroids. The risk was also notably higher in women who retained both ovaries. In the other study 20.6% women after hysterectomy were reached menopause during a five-year follow-up. Anti-Müllerian hormone (AMH) indicates ovarian follicular reserve. For women under 48, normal AMH level were predictive for reaching menopause within 12 months, whereas decrease in AMH levels raises the risk of early menopause. Due to the decreased follicles, the insufficient secretion of ovarian hormones contributed rise in FSH levels through negative feedback, the FSH/LH ratio rose significantly and become independent predictor of poor ovarian response and is linked to unfavorable outcomes in IVF treatment.

Conclusion

Hysterectomy affect the ovarian reserve which leads to early menopause, increased risk of CHD, stroke, fibroids, closely associated with patient age, disease, and the type of surgery, suggesting these factors should be considered in randomization stratification for future studies aimed at exploring possible effect modifications.

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EP1421

JOINT1059

Effect of growth hormone to spinal growth and recombinant

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Growth hormone (GH) occupies a pivotal role in human growth and development. It not only promotes linear growth but also exerts profound influences on bone metabolism, bone dimensions, and bone mineral density (BMD) in pediatric and adolescent populations through the modulation of bone formation and resorption processes. Notably, the impact of GH on spinal growth has garnered considerable attention. Scoliosis, a complex three-dimensional spinal deformity characterized by lateral curvature of one or more vertebral segments, often accompanied by vertebral rotation and sagittal plane imbalance, poses a significant challenge. Among patients with growth hormone deficiency (GHD), the question of whether GH supplementation may contribute to the onset or progression of scoliosis remains a subject of debate. Recently, numerous scholars have conducted extensive research to explore the relationship between recombinant human growth hormone (rhGH) replacement therapy and scoliosis, yielding a range of findings, some of which are contradictory. This study aims to conduct an in-depth exploration of the effects of GH on spinal growth and to provide a comprehensive analysis of the potential association between rhGH replacement therapy and scoliosis. To achieve this, we will comprehensively review the impacts of GH and insulin-like growth factor 1 (IGF-1) on bone metabolism and bone mass, while also examining the consequences of GHD on bone health. By meticulously synthesizing existing research findings, we seek to elucidate with greater clarity the mechanisms through which GH regulates spinal growth and maintains spinal morphology. Furthermore, this study will specifically focus on the impact of rhGH replacement therapy on adolescent idiopathic scoliosis (AIS), with the objective of providing novel insights and guidance for the prevention and management of this condition. Through this comprehensive examination, we aspire to offer more refined diagnostic and treatment recommendations for patients with GHD and scoliosis.

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EP1422

JOINT842

Leg ulcer and klinefelter's syndrome: cause or coincidence? a case report

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Introduction

Leg ulcers are chronic cutaneous defects with no spontaneous cicatrization. Management is often multidisciplinary, involving plastic surgeons, dermatologists and vascular surgeons. The endocrinologist will be required in cases of diabetes or associated complicating endocrinopathy. We report through this observation a patient with recurrent bilateral venous leg ulcers, in whom Klinefelter's syndrome was confirmed.

Observation

49-year-old patient, followed in our training for a klinefelter syndrome. Having a history of profound venous thrombosis under a venous contension. A recurrence of venous ulcer was the main reason for this hospitalisation. Venous Doppler revealed bilateral ostial incontinence and multiplevaricose veins with incontinent perforators. Management was medical, with compression between 20 and 30 mmHg. Prevention includedmaintenance of effective contention with anticoagulation since surgery was not an option. The evolution was favorable after equilibration of diabetes, testosterone administration andoffloading mechanical tissue stress. We discuss through this case the physiopathology of lower extremity ulcers in Klinefelter'ssyndrom.

Discussion and Conclusion

Klinefelter's syndrome, first described in 1942 by Harry F. Klinefelter, is the most commoncongenital abnormality causing primary hypogonadism, occurring in 1 in 500 to 1 in 1000 livebirths. In a series of Klinefelter's patients observed for up to a 20-year period, the prevalence ofleg ulcers was 6–13%. The etiology of lower limb ulcers in these patients is multifactorial, with chronic venousinsufficiency, obesity, arteriopathy and, in particular, reduced fibrinolysis due to high levels of PAI-1, which may explain the thrombosis of cutaneous microvessels or venous thrombosis leading topost-phlebitic disease, as occurred in our patient. On the other hand, there is a loss of endothelial inflammatory control due to the decrease oftestosterone levels, as confirmed by the improvement under androgen therapy. This case illustrates an under- recognized complication of Klinefelter's syndrome. Thepathogenesis of ulcers in this endocrinopathy is unclear, but associations with abnormalities of fibrinolysis and prothrombotic states are reported.

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EP1423

JOINT2576

A rare case of coexisting turner syndrome and mayer-rokitansky-küster-hauser syndrome

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Turner syndrome and Mayer-Rokitansky-Küster-Hauser (MRKH) are congenital conditions that affect female reproductive development. The presence of these two syndromes in a person is very rare in our clinical work, but they remain one of the most main causes of primary amenorrhea. So, Turner syndrome is responsible for short stature, gonadal dysgenesis and cardiovascular abnormalities. On the other part, MRKH is characterized by congenital aplasia of the uterus and upper two-thirds of the vagina. Our case is about a 14 year old female that came in the Specialty Polyclinic Nr.3 in Tirana with two main complaints, the absence of menstrual cycle (primary amenorrhea) and short stature. During the physical examination, was observed the lack of secondary sexual characteristics, webbed neck, short stature. *Hormonal analyses* revealed **hypergonadotropic hypogonadism**: LH 25.7mUI/ml [2.4-12.6]; FSH 94.8mUI/ml [3.5-12.5]; estradiol < 5 pg/ml [< 91 pg/ml]; Progesterone 0.073ng/ml [0.2-1.5]**, low value of GH and somatomedin C**: IGF-1 200ng/ml [191-496]; **subclinical hypothyroidism**:TSH 4.92 uUI/ml [0.51-4.3]. Karyotype examination showed the mosaicism pattern of Turner syndrome 45,X/47,XXX. Radiological examination like pelvic ultrasound and magnetic resonance (MRI) demonstrated ovary and uterus agenesia, also the absence of upper vagina. After these examinations and the multidisciplinary consultations, the patient was diagnosed with a rare combination of Turner syndrome and MRKH syndrome. The treatment consisted in the hormone replacement therapy like: somatotropin, gonadotropin and levothyroxine. In conclusion, reported cases with the combined presence of Turner and MRKH syndromes are unusual and rare. For appropriate diagnosis and treatment is necessary the multidisciplinary collaboration and management, including endocrinologist, pediatrician endocrinologist, gynecologist, geneticist and psychological care.

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EP1424

JOINT1658

An atypical case of premature pubarche

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Introduction
Premature pubarche is defined as the development of pubic hair before the age of 8 in girls and 9 in boys. It is an expression of premature adrenarche, which refers to an early increase in adrenal androgen secretion, a phenomenon that normally precedes gonadal maturation by one to two years. Premature pubarche can be classified as idiopathic or due to underlying conditions such as adrenal hyperplasia or exposure to exogenous androgens.
Case Presentation
A 6-year-and-10-month-old girl was referred for the onset of secondary sexual characteristics, presenting with pubertal development P =(Tanner pubic hair stage) 2, B (Tanner breast stage) 1-2 on the left, B1 on the right. Laboratory tests showed prepubertal basal LH and increased DHEAS (82.00 µg/dl); FSH, cortisol, insulin, fT4, TSH, IGF-1, δ4-androstendione were within normal limits. ACTH stimulation test demonstrated normal 17-OH-progesterone levels. Pelvic ultrasound revealed a transitional-type uterus and ovarian volume at the upper limit for her age. GnRH stimulation test was performed showing prepubertal LH values (peak LH 3 mU/ml) without inversion of the FSH/LH ratio and in line with prepubertal estrogen levels (< 5 pg/ml). Bone age was advanced (9 years and 6 months). Growth was between the 90th and 97th percentile above the genetic target, but when corrected for bone age, it fell within the genetic target range. After 6 months, the breast bud regressed and pelvic ultrasound confirmed a transitional-type uterus and ovarian volume at the upper limit for her age. At the next visit, the girl presented pubertal development P3 B2 on the right and B1 on the left. ACTH stimulation test and a triptorelin test were repeated and remained normal. Hormonal evaluations continued to indicate a prepubertal status and tumor markers (CA 19.9, CEA, CA125, alpha-fetoprotein) were negative, but an increase in DHEAS (140.00 µg/dl) was noted. Bone age remained advanced by 2 years. Based on clinical history, the diagnostic tests performed and the blood test results, a diagnosis of atypical premature pubarche was established.
Discussion and Conclusions
Unlike typical cases of premature pubarche, which often progress slowly without significant clinical consequences, atypical cases present with more pronounced signs of androgen excess, such as accelerated growth, acne, and advanced bone age. These patients may require extensive evaluation to rule out underlying conditions. Long-term follow-up is crucial to monitor potential metabolic or endocrine complications, including hyperandrogenism, polycystic ovary syndrome, and metabolic syndrome.

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EP1425

JOINT926

Aromatase defficiency: a rare cause of female ambiguous genetalia

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Introduction
Aromatase deficiency results from autosomal recessive inheritance of mutations in the CYP19A1 gene. It gives rise to ambiguous genitalia in 46,XX fetuses. At puberty, affected girls have hypergonadotropic hypogonadism, do not develop secondary sexual characteristics, and exhibit progressive virilization **Case:** 16 years old girl who was referred to a urologist in our institution at the beginning of 2020 (she was 12 years old then) as a case of ambiguous genitalia for genital construction surgery. She is a product of full term normal vaginal delivery, no history of maternal virilization during pregnancy. Ambiguous genitalia was diagnosed at birth, her chromosomal analysis confirmed 46 XX genetic sex. No genital constructive surgery done at early life, the parent raise her as a girl and they lost follow up. When she was 12 years old the mother seeks medical advice due to primary amenorrhea Unfortunatly she lost follow up due to Covid pandemic. Presented again in 2022. **Family history:** Parents are first degree relatives History of one female maternal cousin with ambiguous genitalia **Examination:** Height: 160cm (on the 25 percentile) Weight 65 kg (above 90 percentile) She has hirsutism with Acanthosis nigricans No breast development **Genitalia Examination:** Clitromegaly Fusion of labioscrotal fold **Laboratory investigations:** Estradiol less than 18 pmol/l(22-2-5) LH 18.3 IU/l(1.0-11.1) FSH 30 IU/l(0.87—8.8) Total testesteron 0.76 nmol/l(0.069-2.71) Free testesteron index 1.56 (0.5-6.5) DHEAS 4.1 micmol/l(1.7-9.9) Pelvic US The uterus and ovaries are not clearly visualized. **Pelvic MRI** A thin vertically oriented fluid filled structure is noted behind the urinary bladder, It measured 2.3x.2.2 cm and is thought to be mullerian duct remnant. No normal vaginal wall or lumen could be visualized. There are two oval structures identified in the lower part of the pelvis, measure 1.2 x0.8 cm in the right and 1.9x0.8 on the left thought to be ovaries, few tiny bilateral follicles are present largest measures 3.1mm. **Examination under anesthesia:** Common urogenital sinus 3 cm with 2 opening. Short vagina with underdeveloped wall The distance from external common urogenital opening till vaginal opening is 3.5 cm (high confluence) **Genetics study showed:** A homozygous pathogenic variant was identified in the CYP19Ai gene. Patient was started on oral estrogen Follow up MRI showed increase in the size of vagina and uterus so the patient was planned for genital constructive surgery.
Conclusions
This is a case of aromatase deficiency with late diagnosis at adolescent.

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Thyroid

EP1426

JOINT2587

Warthin-like subtype of papillary thyroid cancer – a single-center experience, preliminary report

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Introduction
Papillary thyroid cancer of the Warthin type (WLPTC) is a rare subtype of papillary thyroid cancer named for its similarity to Warthin's tumor of the salivary glands. Histopathologically, it is characterized by the formation of

papillary like structures, the presence of oxyphil cells, and lymphocytic infiltration. WLPTC has been shown to occur more frequently in women, especially in the 4th decade of life, and is often associated with autoimmune thyroid disease.
Aim of the Study
A retrospective review of data from 30 patients with WLPTC diagnosed from 2021 to 2025 was performed. The aim of the analysis was to characterize the patients, including demographic data, histopathological findings, and treatment course. In the group of 30 patients, the majority were women (n = 26, 86%) and the remainder were men (n = 4, 14%). The mean age of the patients was 46 ± 11 years, with a median of 49 years. According to the TNM classification, the distribution was as follows: pT1a in 13 patients (43%), pT1b in 12 patients (40%), and pT2 in 5 patients (16%); no nodules were larger than 4 cm. Multifocality was observed in 24 cases (80%), and coexisting subtypes—classic, follicular, oncocytic, and hobnail—were identified. Lymph node metastases were confirmed in the central compartment (pN1a in 5 of 29 cases, 17%) and in the lateral compartment (pN1b in 1 of 29 cases, 3%). No distant metastases were found. In 18 cases (60%), the nodule was found to be intrathyroidal; in 5 cases (17%), there was extension into the capsule; and in 7 cases (24%), microscopic extrathyroidal extension was observed. Angioinvasion was present in 5 cases (17%). Coexisting autoimmune thyroiditis was found in 26 cases (86%). According to the AJCC 8th edition classification, 100% of the patients were classified as Stage I. Based on the ATA 2015 risk stratification: 9 out of 29 patients (31%) were assessed as low risk, and 20 out of 29 patients (69%) as intermediate risk. In our group, 29 out of 30 patients (96%) received radioactive iodine (RAI) treatment; the response to treatment was excellent in 26 cases (90%), with 1 case showing a biochemically incomplete response, while 3 patients are awaiting results.
Conclusions
The Warthin subtype, although very characteristic, is rarely diagnosed. It is associated with autoimmune thyroiditis, exhibits a clinical course like other papillary carcinoma subtypes, and has a good prognosis that also depends on the coexisting subtype.

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EP1427

JOINT1221

Serum proteomic analysis reveals insights into the mechanism of action of teprotumumab, an insulin-like growth factor-1 receptor inhibitor, in patients with chronic thyroid eye disease (TED)

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Background
TED is a heterogenous disease, with symptoms that can burden daily life. Patients with chronic TED may be particularly challenging to diagnose and treat. Insulin-like growth factor-1 receptor (IGF-1R) plays a key role in TED pathogenesis. Teprotumumab, a fully human monoclonal IGF-1R inhibitor antibody, recently demonstrated proptosis improvement in a trial of patients with chronic, low disease activity TED. This trial represents a significant step for a population traditionally treated with decompression surgery and recalcitrant to pharmacotherapy. To further understand teprotumumab's impact on biomarkers and signaling pathways, we examined serum proteomics to elucidate global pathways impacted by teprotumumab in chronic TED.
Methods
Patients in the trial (NCT04583735) had clinical activity score (CAS) ≤1 and TED duration 2-10 years. Serum samples were collected from placebo ($n = 20$) and teprotumumab ($n = 41$) patients at baseline and weeks 3, 12 and 24 and analyzed on the Olink Explore 3072 platform. Serum IGF-1 levels were analyzed with the R&D Quantikine assay.
Results
In samples from teprotumumab-treated patients, drug target engagement was validated and confirmed through the IGF-1 immunoassay. Modulation of IGF-1 pathways (i.e., soluble IGF-1R, and insulin-like growth factor binding proteins [IGFBPs] 1-3) was also observed post-teprotumumab treatment in the Olink assay. Additionally, teprotumumab treatment inhibited key proteins that are elevated in tissues of TED patients. These included proteins involved in collagen formation and extracellular matrix (ECM) production, such as COL1A1, OMD, and MMP1; decreased by 2.07, 1.82 and 1.60-fold compared to placebo after 24-week treatment, respectively.
Conclusion
Previous studies have demonstrated that collagen accumulation results in expansion of the ECM that causes destructive tissue remodeling,[1,2] a hallmark of TED. Our findings underscore the pivotal role of IGF-1R activation in TED and confirm target engagement and modulation with teprotumumab in these patients with low CAS, chronic TED. Global proteins associated with the disease were altered by teprotumumab, particularly in pathways related to IGF-binding and ECM which ultimately may lead to disease modification. These insights strengthen our understanding of teprotumumab's therapeutic mechanisms and its role in the management of chronic TED.
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EP1428

JOINT215

Comparison of hematologic and autoimmune status of patients with Graves' disease and autoimmune thyroiditis during surgical treatment

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The purpose
of the study was to compare the hematological and immunological parameters of patients with Graves' disease (GD) and autoimmune thyroiditis (AIT) when performing different volumes of surgical intervention.
Material and Methods
On 28 patients with GD and 36 patients with AIT with anemia performed total thyroidectomy (TT) and subtotal thyroidectomy (ST). HCB, RBC, HCT, MCV, MCH, MCHC, serum iron (Fe) and ferritin (Fr) were determined. Immune status was assessed by the level of CD3+, CD4+, CD8+, CD4+/CD8+, CIC, erythrophagocytosis, TRAb, TPOAb.
Results and discussion
Before surgery, more pronounced changes are observed in the group of patients with AIT statistically significant changes are noted in the level of MCV, MCH, Fe, Fr in comparison with the corresponding indicators of the group of patients with GD. Immune disorders expressed in immunodeficiency of the cellular component of immunity and activation of the humoral component, are observed in both groups of patients, only the level of CD4+ helper cells is significantly lower in patients with AIT ($P < 0.05$). A year after ST, hematological disorders worsened in both groups of patients compared to controls. At the same time, in terms of the values of HGB, RBC and HCT indicators, both groups differ significantly from each other and more pronounced changes are observed in individuals with GD. A deterioration is also observed among indicators of immune status (CD3+, CD4+, CD4+/CD8+, CIC) and are more pronounced in patients with AIT ($P < 0.05$). A year after TT, hematological parameters improved significantly in patients of both groups and were practically no different from the control group. Only the hematocrit level in individuals with AIT (37,9± 0,4%)still differs from the corresponding indicator for controls and patients with GD ($P < 0.05$). By this time, the immunological parameters of both groups had approached the control ones.
Conclusions
Although GD and AIT are autoimmune diseases with different clinical presentations and different mechanisms for the development of anemia, the results obtained are unidirectional. Performing TT in patients with GD and AIT with anemia leads to the cessation of the autoimmune process and improvement of hematological parameters against the background of euthyroidism, achieved through levothyroxine replacement therapy. The preservation of thyroid tissue during ST in both groups of patients apparently contributes to the further aggravation of autoimmune disorders and deterioration of hematological parameters, despite the euthyroid hormonal background of the patients.

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EP1429

JOINT3803

The role of procalcitonin and ProGRP in the follow-up of medullary thyroid carcinoma

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Introduction
Calcitonin (Ctn) and carcinoembryonic antigen (CEA) are the primary tumour markers for medullary thyroid carcinoma (MTC) follow-up. Procalcitonin (ProCtn) and Progastrin-releasing Peptide (ProGRP) have been suggested as complementary markers for MTC, but the available data are still limited.
Aims
To evaluate the performance of ProCtn and ProGRP in post-surgical follow-up of MTC.
Materials and methods
Ctn, ProCtn, and ProGRP levels were measured at the last follow-up in a total of 85 patients: 21 controls with non-MTC thyroid disease and 64 patients with surgically treated MTC.
Results
In the control group, all patients had normal Ctn, ProCtn and ProGRP levels. Among the 64 patients with MTC, 35 (54.7%) were female, with a median age at diagnosis of 60 years. 46 patients had sporadic MTC and 18 hereditary MTC. The median follow-up time was 93.7 months. At the end of the follow-up, 25 patients (39.1%) showed no evidence of disease, 27 (42.2%) presented with biochemical evidence, and 12 (18.8%) exhibited structural evidence. ProCtn and Ctn ($r = 0.939$) and ProGRP and Ctn ($r = 0.781$) values were strongly correlated ($P < 0.001$). Median ProCtn and ProGRP values differed across the groups - no evidence of disease, biochemical evidence, and structural evidence - at 0.06 ng/ml, 0.7 ng/ml, and 9.8 ng/ml for ProCtn, and 40.2 pg/ml, 62.6 pg/ml, and 536.6 pg/ml for ProGRP, respectively ($P < 0.001$). No patients with structural disease had normal Ctn levels. Among those with elevated Ctn levels of ≤ 150 pg/ml, 10/20 (50%) had normal ProCtn, and 14/18 (77.8%) had normal ProGRP. None of the patients with elevated Ctn and normal ProCtn or ProGRP levels showed evidence of structural disease. The most accurate ROC-derived cut-off values for identifying structural disease were settled at 138.4 pg/ml for Ctn [AUC: 0.94 (95%CI 0.88-1), $P < 0.001$] with 91.7% sensitivity, 82.7% specificity, 55% positive predictive value (PPV), and 97.7% negative predictive value (NPV); at 1.76 ng/ml for ProCtn [AUC: 0.96 (95%CI 0.9-1), $P < 0.001$] with 90.9% sensitivity, 87.8% specificity, 62.5% PPV, and 97.7% NPV; and at 161.4 pg/ml for ProGRP [AUC:0.98 (95%CI 0.94-1), $P < 0.001$] with 88.9% sensitivity, 97.9% specificity, 88.9% PPV, and 97.9% NPV.
Conclusions
ProCtn and ProGRP strongly correlate with Ctn in MTC follow-up. The established cut-off values for Ctn and ProCtn demonstrate excellent sensitivity and NPV in detecting structural disease, while ProGRP provides high specificity, PPV, and good sensitivity. These findings suggest that they may be promising complementary markers, but further research is needed to validate their clinical utility.

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EP1430

JOINT2711

Resection of the thyroid isthmus as a surgical treatment method for well-differentiated thyroid cancer in selected patients

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Introduction
We present a study aimed at exploring the advantages and disadvantages of isthmusectomy (IE), as well as determining the indications and limitations for its application. Considering the relatively favorable prognosis associated with well-differentiated thyroid cancer (WDTC), there is growing interest in minimizing the extent of invasive procedures and the risk of surgical complications. Currently, there are no recommendations regarding the extent of thyroid resection for tumors confined to the isthmus. However, scientific evidence supports IE as a potentially safe and effective method.
Materials and Methods
A retrospective analysis was conducted to evaluate the treatment outcomes of 32 patients who underwent internal excision for tumors confined to the isthmus at the Endocrinology Research Centre (median age: 47years [25;70], 78.13% under 55 years). Demographic data, clinical and pathological characteristics of tumors based on ultrasound findings, results of fine needle aspiration biopsy (FNAB), and morphological examination (ME) of postoperative specimens were recorded. In cases with confirmed malignancy staging was performed according to the American Joint Committee on Cancer (AJCC) system (8th edition) and risk stratification for recurrence.
Results
FNAB results confirmed malignant thyroid tumors in 11 patients (34.4%) (Bethesda VI), in 8 patients (25,0%) a Bethesda V, in 13 patients (40.6%) a Bethesda IV. Histologically, WDTC was confirmed in 22 patients, all staged as I: T1a (50.0%), T1b (40.9%), T2 (9.1%). The mean tumor size was 15 mm [6;32]. ME revealed metastases in adjacent lymph nodes (LN) (N1a) in 2 patients, each measuring less than 1 cm, with fewer than 5 affected LN. 21 patients (95.5%) with confirmed WDTC were at low risk, while 1 patient (4.5%) was classified as high risk for disease recurrence. Papillary thyroid cancer was confirmed in 21 patients, with high-grade differentiated thyroid carcinoma diagnosed in 1 patient who subsequently underwent total thyroidectomy. Regarding early postoperative complications, only one patient experienced transient hypocalcemia. The median follow-up period was 18 months [8;34] with no reported recurrences of the disease. Patient observations are ongoing.
Conclusions
The findings indicate the potential of IE as a surgical treatment for lesions confined to the isthmus, provided that an appropriate assessment of the characteristics of the detected lesion and the overall health status of the patient is conducted at the preoperative stage. The implementation of IE into surgical practice may lead to a reduction in the risks of typical postoperative complications associated with this localization, such as recurrent laryngeal nerve injury, hypoparathyroidism, and hypothyroidism.

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EP1431

JOINT3736

Medullary thyroid carcinoma: a 15-year case series

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Introduction
Medullary thyroid carcinoma (MTC) accounts for up to 5% of thyroid carcinomas and can exhibit variable clinical behaviour. Nearly 25% are associated with multiple endocrine neoplasia type 2 syndrome (MEN2) or familial isolated MTC.
Objectives
To evaluate the characteristics and clinical evolution of patients with MTC followed at our institution.
Methods
Retrospective analysis of the medical records of patients diagnosed with MTC between 2009 and 2024.
Results
Seventy-six patients were identified (55.3% women), with a mean age at diagnosis of 61 ± 14.1 years. Preoperative diagnosis was established in 32.9% ($n = 25$) of patients. At diagnosis, staging was as follows: stage I ($n = 32$), II ($n = 15$), III ($n = 6$), IVa ($n = 15$), and IVc ($n = 8$). Germline pathogenic *RET* variants were identified in 14 of 67 patients (20.9%), while somatic variants were identified in 8 of 15 patients (53.3%). Surgery was performed in 94.7% ($n = 72$), including hemithyroidectomy (n = 8), total thyroidectomy (TT) ($n = 20$) - 7 with two-staged surgeries, TT with bilateral recurrent dissection ($n = 29$), and TT with bilateral recurrent + lateral neck dissection ($n = 15$). The median tumour size was 14 mm, with 25 of 67 patients (37.3%) presenting microcarcinomas. R0 resection was achieved in 52 of 62 patients (83.9%). Vascular invasion was observed in 12 of 50 cases (24%), while extrathyroidal extension was observed in 12 of 63 cases (19%). Local cervical recurrence occurred in 18.8% ($n = 13$) (median time post-surgery: 6.5 months), treated surgically in 9 cases; the remaining patients were kept under surveillance. Additional therapy was performed in 13.2% of patients ($n = 10$): 9 had radiotherapy (cervical, $n = 6$; bone, $n = 3$), and 3 received tyrosine kinase inhibitors. Median follow-up was 67.5 months (IQR 24.8 – 121). At the most recent evaluation, 46.1% ($n = 35$) of patients were disease-free, 30.3% ($n = 23$) had biochemical evidence of disease, and 23.7% ($n = 18$) had structural disease (locoregional, $n = 4$; distant, $n = 14$ - bone ($n = 7$), liver ($n = 5$), lung ($n = 8$)). Among those with structural disease, 72.2% ($n = 13$) showed disease progression. A total of 21.1% of patients ($n = 16$) died, with 10 of these deaths attributed to MTC. Median overall survival was 66.5 months (IQR 25.5 – 119.3).
Conclusions
The importance of long-term follow-up is emphasized due to the possibility of recurrence or disease progression. Genetic testing is essential not only for individual prognosis but also for familial genetic counselling, in addition to enabling targeted systemic therapy when indicated.

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EP1432

JOINT1338

Cardiovascular and metabolic markers after thyroid cancer treatment: a fine balance of long-term outcomes

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Introduction
Differentiated thyroid carcinoma (DTC), although the most common endocrine malignancy, has a better overall survival rate than most malignancies. It has been presumed that intermediate and high-risk tumors require long term suppression with thyroid hormones in order to prevent thyroid stimulating hormone (TSH) tumor growth. Given the interplay between cardiovascular system, metabolic parameters and thyroid hormones, long term subclinical or overt hyperthyroidism might additionally impact negatively the survival of these patients. Moreover, radioactive iodine therapy (RAI) can also play a role in the development of cardiovascular pathology of these patients. Not enough studies investigate this fine balance and current recommendations are based on moderate quality evidence with heterogenous data.
Objective
We performed a retrospective observational study in order to investigate the relationship between cardiovascular and metabolic profiles of patients with DTC who underwent total thyroidectomies in our hospital from 2010-2024. Mean follow-up time was 5.34 years (SD = 4.76).
Results
A total of 144 patients were included, median age at diagnosis 52.5 years (IQ $r =$ 22), 88.19% females. Papillary thyroid cancer accounted for 93.62% of cases and 72.83% were stage I. Fifty-five (38.19%) were under suppressive therapy (defined as TSH < 0.5 uUI/ml) and 64.58% underwent RAI treatment with a median of 50 (IQ $r = 125$) mCi doses. We compared metabolic profiles of TSH-suppressed and non-suppressed groups, which were similar in terms of age, BMI and gender. We found no statistically significant differences between glycemia, HbA1c, lipid profiles, systolic and diastolic blood pressure and heart rate in these two groups. Fibrinogen levels were higher (363.83 +/- 71.69 mg/dl vs 319.77 +/- 51.08, one-sided p = 0.029) in patients with suppressed TSH. Same analysis was performed with respect to RAI treatment and higher heart rate was found in patients who received RAI therapy ($P = 0.014$). Not enough patients developed cardiovascular pathologies after DTC treatment in order to achieve statistical significance.
Conclusion
More studies with longer follow-up periods that also investigate cardiovascular and metabolic outcomes are needed in order to assess and customize life-long management of patients with DTC. The possible low-grade inflammation and elevated heart rate could be indicative of future cardiometabolic negative outcomes in these patients.

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EP1433

JOINT1999

The value of intraoperative frozen section in surgical management of thyroid nodules

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Introduction
Nodular thyroid pathology poses the problem of its histological nature on which the therapeutic approach depends. Intraoperative frozen section, by giving the rapid diagnosis of benignity or malignancy, conditions the immediate surgical procedure. The aim of this work is to study the sensitivity and specificity of intraoperative frozen section in thyroid pathology and to identify its limits.
Materials and Methods
This is a retrospective study having collected over a period of two years, 120 patients operated on for thyroid pathology. The average age was 46 years (range 15 to 84 years). A female predominance was noted with a sex ratio of 0.17. Preoperative thyroid cytology was performed in 9 cases. The tumors were benign in 77 cases (64.2%) and malignant in 43 cases (35.8%). We compared the results of intraoperative frozen section with the definitive histological examination.
Results
The intraoperative frozen section concluded to a benign lesion in 90 cases (75%), a malignant lesion in 29 cases (24.1%). It was doubtful in one case (0.9%). The doubtful case corresponded to a malignant lesion on the definitive histological examination. No false positive (FP) was reported. The sensitivity of the extemporaneous examination for all histological types was 69% and the specificity was 100%. The predictive positive value was 100% and the predictive negative value was 85.5%. The diagnostic efficiency was 88.3%.
Conclusion
The reliability of the intraoperative frozen section of the thyroid is widely demonstrated. Our study showed a perfect specificity of this examination; however the difficult interpretation of thyroid lesions of follicular architecture and microcarcinomas explains a sensitivity of 69%.

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EP1434

JOINT3394

Radioiodine-refractory differentiated thyroid cancer in children and adolescents: a retrospective single-center study

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Introduction
Differentiated thyroid cancer (DTC) in pediatric patients is rare but often aggressive, with a high prevalence of regional and distant metastases. Tailored management strategies are particularly critical for radioiodine-refractory (RAIR) cases, which represent 10–30% of all DTCs. Current RAIR classification systems lack pediatric-specific criteria, necessitating new frameworks to address the unique clinical course and therapeutic needs of this population.
Objectives
To evaluate outcomes in pediatric DTC patients treated with surgery and radioiodine (RAI) therapy, with a focus on RAIR cases and those presenting with advanced disease. Additionally, to propose a new RAIR classification based on iodine avidity and therapeutic outcomes.
Materials and Methods
A retrospective review of medical records for 278 pediatric DTC patients treated between 2008 and 2022 was conducted. Patients underwent surgery followed by RAI therapy, with follow-ups every 3 to 6 months. Advanced cases were identified by high-risk presentation and resistance to RAI therapy. Kaplan-Meier analysis was used to assess progression-free survival (PFS). Cox regression adjusted for age, sex, and interaction terms was performed to evaluate predictors of outcomes.
Results
Among 278 patients, 39 (14%) had advanced disease. In this subgroup, 4 achieved remission, 29 had disease stabilization, and 6 experienced biochemical or structural progression, with one patient requiring lenvatinib therapy. The PFS rate among RAIR patients was 84.62%, with an overall 5-year survival rate of 100%. Patients with RAI-non-avid metastases exhibited poorer outcomes in terms of PFS and remission probability.
Conclusions
This study highlights the need for personalized therapeutic approaches for pediatric DTC patients. A new classification system categorizing RAIR cases based on iodine avidity and therapeutic outcomes should be proposed. This framework aims to guide treatment and follow-up strategies, potentially informed by the molecular and genetic distinctions between iodine-avid and non-avid subgroups. Patients with non-avid metastases demonstrated worse prognoses, underscoring the importance of tailored interventions.

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EP1435

JOINT3513

The role and limitations of fine-needle aspiration cytology in thyroid nodule diagnosis

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Background
Fine-needle aspiration cytology (FNAC) is the gold standard for evaluating thyroid nodules, offering a minimally invasive and ultrasound-guided approach to distinguishing benign from malignant lesions. This technique plays a critical role in optimizing patient management by guiding therapeutic decisions and minimizing unnecessary surgeries.
Objective
To assess the diagnostic accuracy of FNAC in the management of thyroid nodules and identify its limitations.
Methods
This retrospective cross-sectional study analyzed FNAC results from patients who underwent thyroid nodule surgery at our ENT Department over a five-year period (January 2018 – December 2022).
Results
A total of 333 patients were included, with a mean age of 47.45 years and a strong female predominance (male-to-female ratio of 1:5.8). The primary mode of detection was a palpable cervical mass (57.35%), while 15.6% were incidental findings. Multinodular goiters were more prevalent (61.6%) than solitary nodules (38.4%). Ultrasound classification revealed that 52% of nodules were categorized as **EU-TIRADS <4**, while 48% were classified as **EU-TIRADS ≥ 4**. FNAC was performed on 75 patients (22.5%). The results were distributed as follows: 14.7% non-diagnostic (Bethesda I), 44% benign (Bethesda II), 10.7% atypia/follicular lesion of undetermined significance (Bethesda III), 6.6% follicular neoplasm/-suspicious for follicular neoplasm (Bethesda IV), and 24% suspicious for malignancy (Bethesda V). No cases were classified as Bethesda VI (malignant). Final histopathological analysis confirmed benign pathology in 48 cases, with FNAC correctly identifying 23 (TN = 47.9%). Among 27 malignant cases, FNAC correctly diagnosed 17 (T P = 70.8%). The overall diagnostic efficacy of FNAC was 53.3%.
Conclusion
FNAC remains a crucial diagnostic tool for thyroid nodules, but its performance can be enhanced through systematic ultrasound guidance to reduce false-negative rates. Optimizing this technique within a multidisciplinary framework would refine diagnosis and improve patient management.

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EP1436

JOINT2364

A problem necessitating a reemphasized solution: a case of hypothyroidism presenting as a new pericardial effusion in a patient with helicobacter pylori infection treated with proton-pump inhibitor

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Background
Oral Levothyroxine (LT4) is the primary treatment for hypothyroidism and requires an acidic gastric pH for absorption. On the other hand, Proton Pump Inhibitors (PPIs) are the most effective treatment for gastric acid suppression. Simultaneous use of LT4 and PPI can be challenging even for experienced physicians.
Case Presentation
A 70-year-old female with Hypothyroidism and Helicobacter pylori infection, who is compliant with her Levothyroxine and Pantoprazole, presented to the hospital with a 3-week onset of fatigue and chest pain. She denied lethargy, constipation, cold intolerance, weight gain, or any bleeding. Vital signs showed T 36.8C, HR 63bpm, and BP 110/60mmHg. Physical examination showed intact sensorium, no thyromegaly, edema, murmurs, or abnormal lung and abdominal findings. Diagnostic tests were remarkable for TSH 31.33 mIU/l(0.5-5 mIU/L), FT4 0.6 ng/dl (0.8-1.8 ng/dl), normal Troponin, EKG with low voltage QRS, chest X-ray showed cardiomegaly, echocardiogram showed new pericardial effusion without tamponade. The cardiology team suggested no urgent intervention. The endocrinology team increased her levothyroxine dose; the pharmacy was consulted for an LT4 liquid or gel formulation however, it was unavailable. Her Pantoprazole was switched to Famotidine which was administered 4 hours after LT4. Her symptoms improved, and she was discharged with strict follow-up for thyroid function testing and a repeat echocardiogram.
Discussion
PPIs suppress gastric acid for 48 hours due to their irreversible binding to H-K ATPase on parietal cells. Previous studies showed that using PPI in the morning or night while on LT4 causes an almost equal degree of TSH elevation. Alternatively, since Histamine 2 Receptor Blockers (H2RB) suppress acid secretion for only 4 hours, LT4 can be given 4 hours after H2RB administration. Increasing LT4 doses may be considered but can predispose patients to side effects. Interestingly, LT4 gel capsules and liquid formulations do not require acidic pH for absorption and are unaffected by PPI. Rectal and IV LT4 are options for acute needs but are tedious for maintenance administration.
Conclusion
Patients on LT4 requiring concurrent acid suppression can benefit from H2RB and Gel coated or liquid formulations of LT4. Patients should be re-educated regarding the need for strict outpatient follow-up with close monitoring of thyroid function tests.
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EP1437

JOINT3784

Thyroid nodules in acromegaly: a study of 78 cases

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Introduction
Acromegaly is a condition often associated with thyroid diseas. The aim of this study was to analyze the incidence of thyroid nodules, including thyroid cancer, in patients with acromegaly.
Material and Patients
This is a retrospective descriptive study involving 78 acromegalic patients hospitalized in the endocrinology department of CHU Ibn Rochd in Casablanca from January 2005 to December 2024. All patients underwent a morphological thyroid assessment. Statistical analysis was performed using Excel.
Results
The average age of the patients was 48 years (range: 18-72), with a male-to-female ratio of 0.33. The average duration of the disease was 8 years. The average IGF-1 level was 582 ng/ml, which is 2.62 times the normal value. Thyroid morphological abnormalities were found in 52 patients. A multinodular goiter was discovered in 85.7% of patients, while 14.3% of patients had a single nodule. The nodule size was less than 10 mm in 71% of the patients and greater than 10 mm in 22% of the patients. Among these nodules, 46.8% were classified as EUTIRADS 3 and 23,4 % were EUTIRADS 4. Therefore, 39% of our patients underwent fine needle aspiration and 23.4% returned a category 3 result according to the Bethesda classification. Additionally, three cases of papillary thyroid carcinoma were diagnosed.
Conclusion
This study highlights the high prevalence of thyroid abnormalities, particularly multinodular goiter, in patients with acromegaly. The majority of thyroid nodules were classified as moderate to high suspicion of malignancy. underscoring the need for careful monitoring and early diagnosis of thyroid cancer in acromegalic patients. These findings emphasize the importance of regular thyroid assessments in this patient population.

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EP1438

JOINT1634

Report of two cases of thyroid hormone resistance syndrome with developmental disorders in young children

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Thyroid hormone resistance syndrome (RTH) is a rare endocrine disease mainly caused by thyroid hormone receptor (THR) deficiency, characterized by elevated free thyroid hormones (FT3, FT4) and unsuppressed thyroid stimulating hormone (TSH). In this study, we report two cases of RTH in young children, both with developmental disorders. Child 1 was a 4-year-old boy who presented to the clinic with language delay, global developmental delay, mental retardation, and thyroid function showing elevated FT3 and FT4 and normal or elevated TSH. Genetic testing revealed a de novo heterozygous mutation in the thyroid hormone receptors beta (THRB) gene c.1373T>C, resulting in a change in amino acid at

position 458 of THRB from valine to alanine (p.Val458Ala) in the form of generalized thyroid hormone resistance (GRTH). Child 2 was a 2-year-old boy who presented to the clinic with abnormal thyroid function, characterized by growth retardation, severe low body weight, and emaciation, accompanied by tachycardia as a symptom of thyrotoxicosis. Genetic testing revealed a de novo heterozygous mutation in the THRB gene c.959G > A, resulting in a change in amino acid 320 of THRB from arginine to histidine (p.Arg320His), which was considered to be a selective pituitary thyroid hormone resistance (PRTH) type. We used β-blockers to control symptoms in child 2 with hyperthyroidism and developed individualized nutritional support programs for two children with growth and developmental disorders.The clinical manifestations of thyroid hormone resistance syndrome are complex, and early genetic testing can help reduce misdiagnosis and underdiagnosis. Its treatment is symptomatic and inappropriate methods such as antithyroid drugs, thyroidectomy and ablation therapy should be avoided.

Keywords
thyroid hormone resistance syndrome;thyroid hormone receptors beta;children;-developmental disorders;genetic testing.

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EP1439

JOINT2380

An unusual case of a patient alternating from hypothyroidism to hyperthyroidism following COVID-19 infection

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Introduction
Hashimoto's thyroiditis and Graves' disease are the most prevalent autoimmune thyroid disorders. Antibodies targeting the TSH receptor (TRAbs) may be either stimulatory (TSAbs), leading to hyperthyroidism, or blocking (TBAbs), resulting in hypothyroidism. In rare instances, patients may switch from TSAb to TBAb or vice versa, thereby exhibiting alternating hyper- and hypothyroidism. Although the shift from hyperthyroidism to hypothyroidism is commonly observed in clinical practice, progression from hypothyroidism to hyperthyroidism is notably uncommon. Herein, we describe a patient who presented initially with severe hypothyroidism and subsequently transitioned to hyperthyroidism following COVID-19 infection.
Case Presentation
A 57-year-old Caucasian female, smoker, with no previous history of thyroid disease, presented to the emergency department with profound fatigue, lethargy, weight gain, and diffuse edema. The patient reported mild proximal muscle weakness, hoarseness, and memory disturbances. Her medical history included obesity, hyperlipidemia, hypertension, and nephrolithiasis. On physical examination, she appeared myxedematous, with generalized edema, psychomotor retardation, hoarseness, and bradycardia. Laboratory investigations revealed markedly elevated TSH (83.93 μIU/ml), reduced free T4 (<0.42 ng/dl), high anti-TPO antibodies (>1,000 IU/ml), and elevated CPK (1106 U/L). Treatment with liquid levothyroxine was initiated, which resulted in rapid clinical improvement. Subsequently, the patient contracted COVID-19 infection and after a 13-day hospitalization, she was discharged with further clinical and biochemical improvement. One month later, at outpatient follow-up, she was euthyroid and in stable condition. However, two months post-COVID-19 infection, she developed clinical features indicative of hyperthyroidism, including weight loss, palpitations, nervousness, and fatigue in the absence of neck pain, tenderness, or fever. Laboratory evaluation showed a suppressed TSH level (0.011 μIU/ml; normal range: 0.25–3.43 μIU/ml). Despite the reduction of her levothyroxine dosage, her symptoms persisted. A subsequent workup revealed further TSH levels reduction <0.0083 μIU/ml, with normal FT3 and FT4 levels. Notably, thyroid-stimulating immunoglobulins (TSI) were tested positive, prompting initiation of thiamazole therapy alongside continued levothyroxine treatment, following a "block and replace" strategy. Under this combined regimen, the patient remains asymptomatic, euthyroid, and in good overall health.
Conclusions
This case underscores a rare instance of hypothyroidism transitioning to hyperthyroidism, highlighting the potential for alternating stimulatory and blocking TSH receptor antibodies. These findings may be particularly relevant following COVID-19 infection, suggesting that viral infections may trigger or exacerbate underlying autoimmune processes. Further research is warranted to elucidate the immunological mechanisms contributing to this unusual thyroid function shift and optimize management strategies for similar complex cases.

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EP1440

JOINT3057

Chemotherapy-induced hypothyroidism: a crucial diagnostic challenge

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Introduction
Severe hypothyroidism is a rare but possible endocrine complication following chemotherapy. It may be linked to an autoimmune thyroiditis triggered by cytotoxic agents. This poster presents a case of severe thyroid dysfunction in the context of post-chemotherapy follow-up for Ewing's sarcoma.
Clinical Case
We report the case of a 24-year-old patient followed for Ewing's sarcoma of the jaw, who underwent surgery, followed by a pulmonary metastatic relapse. The patient had surgery and adjuvant chemotherapy, and was referred for exploration of thyroid hypermetabolism discovered during a PET scan performed as part of the staging assessment. Laboratory tests revealed a TSH > 100 μUI/ml and positive anti-thyroglobulin antibodies, compatible with severe hypothyroidism. A cervical ultrasound showed signs of thyroiditis. Management consisted of introducing hydrocortisone at 10 mg/day for 5 days, followed by a gradual introduction of levothyroxine to an optimal replacement dose. Clinical and biological monitoring allowed for gradual improvement in hormonal parameters and symptoms.
Scientific Discussion
Although chemotherapy is necessary to treat aggressive malignant conditions, it can trigger thyroid inflammation through immune mechanisms, notably by the production of anti-thyroid antibodies such as anti-thyroglobulin and anti-thyroid peroxidase antibodies, which damage the gland and induce hypothyroidism. It can also have a direct toxic effect due to the use of certain chemotherapy agents, such as alkylating agents and anthracyclines. Management of this condition relies on thyroid hormone replacement with levothyroxine, with a cautious approach depending on the severity of the dysfunction.
Conclusion
Hypothyroidism is a recognized complication of chemotherapy, often under-diagnosed. This case highlights the importance of screening for thyroid dysfunction in patients who have received treatments likely to affect thyroid function, particularly aggressive treatments like alkylating agents, and especially when atypical symptoms or suggestive imaging findings are present. Prompt and appropriate management helps prevent complications and significantly improves the patients' quality of life.

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EP1441

JOINT3883

Hyperthyroidism and pregnancy: specificities of the first trimester

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Introduction
Hyperthyroidism is a common endocrinopathy during pregnancy, often presenting as transient gestational hyperthyroidism in the first trimester. If uncontrolled, it poses a risk of maternal and fetal complications, potentially threatening vital prognosis.
Study Objective
Evaluate the clinical and therapeutic profile of first-trimester hyperthyroidism in pregnancy.
Materials and Methods
A prospective study was conducted in our Department, including 168 patients diagnosed with hyperthyroidism in the first trimester (January 2019 to September 2024). Statistical analysis was performed using SPSS software.
Results
The average age was 26 years, with a mean gestational age of 11 weeks. A personal history of thyroid disease was reported in 16 patients. The predominant symptom was pregnancy-related vomiting, present in 98% of the patients. The mean ultrasensitive TSH was 0.04 mIU/l,the mean free T4 (T4L) was 12 ng/l,ranging from 1.1 to 11 times the normal values, and the mean free T3 (T3L) was 5.7 ng/l,ranging from 1.1 to 3 times the normal values. Graves' disease was identified in four patients, and toxic goiter in five. Sixty-five percent of patients were treated with synthetic antithyroid drugs and beta-blockers, 16% with beta-

blockers alone, 7.5% with beta-blockers and corticosteroids, and 2.5% with synthetic antithyroid drugs alone. For the remaining patients, simple monitoring was implemented. Symptoms of hyperthyroidism disappeared in 75% of patients, with normalization of thyroid function by 16 weeks of gestation. As for obstetric complications, 2 fetal deaths were recorded.
Conclusion
This study demonstrated that The most common cause of Hyperthyroidism in the First Trimester is transient gestational hyperthyroidism. Antithyroid drugs (ATDs) were reserved for severe forms With a favorable outcome in the majority of patients After adequate care.

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EP1442

JOINT679

Synchronous papillary thyroid cancer and malignant neoplasms: Hodgkin lymphoma and nasopharyngeal carcinoma

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Objectives
Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer. Its co-occurrence with Hodgkin's lymphoma (HL) and nasopharyngeal undifferentiated carcinoma (UCNT) is extremely rare. The aim of this study is to investigate the clinical characteristics and treatment challenges associated with this unusual situation.
Methods
We conducted a retrospective analysis of three cases of synchronous tumours involving the thyroid gland, which were reported in our department.
Results
This report presents the cases of three female patients aged 27, 51, and 70 years, respectively. One patient presented with fever and night sweats, another with a suspicious thyroid nodule, and the third with multiple cervical lymph nodes and unilateral epistaxis. Physical examination revealed cervical lymphadenopathies in all three cases, an indurated thyroid nodule in one case, and a suspicious tumoral process in the nasopharynx in another case. All patients underwent a neck ultrasound. Two patients underwent a body scan in addition to a nasopharyngeal scan. All patients underwent a thyroid fine needle aspiration, with one patient also receiving a nasopharyngeal biopsy and two patients receiving an adenectomy. The diagnosis of papillary thyroid carcinoma (PTC) was made in two cases with Hodgkin's lymphoma (HL) and in one case with undifferentiated carcinoma (UCNT). Initially, all three patients underwent total thyroidectomy with lymph node dissection. Subsequent treatment for the other neoplasms after surgery included chemotherapy for the two cases of Hodgkin's lymphoma and radiotherapy associated with chemotherapy for the undifferentiated carcinoma of the nasopharynx. The radioactive iodine treatment was delayed following the management of synchronous cancer.
Conclusion
the synchronous occurrence of differentiated thyroid cancer and malignant tumors presents a significant diagnostic and treatment challenge. It is important to note that the presence of a suspicious lymph node in papillary thyroid carcinoma may indicate the presence of other concurrent head and neck malignant tumors.

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EP1443

JOINT2804

Recurrent thyroid-associated ophthalmopathy in hashimoto's thyroiditis: a case report

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Introduction
Thyroid-associated ophthalmopathy (TAO) is predominantly linked to Graves' disease, manifesting in approximately 25-50% of such patients. However, its association with Hashimoto's thyroiditis (HT) is rare, with only isolated reports in the literature. The presence of recurrent TAO in HT is even more uncommon and presents unique diagnostic and therapeutic challenges. This case highlights recurrent moderate-to-severe TAO in a patient with HT, requiring systemic corticosteroid therapy.
Case Presentation
An 80-year-old female with a 15-year history of hypothyroidism secondary to HT, diabetes mellitus, and hyperlipidemia presented with progressive orbital symptoms, including erythema, swelling, diplopia, and burning sensations. Examination revealed bilateral proptosis (Hertel: 22 mm in the right eye, 23 mm in the left eye), conjunctival hyperemia, and a Clinical Activity Score (CAS) of 5/7, indicating active and moderate-to-severe TAO. The patient was receiving treatment with levothyroxine (75 µg/day), rosuvastatin (10 mg/day), and linagliptin (5 mg/day). Laboratory investigations demonstrated normal TSH (1.22 mIU/L), normal free T3 (4.05 pmol/L), normal free T4 (16.9 pmol/L), and significantly elevated thyroid receptor antibody (TRAb) (19.97 IU/L). Anti-thyroid peroxidase (Anti-TPO) and anti-thyroglobulin (Anti-Tg) antibodies were positive. Orbital magnetic resonance imaging (MRI) revealed no evidence of compressive optic neuropathy. The patient received a cumulative dose of 4.5 g of methylprednisolone over 12 weeks. Following treatment, the CAS decreased to 1/1, and the ophthalmopathy became inactive. However, 11 months after completing therapy, ocular symptoms recurred, with a CAS of 4/4 and an increased bilateral Hertel measurement of 24 mm. Thyroid function tests revealed TSH: 16 mIU/l,normal free T4 levels, and an elevated TRAb level of 27 IU/L. The levothyroxine dosage was increased and a 6-week course of methylprednisolone therapy was planned for active ophthalmopathy.
Conclusion
The pathogenesis of TAO in HT remains poorly understood, it may involve a different immunopathogenic mechanism, primarily mediated by TRAb and local inflammatory cytokines. Recent case reports have highlighted instances of TAO in patients with Hashimoto's thyroiditis, even in the absence of TRAb. Corticosteroids are the first-line therapy for active disease. Our patient received a cumulative dose of 4.5 g of methylprednisolone over 12 weeks, leading to a temporary resolution of symptoms. However, relapse occurred 11 months post-treatment, requiring a second cycle of steroid therapy. Optimizing thyroid hormone replacement is crucial in hypothyroid TAO cases, as untreated hypothyroidism may exacerbate orbital inflammation. In summary, while TAO is uncommon in HT, clinicians should remain vigilant for ocular manifestations in these patients.

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EP1444

JOINT3275

Hormonal effects of the thyroid gland in breast cancer chemotherapy

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Breast cancer (BC) is the most common malignancy among women and a leading cause of mortality worldwide. Its rising prevalence makes it a significant public health concern. Despite extensive research, the potential link between thyroid dysfunction and BC remains controversial. The thyroid gland regulates metabolism, immune response, and cell growth, potentially influencing cancer progression. However, studies provide conflicting evidence regarding whether thyroid diseases, such as hypothyroidism, hyperthyroidism, and autoimmune disorders, contribute to BC development or progression. Understanding the impact of thyroid function on BC patients undergoing chemotherapy is crucial for improving treatment strategies and patient outcomes.
Purpose
this study aims to assess thyroid function in BC patients undergoing chemotherapy and its changes during treatment.
Material and Methods
By measuring key thyroid biomarkers and analyzing their variations, the research seeks to determine whether thyroid dysfunction plays a role in BC progression or is a consequence of chemotherapy. Additionally, it examines the relationship between thyroid hormone levels and lymph node involvement, a critical prognostic factor. The study included 86 BC patients and 30 healthy controls. Assessments included:

- Measurement of thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), and anti-thyroid peroxidase antibodies (anti-TPO).
- PET-CT analysis of 18-FDG uptake in the thyroid gland.
- Evaluation of lymph node involvement via clinical and radiological data.
- Statistical analysis using SPSS v.19, with $P < 0.05$ considered significant.

The results. BC patients exhibited significant differences in thyroid function compared to the control group:.

- Lower TSH (1.72 $\pm$ 0.89 vs. 2.1 $\pm$ 0.74 µIU/ml, $P = 0.042$).
- Lower T3 (1.23 $\pm$ 0.34 vs. 1.56 $\pm$ 0.41 nmol/l,$P = 0.035$).

• Higher T4 (17.8 ± 3.5 vs. 14.2 ± 3.1 pmol/l,$P = 0.028$).
• Higher anti-TPO (64.5 ± 20.3 vs. 48.1 ± 18.7 IU/ml, $P = 0.017$)
No significant thyroid function differences were found between invasive and ductal BC. However, lymph node involvement varied significantly ($P = 0.018$), suggesting a possible link between thyroid function and tumor aggressiveness.
Conclusion
BC patients show significant thyroid hormone alterations, indicating a possible interplay between thyroid function and BC. However, no direct causative link is established. Chemotherapy may contribute to thyroid imbalances. Autoimmune thyroid involvement warrants further study. Routine thyroid monitoring in BC patients could help prevent complications. Further large-scale research is needed to clarify these findings and optimize treatment strategies through a multidisciplinary approach involving oncologists and endocrinologists.

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EP1445

JOINT680

Surgical treatment of grave's disease in children: a report of five cases

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Objective
To analyze the epidemiological and clinical features of children who underwent thyroid surgery for Grave's disease at our departmet and to evaluate the indications and outcomes of surgical treatment.
Materials and Methods
This retrospective study includes five pediatric cases of thyroid surgery performed between 2010 and 2022 for Grave's disease.
Results
The mean age was 16.8 years (10-17 years), and all patients were female. The average time from diagnosis to surgery was 20.3 months. At diagnosis, 60% of patients had multinodular goiters, while 40% had diffuse and homogeneous goiters. Median FT4 and TSH levels were 12.8 pmol/land 0.05 mU/l,respectively. Surgical indications included thyroid nodules (60%, with compression in one case), resistance to medical treatment (20%), and severe ophthalmopathy (20%). Total thyroidectomy was performed in all cases, with no malignancy detected. Postoperative complications were minimal, with only one case of transient hypocalcemia.
Conclusion
Total thyroidectomy is a safe and effective treatment for pediatric Grave's disease, particularly in cases of treatment resistance or severe manifestations. When performed by experienced surgeons, it provides definitive management with a low risk of complications.

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EP1446

JOINT3314

Primary hyperparathyroidism in a 12-year old girl caused by an ectopic mediastinal adenoma: a case report

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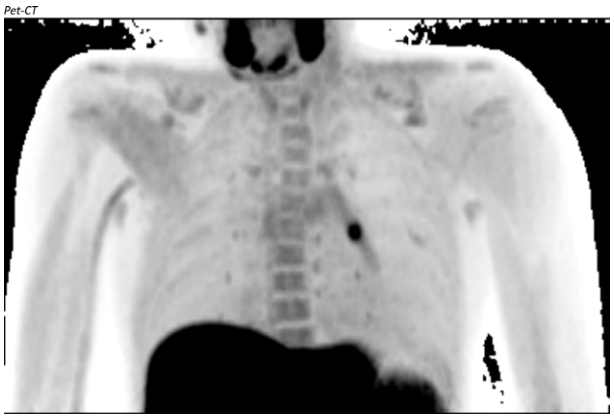
Background
We describe the case of a 12-year-old girl who presented with the incidental laboratory finding of primary hyperparathyroidism.
Case Presentation
The girl had an elevated calcium level in a laboratory test done by her paediatrician to check for a suspected viral infection. As calcium and parathyroid hormone (PTH) levels were repeatedly elevated, she was referred to our centre for further diagnosis. The athletic girl presented without symptoms and had all laboratory signs of primary hyperparathyroidism including elevated serum levels of calcium (3.10 mmol/l[reference range: 2.10-2.55]) and PTH (120 pg/ml [17-74]) and hypercalciuria (Ca/creatinine 0.73 mmol/mmol Crea [<0.61]). Renal ultrasonography showed no evidence of nephrocalcinosis. Cervical sonography failed to identify a suspected site of adenoma in loco typico. PET-CT showed an ectopic adenoma in the mediastinum close to the thymus tissue (Figure). Family history of endocrine neoplasia was negative, genetic testing for MEN-1 and MEN-2 was initiated, results are still awaited. The resection was successfully performed via lateral thoracoscopy, requiring one-lung ventilation.
Conclusions
This is a rare case of primary hyperparathyroidism due to ectopic parathyroid adenoma in a 12-year-old girl. Primary hyperparathyroidism is rare in children with a prevalence of 2–5 cases/100,000. Hyperparathyroidism due to an ectopic adenoma is even rarer in children, with very few cases reported in the literature. Ectopic parathyroid glands are the result of abnormal migration of the parathyroid gland during development. Because of the line of migration from the angle of the mandible to the mediastinum, they are often located in the anterior mediastinum, embedded in the thymus.



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EP1447

JOINT1960

Fahr's syndrome: the hidden neurological face of hypocalcemia

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Introduction
Fahr's syndrome is a rare anatomoclinical entity whose primary etiology is either primary or postoperative hypoparathyroidism. It is characterized by bilateral and symmetrical intracerebral calcifications, mainly located in the basal ganglia, and is most often associated with disturbances in phospho-calcium metabolism.
Case Report
We report the case of a 29-year-old female patient with a history of total thyroidectomy in 2015, who presented to the emergency department with tonic-clonic seizures. Laboratory tests revealed hypocalcemia at 1.27 mmol/l(normal range: 2.25–2.60). Renal and hepatic function tests were normal, and the electrocardiogram showed no abnormalities. Brain CT imaging revealed bilateral and symmetrical intracerebral calcifications in the basal ganglia, supporting the diagnosis of Fahr's syndrome. Further investigations showed hyperphosphatemia at 2.38 mmol/l(normal range: 0.8–1.45) and a markedly reduced parathyroid hormone (PTH) level of less than 4 pg/ml (normal range: 12–72). Magnesium levels were also low. The diagnosis of Fahr's syndrome was established, and the patient was started on replacement therapy with calcium, vitamin D, and magnesium, along with an anticonvulsant. After three months, clinical and biochemical improvement was observed.
Discussion
Fahr's syndrome is classically defined by the triad of symmetrical basal ganglia calcifications, neuropsychiatric symptoms, and parathyroid gland dysfunction. The pathophysiological mechanisms underlying intracerebral calcifications in Fahr's

syndrome remain poorly understood. Most authors suggest a metabolic disorder of oligoglial cells, leading to mucopolysaccharide deposits and secondary vascular, perivascular, and calcified lesions. These calcifications predominantly affect the small blood vessels of the basal ganglia. Clinically, they often manifest as neuropsychiatric disturbances. Fahr's syndrome generally has a favorable prognosis, and correcting phosphocalcium metabolism disorders frequently leads to significant improvement.
Conclusion
In cases of phosphocalcium metabolism disturbances, particularly in the presence of associated endocrine disorders, intracerebral calcifications should be systematically investigated. Treatment is based on correcting phosphocalcium metabolism abnormalities.

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EP1448

JOINT2336

Do patients with Ehlers–Danlos syndrome and a history of fractures have abnormal thyroid hormone profiles?

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Background
Joint hypermobility and instability are among the key risk factors for fractures in patients with Ehlers–Danlos syndrome (EDS). Abnormalities in thyroid hormone profile may be associated with the condition of bones and predisposition to fractures. The purpose of this study was to assess thyroid hormone profiles in patients with hypermobile or classical EDS and a history of fractures.
Material and Methods
The study involved a prospective assessment of 30 female patients with either hypermobile or classical EDS. The patients were divided into two groups. Group 1 comprised patients with no history of fractures ($n = 13$), and group 2 comprised patients with a history of fractures ($n = 17$). All patients underwent an assessment of thyroid hormones and parameters of calcium of phosphate metabolism.
Results
The assessed groups showed no differences in terms of such parameters as thyroid stimulating hormone (TSH) (1.691 ± 0.772 vs. 2.439 ± 1.644, $P = 0.209$ [μIU/ml]), free triiodothyronine (fT3) (3.542 ± 0.802 vs. 3.262 ± 0.495, $P = 0.516$ [pg/ml]), free thyroxine (fT4) (1.335 ± 0.15 vs. 1.354 ± 0.276, $P = 0.630$ [ng/dl]), anti-thymocyte globulin (ATG) (25.623 ± 29.141 vs. 41.312 ± 63.209, $P = 0.99$ [IU/ml]), or anti-thyroid peroxidase (ATPO) (49.385 ± 139.919 vs. 26.259 ± 31.054, $P = 0.902$ [IU/ml]) levels. There was no significant correlation between fractures and TSH (Spearman's R 0.237, $P = 0.207$), fT3 (Spearmans R -0.124, $P = 0.513$), fT4 (Spearman's R -0.496, $P = 0.624$), ATPO (Spearman's R 0.029, $P = 0.878$), or ATG (Spearman's R 0.029, $P = 0.878$) levels.
Conclusions
Positive history of fractures in patients with EDS is not associated with thyroid hormone profile abnormalities.

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EP1449

JOINT134

A single-center experience with papillary thyroid carcinoma arising from a thyroglossal duct cyst

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Introduction
The thyroglossal duct cyst is a congenital cyst that arises during the embryological development of the thyroid, resulting from incomplete obliteration of the thyroglossal duct. Malignant transformation is rare (<1%), with papillary thyroid carcinoma being the most common malignancy encountered. Treatment remains controversial, particularly concerning the need for additional interventions following Sistrunk's procedure, such as total thyroidectomy, lymph node dissection, and radioiodine therapy.
Aims
To assess the experience of our center in the management of papillary carcinoma arising from a thyroglossal duct cyst.
Materials and Methods
A retrospective study of patients diagnosed with papillary carcinoma arising from a thyroglossal duct cyst, followed at our center between 1987 and 2023.
Results
A total of 10 patients were included in the study, with a predominance of females ($n = 6$). The median age at diagnosis was 59 years. All patients initially presented with a painless cervical mass. In 9 cases, the diagnosis was established postoperatively. Seven patients underwent Sistrunk procedure, while 3 underwent cyst excision. Total thyroidectomy was performed in all cases, with 3 patients undergoing the procedure during the same surgical time and 7 in a subsequent operation. During total thyroidectomy, prophylactic central compartment lymph node dissection was performed in 4 patients, and 1 of these also underwent lateral cervical lymph node dissection due to the presence of lymphadenopathy. Papillary carcinoma was concurrently identified in the thyroidectomy specimen in 5 patients; 4 of these were microcarcinomas, and the remaining had a tumor measuring 12 mm. Lymph node metastases were identified in 3 patients. Nine patients received radioactive iodine therapy. An excellent response was observed in 9 patients, while 1 patient remains under surveillance with a biochemical incomplete response, exhibiting a stable thyroglobulin level of less than 1.8 ng/ml. The median follow-up period was 131 months.
Conclusions
Currently, there are no universally accepted guidelines for the management of papillary carcinoma arising from a thyroglossal duct cyst. While fine-needle aspiration cytology is commonly used, its diagnostic accuracy is limited, with the majority of diagnoses being confirmed postoperatively through histopathological examination. The diagnosis of papillary thyroid carcinoma originating from a thyroglossal duct cyst requires a thorough evaluation of both the thyroid gland and bilateral cervical lymph nodes. Regarding treatment, the favorable outcomes observed in our cohort suggest that an overly aggressive approach may not be necessary in most cases. Instead, an individualized treatment strategy, tailored to each patient's specific risk factors, may be more appropriate.

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EP1450

JOINT1054

Steroid-responsive encephalopathy in graves' disease: a rare case of neuropsychiatric symptoms in thyroid autoimmunity

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Introduction
Graves' disease is an autoimmune syndrome primarily characterized by hyperthyroidism, which can also present with goiter, ophthalmopathy, and myxedema. Hyperthyroidism results from thyrotropin receptor antibodies (TRAb) that stimulate thyroid hormone production. While steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) is often linked to Hashimoto's thyroiditis, its occurrence in Graves' disease is rare. SREAT typically presents with confusion, altered consciousness, and seizures, and may involve autoimmune vasculitis rather than abnormal thyroid hormone levels. We report a rare case of SREAT in a patient with Graves' disease, presenting with severe neuropsychiatric symptoms.
Methods
A 48-year-old woman presented to the emergency department with disorientation, disinhibition, speech impairment, inability to walk, and visual hallucinations. Her history included depression, anxiety, and recent hyperthyroidism diagnosis.
Results
Extensive diagnostic testing revealed elevated thyroid hormones, suppressed TSH, high anti-TPO antibodies, TRAb, and TSI, leading to a diagnosis of SREAT associated with Graves' disease. Treatment with high-dose intravenous methylprednisolone, followed by oral corticosteroid tapering, resulted in complete neurological and psychiatric recovery.
Conclusions
This case underscores the importance of recognizing SREAT in patients with Graves' disease and neuropsychiatric symptoms. Prompt diagnosis and corticosteroid therapy can lead to full recovery, highlighting the need for clinical awareness of this rare condition. Further research is essential to improve diagnostic precision and treatment protocols for SREAT in thyroid autoimmunity.

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EP1451

JOINT2901

Routine clinical analysis of BRAFV600E and TERT promoter variants in advanced thyroid carcinomas

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Background
Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, generally characterized by a good prognosis. However, a small percentage of PTCs demonstrates a higher aggressiveness and poor outcomes. Recent WHO 2022 classification of thyroid tumors introduced a group of differentiated high-grade thyroid carcinomas (DHGTC), along with poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid carcinomas (ATC) as advanced thyroid cancers. Due to the heterogeneity of diagnostic criteria and the rarity of the disease, molecular characterization of these tumors is needed.
Objectives
This is a single-center study investigating the presence of BRAFV600E and *TERT* promoter variants C228T and C250T in a group of patients routinely investigated for these genetic markers.
Materials and methods
All cases were successfully investigated by Sanger sequencing for the BRAFV600E, C228T and C250T *TERT* promoter variants using genomic DNA extracted from formalin-fixated paraffin-embedded (FFPE) tumor material.
Results
We included in the analysis a group of 23 patients (18-83 y) tested from 2023 to 2024 due to an adverse course of disease (loco-regional or distant metastases, radioiodine treatment resistance, high-risk histopathological features). After histopathological characterization, there were 13 DHGTC, 1 iefvPTC (invasive encapsulated follicular variant of papillary thyroid carcinomas), 4 PDTCs and 3 ATCs. We also included 2 patients with invasive PTC, molecularly tested in their nodular metastasis. The overall occurrence of BRAFV600E variant was 19/23 cases (82,6%). C228T was identified in 5/23 cases (21.7%). We did not identify C250T variant in any cases. Simultaneous presence of BRAFV600E and C228T was observed in 5 cases (3 PDTCs and 2 DHGTC). The co-occurrence of the variants was observed in patients older than 45 y.o, except for one patient of 32 y.o, with nodular metastasis and invasive PTC. Another patient had both variants in microPTC, coexisting with a medullary thyroid carcinoma on the same lobe.
Conclusions
A proper molecular stratification is crucial to select the group of patients at high risk of unfavorable PTC course and simultaneously to avoid overtreatment in low-risk cases.

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EP1452

JOINT662

Thyroid cancers in children: pathological and therapeutic specificities

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Introduction
Thyroid cancers in children are rare but often present with distinct clinical features, including higher rates of malignancy and advanced disease at diagnosis.
Objective
To analyze the clinical, paraclinical and therapeutic characteristics of pediatric thyroid cancers.
Methods
A retrospective review of children under 18 years of age who underwent surgery for thyroid nodule between January 2000 and December 2024 was conducted.
Results
Among 4920 surgeries for thyroid disease, only 29 cases (0.6%) involved children, with a mean age of 14.4 years. Most patients presented with anterior cervical swelling (82.7%), with a mean symptom duration of 11 months. Ultrasonography revealed single thyroid nodules in 58.6% and multinodular goiters in 41.4%, with malignancy suspected in 17.2%. Fine-needle aspiration cytology was performed in seven cases, confirming papillary thyroid carcinoma (PTC) in two patients. Surgical indications included compressive symptoms (51.7%), nodules >3 cm (38%), Bethesda IV cytology (6.9%), and suspected metastasis (3.4%). Total thyroidectomy (was performed in 27.6%, while hemithyroidectomy was performed in 44.8%. Lymph node dissections were performed in 27.6% of cases. Histopathological examination revealed benign lesions in 86.2% of cases, including multinodular goiters, adenomas, and lymphocytic thyroiditis. PTC was diagnosed in four patients (13.8%), with advanced disease (lung metastases) in one case. Complications occurred in 48.3% of cases, primarily transient hypoparathyroidism (41.3%). Radioactive iodine therapy was administered in PTC cases, with favorable outcomes and no recurrence reported after follow-up of 15 months.
Conclusion
Thyroid cancers in children are rare, with most lesions being benign. However, papillary thyroid carcinoma can occur, often at advanced stages. Early detection and tailored treatments, including surgery and radioactive iodine, are essential. Despite challenges, outcomes are generally favorable with multidisciplinary care.

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EP1453

JOINT2105

Relationship between high bone turn over and tsh receptor antibodies in patients newly diagnosed with Graves' disease

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Background
Graves' disease is the most common etiology of hyperthyroidism which is a cause of secondary osteoporosis. Thyrotropin (TSH) is known to affect directly the bone metabolism through the TSH receptor and TSH receptor antibodies (TRAb) may have an important role in bone turn-over. This study aimed to determine the correlation between TRAb and bone remodeling markers (BRMs) in patients newly diagnosed with Graves' disease.
Patients and methods
We performed a cross-sectional study at the endocrinology department of Charles Nicolle Hospital in Tunis, Tunisia including newly diagnosed patients with Graves' disease from Juin to Decembre 2023. Subjects with co-morbidities (hyper or hypoparathyroidism, inflammatory bowel disease, malabsorptive disorder, renal disease, chronic liver disease, Cushing's disease, hypogonadism), pregnant, breast-feeding or menopausal women or history of drug use (steroid, bisphosphonates, calcium or vitamin D) were not included in the study. BRMs involving total alkaline phosphatase (ALP), osteocalcin (OSC) and Carboxy-terminal telopeptide of type I collagen (CTX-I) were assessed in Clinical Biochemistry and Hormone Laboratory of Pateur Institute.
Results
Our study population consisted of 34 patients newly diagnosed with Graves' disease with a higher prevalence of female subjects (76,5%). Mean age of participants was 38,5 $\pm$ 10,4 years. Mean level of free thyroxine (FT4) and TSH were respectively 3,5 $\pm$ 1,9 ng/dl [NR: 0,7–1,8 ng/dl] and 0,02 $\pm$ 0,01 mUI/l[NR: 0,4 – 4 mUI/L]. Mean level of TRAbs was 20,4 $\pm$ 12,6 UI/l[NR: $<$ 2UI/L]. Elevated levels of ALP, osteocalcin, and CTX-I were observed in 24,2 %, 42,4%, and 45,5 % of patients, respectively, based on laboratory reference ranges. TRAb levels were positively and significatively correlated to PAL ($P = 0,01$) and osteocalcin ($P = 0,03$). Although TRAb levels vary in the same direction as CTX levels, this association wasn't significant ($P > 0,05$). Receiver operating characteristic (ROC) analysis identified a significant TRAb cut-off value for predicting elevated ALP and osteocalcin levels. The ROC-determined cut-off was 44 UI/l,with a sensitivity of 66.7% and a specificity of 87.5% for predicting elevated ALP. The same cut-off value predicted elevated osteocalcin with a sensitivity of 83.3% and a specificity of 44.4%.
Discussion and Conclusion
This study reveals a positive correlation between TRAb and BRMs in patients newly diagnosed with Graves' disease. This suggests a detrimental impact of TRAb on bone metabolism in the context of hyperthyroidism. Importantly, normalization of the autoimmune abnormality occurs significantly later than the restoration of euthyroidism, with TRAb levels gradually disappearing over an extended period.

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EP1454

JOINT3735

Thyroglossal duct cysts: diagnosis and management

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Introdution
Thyroglossal duct cysts (TGDCs) are the most common congenital midline neck masses in the pediatric population. TGDCs result from incomplete involution of the thyroglossal duct, which guides the descent of the thyroid gland from the base of the tongue to the thyroid. There are several indications for their removal, including recurrent infections, sinus formation and risk of malignancy. This article reviews the clinical presentation, diagnosis, and surgical management of TGDCs in children.
Material and method
This is a retrospective study conducted in the ENT department at Fattouma Bourguiba Hospital in Monastir over a four-year period, from January 2021 to December 2024, involving 45 cases of thyroglossal duct cysts.
Observation
The mean age was 6.37 years, with extremes ranging from 3 to 15 years, and the sex ratio was 0.83 (20 males/24 females). One child had previously undergone surgery for hydrocele. These children presented with cervical swelling that had developed since birth, with a history of infection in 9 cases. On examination, an infrahyoid swelling ranging from 0.5 to 4 cm was noted, mobile on tongue protrusion and swallowing, with the presence of a fistula and serous discharge in 9 cases. Ultrasound findings were consistent with a thyroglossal duct cyst in all 45 cases. Surgical excision using the modified Sistrunk procedure was performed in all cases with an uneventful postoperative course.
Conclusion
A persisting thyroglossal duct may lead to cysts or fistulas. The most common method of treatment is complete resection through the Sistrunk procedure. This technique effectively removes the cysts and reduces recurrence rates.

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EP1455

JOINT1557

Long-term follow-up of nodular goiter – experience in fukushima area of north-east Japan

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Background
Benign thyroid nodules (NOD) has been generally considered to have no operative indication. However, long-term course is still unclear. In the present study, we reviewed 18 years' NOD cases, including a year of nuclear power plant accidents (NPP, 2011), to find out its natural course.
Patients and Methods
6,553 Japanese patients (2007-2024), who live in iodine rich lands of Fukushima, visited our thyroid clinic; mean age, 60 (female, 81%). Follow-up study was performed in 1,551 patients (4,883 times; 0- 18 years). Assays: Serology was performed for thyroid peroxidase antibody (TPO), anti-thyroglobulin antibody (TgAb), thyroid stimulating hormone receptor antibody (TRAb) and, in some patients, thyroid stimulating hormone antibody (TSAb). Hormonal assay was performed for free thyroxine (F-T4), free triiodo-thyronine (F-T3), thyroid stimulating hormone (TSH) and thyroglobulin (Tg). Cytology of NOD: Fine needle aspiration cytology (FNA); class 1 (normal), 7.3%; class 2 (benign), 42%; class 3 (malignancy not ruled out), 2.3%; class 4 (suspicious), 0.2%; class 5 (malignant), 3.0%; Solid 57%,?Cyst?43%. Changes of NOD: Enlargement rates of nodules (VR%, size%) were calculated from a formula; current VL(volume) /initial VL and size/initial size (of FNA nodules).
Results
1) VR%: 24% down and(vs) 12% (46% no change: 1-year), 20% vs 15% (56%: 2-year). 16% vs 13% (49%: 3-year), 28% vs 11% (52%: 5-year) and 9.7% vs 5.3% (74%: 10 year). 2) Factors related with VR% (over 10 years): 3 factors had significant; thyroglobulin (Tg) as a UP factor, Tg/VL and age as DOWN factor. 3) Prediction of VR% after 5 years: a) Size at first visit: Increased size was 50% in 10-15 mm (initial size), whereas unchanged (60%) or decreased (27%) in 20-29mm. b) Tg: Tg/VL was associated with TgAb. 4) Influence of NPP accidents: There was no influence to statistics of NOD.
Discussion
A half of NOD remained unchanged/reduced. Up VL (200%-) generally observed in small NOD. Long term follow-up seemed not always necessary if FNA confirmed benign. Significance of autoantibodies was unclear. However, we do not know if these results are also applied to non-Japanese people.

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EP1456

JOINT1445

Vitamin D supplementation to prevent post-thyroidectomy hypocalcemia

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Background
Hypocalcemia is a common complication of thyroidectomy, often necessitating hospitalization for calcium supplementation. Previous studies yielded contradictory results on whether cholecalciferol prevents postoperative hypocalcemia, and most were conducted in non-Western countries with different dietary habits and baseline vitamin D levels. Therefore, we aimed to investigate the effect of preoperative cholecalciferol on post-thyroidectomy hypocalcemia in a Dutch population.
Methods
Patients who underwent thyroidectomy between 2023-2025 received 100,000 IU cholecalciferol one week preoperative ('vitamin D group') and were compared to a historical cohort (2019-2022) who did not receive cholecalciferol supplementation ('control group'). Outcomes included incidence of post-thyroidectomy hypocalcemia (<2.00 mmol/L,24h,48h,72h, >72h postoperative), need for postoperative supplementation, time until normocalcemia, length of hospital stay, and hospital readmission.
Results
Fifty patients received preoperative cholecalciferol and were compared to 154 control patients (82.8% female, median age: 55 years [IQR:43-66]). Hypocalcemia occurred less frequently in the vitamin D group (cumulative incidence: 16.0% vs. 35.1%, $P = 0.01$ for biochemical and 12.0% vs. 24.0%, $P = 0.07$ for symptomatic hypocalcemia). Preoperative cholecalciferol supplementation was associated with a reduced risk of hypocalcemia (OR 0.27,95%CI:0.11-0.68, $P = 0.005$). Furthermore, the vitamin D group demonstrated a lower need for postoperative supplementation (32.0% vs. 53.9%, $P = 0.007$) and faster recovery to normocalcemia (0[0-2] vs. 3[0-11] days, $P = 0.002$). No differences were observed in length of hospital stay and hospital readmissions.
Conclusion
A preoperative dose of 100,000 IU cholecalciferol was associated with a significant reduction in post-thyroidectomy hypocalcemia. With a number needed to treat of 5 patients to prevent one case of hypocalcemia, this inexpensive and safe intervention could be considered for routine use in patients undergoing thyroidectomy.

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EP1457

JOINT1673

Trends of thyroglobulin and dynamic risk stratification in thyroid nodule cancer without radioiodine ablation

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Objective
To analyze the progression of plasma thyroglobulin (Tg) levels and dynamic risk stratification (DRS) in patients diagnosed with differentiated thyroid cancer (DTC) without radioactive iodine treatment in a thyroid unit.
Materials and Methods
A prospective study was conducted on all patients who underwent thyroidectomy or hemithyroidectomy with a diagnosis of DTC and did not receive radioactive iodine treatment between 2020 and 2024. Clinical, biochemical, and imaging data were collected at diagnosis and during follow-up.
Results
A total of 66 patients without radioactive iodine treatment were evaluated (80.3% women, mean age 55.6 ± 11.7 years, 72.7% were diagnosed incidentally and an

average DTC follow-up of 2.0±1.3 years). The most common DTC subtype was classic papillary carcinoma in 42.4% of cases. Total thyroidectomy was performed in 75.8% of patients, while 24.2% underwent hemithyroidectomy. The mean tumor size was 8.0±7.2 mm (30.3% of cases >1 cm). Histopathological characteristics included multifocality in 31.8% of cases, bilaterality in 21.2%, and capsular invasion in 18.2%. The tumor stage was I, with all patients classified as having a low risk of recurrence. When evaluating DRS (Momesso *et al.*) in the total cohort three months after surgery, 39.3% of patients had an indeterminate response (IR), 57.1% had an excellent response (ER), and 3.6% had a biochemical incomplete response. At the end of the mean follow-up, 60.5% had an ER, while 39.5% had an IR (P <0.05). However, there were no significant differences in Tg levels during follow-up, either in the overall sample (1.5±2.3 vs. 1.3±1.2, not significant) or by type of surgery. Among those patients who underwent total thyroidectomy, 88% had Tg <1 ng/ml, whereas 100% of those who underwent hemithyroidectomy had Tg <30 ng/ml. When correlating baseline circulating Tg levels with those from the last follow-up visit, a strong positive correlation was observed (r = 0.916, P <0.001). However, no correlation was found with TSH levels. Finally, when analyzing initial DRS in total thyroidectomy patients in relation to different clinical and histopathological characteristics, no significant differences were found in age, sex, or histological features predicting disease progression, except for a larger tumor size in the IR group (8.7±4.9 vs. 6.4±3.2 mm, P <0.05).

Conclusions

A total of 60.5% of patients exhibited an ER from diagnosis, maintaining stability during follow-up despite not receiving radioactive iodine treatment. DRS was associated only with tumor size and not with other clinical or histological features. Baseline circulating Tg levels correlated with final Tg levels.

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EP1458

JOINT386

Growth profiles in children with congenital primary hypothyroidism before and after the relaunching of newborn screening programme in dr soetomo hospital

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Background

Congenital hypothyroidism (CH) is a common endocrine disease that can cause significant developmental delays and growth failure. The thyroid hormone is essential for adequate growth and development, especially throughout foetal life and early infancy. Newborn screening (NBS) programs have markedly enhanced the early identification and treatment of congenital hypothyroidism. The Indonesian Ministry of Health has relaunched NBS program by the end of 2023. The aim of this study is to compare the growth profile at birth, at the first time of diagnosis, and after treatment of the children with CH who were diagnosed without screening and who were diagnosed through the screening program.

Methods

15 children who had been diagnosed with CH before the relaunching of the NBS program (non-NBS group) and 6 children who were diagnosed by the NBS program (NBS group) were included. fT4, TSH, weight, and height data were obtained from the medical record. Weight and height were transformed into z-scores standard deviation (SDS) according to the WHO growth chart. The data were processed with independent t-test using RStudio, with P < 0.05 considered significant.

Results

The mean age of diagnosis in the non-NBS group was 877 days, and in the NBS group was 24.6 days old. Average fT4 in the non-NBS group is 0.233 ng/dl, and in the NBS group is 0.52 ng/dl. The mean of the TSH level in the non-NBS group is 322.78 mLu/l,and in the NBS group, it is 228.9 mLu/L. There are no differences between birth weight SDS and birth length SDS between the non-NBS group vs. the NBS group (-0.11 vs. -0.92; P = 0.16) and (-0.14 vs. -0.41; P = 0.56), respectively. There are differences in weight SDS between the non-NBS group vs. the NBS group (-2.73 vs. -0.37; P < 0.01) and no differences in height SDS (-2.72 vs. -0.51; P = 0.08). Even after both groups were adequately treated, there are still differences in weight SDS and height SDS in the non-NBS group vs. the NBS group (-2.14 vs. -0.6; P < 0.05) and (-2.5 vs. -0.25; P < 0.05).

Conclusions

Primary congenital hypothyroidism is initially asymptomatic, the diagnosis can be delayed without screening, and the child may be exposed to hypothyroid conditions for a long time, leading to growth failure. Early diagnosis and treatment of congenital hypothyroidism are essential for improving growth and developmental outcomes. The optimal growth potential can be achieved through continuous monitoring and appropriate management.

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EP1459

JOINT2431

A case with TSHB gene mutation presenting with neuromotor retardation

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Introduction

Pathogenic variants in the TSHB gene are known to cause severe isolated central congenital hypothyroidism (CH). Mutations in this gene are associated with congenital central hypothyroidism, secondary hypothyroidism, and Hashimoto's thyroiditis. We present the clinical, biochemical, and genetic features of a patient with a central CH phenotype.

Case

A 9-year-old female patient demonstrated delayed developmental milestones, with head control achieved at 9 months and the ability to walk at 2 years of age. She was born with right femoral agenesis and underwent prosthetic surgery at the age of 2. Additionally, she has sensorineural hearing loss and intellectual disability. During the investigation, at the age of 1.5 years, laboratory findings revealed Free T4: <0.4 ng/dl and TSH: 3.25 µU/ml. As a result, L-thyroxine treatment was initiated. The parents are consanguineous (second-degree relatives) . The other two siblings are healthy and alive, and there is no similar medical history in the family. Karyotype analysis revealed a normal female karyotype (46, XX). A homozygous pathogenic variant, c.205C>T (p.Gln69*), in the TSHB gene (NM_000549.4) was identified. Sanger sequence analysis revealed that parents were heterozygous. Microarray: arr(1-22)x2,(X)x2, normal Pituitary MRI was normal, and all other pituitary hormones, including prolactin (PRL), were secreted at normal levels. Following the initiation of L-thyroxine therapy, the patient showed positive improvements in neuromotor development.

Conclusion

Isolated TSH deficiency is not detected by routine neonatal TSH-based screening, which represents a significant clinical challenge. In particular, infants presenting with neuromotor retardation in neurology clinics should have thyroid function evaluated, including Free T4 and Free T3 levels. In this case, delayed diagnosis and treatment of profound central hypothyroidism contributed to neurodevelopmental delays.

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EP1460

JOINT2676

Harmonization of thyroid function test measurements across multiple immunoassay platforms for a common reference interval

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Background

Thyroid function tests (TFTs) are among the most frequently performed immunoassays in clinical laboratories. However, the lack of standardized reference materials and methods has led to significant variability in results among different manufacturers, making standardization challenging. Additionally, reference intervals (RIs), which are essential for accurate interpretation, vary across analytical methods. This study aims to establish a common RI applicable across multiple automated immunoassay platforms using percentile transformation.

Methods

We analyzed randomly selected samples covering a wide concentration range (TSH: 283 samples, T3: 265 samples, fT4: 283 samples) from Kyung Hee University Hospital at Gangdong. These samples were tested on the three most widely used automated immunoassay analyzers in South Korea (Abbott Alinity i, Beckman Coulter DxI 800, and Roche cobas e801) to measure TFT values simultaneously. Using percentile transformation, regression analysis was conducted to derive recalibration equations. These equations were applied to TFT measurements from 120 healthy individuals, each tested on all three platforms. Healthy individuals were selected based on normal blood test results from a health screening center, absence of

suspected thyroid disease on ultrasound, and negative anti-thyroglobulin antibody (Anti-TG) test and anti-thyroid peroxidase antibody (Anti-TPO) tests. RIs were determined using the nonparametric percentile method (2.5th–97.5th percentiles). The final common RI was derived by integrating the recalibrated results from all three platforms, ensuring a common RI across different methods.
Results
Recalibration effectively minimized method-dependent discrepancies in RI values. The common TSH RI (0.51–4.08 μIU/ml) reduced inter-method variability, narrowing the differences observed across method-specific RIs: Abbott (0.52–4.08), Beckman Coulter (0.49–4.27), and Roche (0.50–3.99). For triiodothyronine (T3), the common RI (0.71–1.41 ng/ml) significantly reduced variations among Abbott (0.84–1.40), Beckman Coulter (0.78–1.47), and Roche (0.65–1.27), demonstrating the most pronounced improvement. Similarly, for free thyroxine (fT4), the common RI (0.84–1.42 ng/dl) narrowed the gap between platform-specific values: Abbott (0.83–1.39), Beckman Coulter (0.83–1.32), and Roche (0.97–1.46). Among the three markers, T3 exhibited the greatest reduction in variability after recalibration, while TSH and fT4 also showed notable improvements in cross-platform consistency.
Conclusions
Harmonization of TFT results using recalibration equations successfully minimized inter-method variability, enabling the establishment of a common RI. This approach improves result interpretation across immunoassay platforms and ultimately enhances clinical decision-making. Future research should validate the RI in independent populations, assess its clinical applicability, and evaluate its stability across different platforms to ensure reliability and facilitate widespread adoption.

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EP1461

JOINT3881

Characteristics of papillary thyroid carcinoma in men

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Introduction
Papillary thyroid carcinoma is the most common type of thyroid cancer. Although it is more prevalent in women, its occurrence in men is often associated with a poorer prognosis.
Objective
In this context, we conducted a descreptive study aiming to highlight the clinical and histoprognostic characteristics of papillary carcinoma in men.
Materials and Methods
Our study included all male patients followed in the endocrinology department of Ibn Rochd University Hospital in Casablanca for thyroid carcinoma between 2000 and 2024.
Results
The study population comprised 59 patients, with an average age of 50 years (mean age: 50 $\pm$ 14.5 years). The follicular variant of papillary carcinoma was the most frequently observed in 35% of patients. Six percent of the patients presented with poor prognostic variants, primarily the oncocytic variant in two cases. Thyroid carcinoma was associated with other neoplasms in 6% of cases. It was unifocal in 71% of patients. Regarding recurrence risk, 5% were at high risk, and 20% at intermediate risk. Lymph node dissection was performed in 13% of cases, with positive findings in three patients. Vascular emboli were present in 16% of cases, and 11% exhibited thyroid capsule invasion. Radioiodine therapy was indicated for 62% of patients. Two patients had secondary metastases, and three retained residual tumor tissue.
Conclusion
Papillary thyroid carcinoma generally has a favorable prognosis. However, its association with the male sex may be linked to a less reassuring prognosis, with a higher frequency of radioiodine therapy and a risk of residual tumor.

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EP1462

JOINT2860

Endocrine surveillance: detecting recurrent graves' disease in ectopic thyroid and primary hyperparathyroidism post-radioiodine treatment

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The occurrence of Graves' disease in ectopic thyroid tissue following total thyroidectomy is a rare event, as is the coexistence of Graves' disease and primary hyperparathyroidism. While both conditions are relatively common in endocrinology practice, their concurrent presentation is unusual, raising the possibility of an association with prior radioiodine (RAI) therapy. RAI-induced hyperparathyroidism has an average latency period of 24 years, with this period decreasing as the patient's age at the time of RAI treatment increases. This case report describes the rare occurrence of recurrent Graves' disease in ectopic thyroid tissue, complicated by primary hyperparathyroidism, in a patient with a history of RAI treatment.
Case Report
A 47-year-old woman with a history of Graves' disease initially presented with an enlarged, nodule-free goiter. Following unsuccessful thionamide treatment, she underwent total thyroidectomy for compressive symptoms and subsequently developed hypothyroidism. Four years later, a progressively enlarging mass appeared in the right anterior neck. Elevated and rising levels of thyroid-stimulating immunoglobulin and thyroid-stimulating hormone receptor antibodies were observed, necessitating levothyroxine dose reduction and eventual cessation due to subclinical hyperthyroidism. Ultrasound revealed a 3 cm, hyperechogenic, hypervascularized nodule in the infrahyoid region. A subsequent scintigraphy confirmed hyperfunctioning ectopic thyroid tissue in this location. Following 10 mCi of I-131 RAI therapy, hyperthyroidism resolved, and cervical ultrasound remained stable for eight years. At that point, an hypoechoic nodular lesion was detected in the right inferior thyroid bed, accompanied by hypercalcemia (11.7 mg/dl), elevated PTH (180 pg/ml), and normal vitamin D levels. Parathyroid scintigraphy confirmed hyperfunctioning parathyroid tissue in the right suprasternal region. The patient underwent right parathyroidectomy, resulting in resolution of hypercalcemia and hyperparathyroidism.
Conclusion
Recurrent Graves' disease due to hyperfunctioning ectopic thyroid tissue after total thyroidectomy is a rare phenomenon. Remnant or ectopic thyroid tissue can become hyperfunctional in the presence of thyroid-stimulating hormone receptor antibodies, leading to growth and presenting as a mass. This case highlights also the rare coexistence of Graves' disease and primary hyperparathyroidism, potentially associated with prior RAI treatment. Post-RAI treatment, we recommend periodic serum calcium level monitoring every 3–5 years. This case emphasizes the importance of long-term follow-up and vigilant surveillance for new or emerging endocrine abnormalities, including hyperparathyroidism, even years after initial therapies.

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EP1463

JOINT3972

Synchronous medullary and papillary thyroid carcinoma: a clinical case

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Introduction
Thyroid carcinomas represent the most common endocrine malignancies, with papillary thyroid carcinoma (PTC) accounting for the majority of cases. Medullary thyroid carcinoma (MTC), arising from parafollicular C cells, is less frequent and follows a distinct clinical course. The coexistence of MTC and PTC in the same patient is an unusual finding with significant implications for diagnosis, genetic screening, and treatment. Understanding the interaction between these malignancies is crucial for optimizing outcomes.
Case Presentation
A 70-year-old male, ex-smoker with a history of arterial hypertension, and coronary artery disease was under investigation for a stable pulmonary nodule. During the work-up a PET DOTA-NOC scan revealed intense radiotracer uptake in the superior pole of the right thyroid lobe, with no uptake in the pulmonary nodule, prompting referral to endocrinology for further evaluation. Biochemical evaluation revealed normal TSH, high calcitonin (285pg/ml; N: $<$9.52) and CEA (5.3ng/ml; N:0-3) levels. Urinary metanephrines were normal. Cervical ultrasound showed two EU-TIRADS 4 thyroid nodules, on the right with 15x8x14mm and on the left with 10x8x11mm. FNA of the right nodule was consistent with medullary thyroid carcinoma. In this context, the patient underwent total thyroidectomy with central compartment neck dissection. Histopathology disclosed a 9mm MTC confined to the thyroid (pT1aN0R0) and

two out of seven central lymph nodes with PTC metastasis, the largest with 3mm and extranodal extension. After full inclusion of the surgical specimen an incidental 3mm PTC was identified in the left lobe (pT1aN1aR0, ATA high risk). Postoperatively, calcitonin levels declined to 1.6 pg/ml, indicating a favorable response. The patient is currently awaiting genetic testing and is scheduled to undergo radioiodine therapy with 150mCi for the PTC.
Discussion
The synchronous occurrence of medullary and papillary thyroid carcinomas is rare, accounting for approximately 19% of all MTC cases and 0.28% of all PTC cases. While MTC originates from parafollicular C cells and is frequently associated with RET mutations, PTC arises from follicular cells and commonly harbors BRAF or RAS mutations. The coexistence of these two malignancies raises questions about potential shared pathogenic mechanisms. Classic genetic alterations found in isolated MTC and PTC do not seem to play a role in synchronous cases, suggesting independent oncogenic pathways. Although the simultaneous presence of these malignancies does not appear to significantly alter their individual clinical behaviors, accurate diagnosis remains challenging. This underscores the need for thorough biochemical and histopathological evaluation to ensure proper management and follow-up.

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EP1464

JOINT3862

Evaluation of the relapse rate in patients with graves disease and its relationship to the great score

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Introduction
Antithyroid drugs are the first step of treatment in patients with Graves' Basedow Disease (GBS). A treatment duration of 12 to 18 months is recommended, however, the relapse rate is high (up to 60% in some series); different authors recommend longer treatments. Vos *et al*. propose a scale (GREAT-Score), which classifies patients into 3 groups according to the risk of recurrence (class-1 lower risk, class-3 higher risk), taking into account age, analytical parameters (T4l, TRAb) and goitre.
Objective
To evaluate relapse in hyperthyroid patients after treatment, according to the duration of treatment and the GREAT-Score.
Material and Methods
Retrospective observational study in patients with GBS diagnosed between June/2020 and December/2020 and their relationship with GREAT Score, with a follow-up of 36 months.
Results
A sample of 54 patients was presented, 76% were women; mean age was 47+/-14.5 years, 33.3% smokers, clinically, nervousness, weight loss, palpitations and ophthalmopathy (67.3%, 46.2%, 29.6, 1.9%, respectively). Regarding the GREAT-Score, 48% were Class 1, 41% Class 2 and 11% Class 3. 59.3% were treated with Carbimazole, 40.7% with Thiamazole. Duration of treatment was less than 12 months in 18.5% of the sample, between 12-18 months in 38.9%, between 18-24 months in 35.2% and above 24 months in 7.4%. 93.8% had no side effects, with hypothyroidism and elevated transaminases (4.2%, 2.1%, respectively). The analytical values (median-ranges) at diagnosis were: TSH 0.01µIUI/ml(0.01-0.01), T4l 3.2ng/dl(1.97-4.58), T3l 9.59pg/ml(5.33-21), TRAb 6. 83U/L(4.04-13.30); at the end of treatment: TSH 1.78µIUI/ml(1.02-2.83), T4l 1.19ng/dl(1.03-1.31), T3l 3.1pg/ml(2.76-3.44), TRAb 1.65 U/L(0.8-1.23). Overall relapse was 46.3%, (66.7% smokers); relapse according to GREAT-Score was 42.3% in Class1 and 50% in class2-3. Relapse according to treatment duration was 60% in those with a duration of less than 12 months, 38% in those with a duration of 12-18 months, 50% in those with a duration of 18-24 months and 25% in those with a duration of 24-30 months.
Conclusions
Relapse in GBS after ATD is high, patients with GREAT-Score class2-3 had a higher relapse than those with class1, and treatment over 24 months had a lower relapse than those with shorter duration. It would be interesting to establish risk profiles (GREAT-Score) prior to pharmacological treatment, thus being able to select those patients who may benefit from longer treatment.

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EP1465

JOINT200

Celiac disease in patients with thyroid disorders: clinical features, diagnosis, and management

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Introduction
Celiac disease and thyroid disorders are both common autoimmune conditions, but their coexistence is less frequently discussed. While both diseases share certain clinical features, their diagnosis can be challenging when they occur together. This study aims to describe the clinical features, diagnostic approaches, and management of patients with celiac disease and thyroid disorders.
Methods
We reviewed the medical records of patients diagnosed with both celiac disease and thyroid disorders at our hospital.
Results
The patients included four women and one man, with a mean age of 22.4 years at the onset of celiac disease (range: 10-39 years). We analyzed the clinical presentation, thyroid function tests, serology, and endoscopic findings. The diagnosis of celiac disease was confirmed by positive anti-transglutaminase antibodies and gastroscopy. The management strategy involved initiating a gluten-free diet for all patients. Among the five patients, thyroid disorders included patent hyperthyroidism in one case, mild hyperthyroidism in one case, hypothyroidism in two cases, and euthyroid thyroidopathy in one case. Celiac disease preceded thyroid dysfunction in three patients, with an average delay of 44 months (range: 24-84 months). In two patients, the diagnosis of celiac disease was concurrent with the thyroid disorder. Clinically, three patients presented with significant weight loss, while one patient had chronic diarrhea. Laboratory findings revealed iron deficiency anemia, malabsorption syndrome, and positive anti-transglutaminase antibodies in three patients. Three patients underwent gastroscopy, which showed typical findings of celiac disease, including flattened and scalloped duodenal folds without mosaic pattern in two cases and a mosaic pattern in one case. All patients were placed on a gluten-free diet, leading to favorable clinical outcomes.
Discussion
Although intestinal absorption disorders can occur in both hyperthyroidism and hypothyroidism independently of celiac disease, celiac disease must be considered in patients presenting with signs of malabsorption. Prompt diagnosis and gluten-free dietary intervention are critical to preventing complications. Recent studies suggest that screening for autoimmune thyroid disorders in patients with celiac disease could be beneficial. The overlapping clinical features of these diseases—such as weight loss, diarrhea, muscle weakness, anxiety, hair loss, and infertility—can complicate diagnosis, especially when hypothyroidism masks some symptoms of celiac disease.
Conclusion
The coexistence of celiac disease and thyroid disorders is relatively common and can complicate diagnosis due to overlapping symptoms. Early recognition of celiac disease in patients with thyroid dysfunction is essential for proper management and to avoid long-term complications.

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EP1466

JOINT880

A decade of thyroid orbitopathy research in albania: a retrospective study from a tertiary referral center

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Introduction
Thyroid Orbitopathy (TO), also referred to as Graves' Orbitopathy (GO), is a complex and impactful complication of Graves' disease (GD). Limited data from Albania highlight the need for a deeper understanding of its presentation and management.
Aim
This 10-year retrospective study conducted at a tertiary referral center in Albania analyses the clinical features, diagnostic challenges, and treatment approaches for GO to enhance disease understanding and improve management strategies.
Methods
Data were systematically collected from 178 patients referred for GO evaluation and treatment over a decade. Patient demographics and clinical characteristics were documented using the European Group on Graves' Orbitopathy (EUGOGO) protocol. Cases were categorized as bilateral (asymmetric or symmetric) or unilateral GO, and clinical features were analyzed to identify distinguishing patterns.

Results
Among 178 patients with GO, the mean age was 44.9 ±14.9 years. Bilateral GO was most common (72.5%), followed by unilateral (17%) and unilateral-to-bilateral (10.5%). Asymmetric GO was observed in 30.9% of bilateral cases. GO onset was often concurrent with GD, with female predominance (72.5%). Mild GO was present in 48%, while 52% had moderate to severe forms. Local treatment was effective for mild cases, while 80% of moderate/severe cases responded positively to intravenous glucocorticoids. Hypothyroidism was a significant risk factor for GO activation.
Conclusion
Clinical management should prioritize the overall presentation of GO, emphasizing individualized treatment approaches. Hypothyroidism was identified as a key risk factor for GO activation, highlighting the need for careful thyroid function management to mitigate disease progression.

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EP1467

JOINT3766

Prevalence of thyroid nudules in children with idiopathic prcocious puberty or early and fast puberty

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Background and Objectives
The aim of the study is to investigate the prevalence of thyroid nodules in children and adolescents with idiopathic central precocious puberty or early and fast puberty.
Methods
From 2020 to 2024, 645 children were diagnosed idiopathic central precocious puberty or early and fast puberty in our center, and accepted thyroid ultrasound examination were enrolled in our study. Results of ultrasound inspections as well as thyroid function were analyzed, and compared with 314 children who had underlying thyroid diseases.
Results
Among 645 children with idiopathic central precocious puberty or early and fast puberty, 254 (39.4%) had thyroid nodules, however, only 85 (27.1%) thyroid nodules were detected in 314 children with underlying thyroid diseases ($P < 0.05$). In children with idiopathic central precocious puberty or early and fast puberty, thyroid nodules were mostly bilateral (70.4%), only 29.6% were unilateral. Ti-RADS showed that 174 cases were grade 1, 60 cases were grade 2, 3 were grade 3, 1 grade 4 and 1 grade 5. Thyroid function was normal, no hyperthyroidism or hypothyroidism was observed. anti-Thyroid antibodies were negative.
Conclusion
Unexpectedly detected thyroid nodules were more than expected in children with idiopathic central precocious puberty or early and fast puberty. The nodular were mostly bilateral. Thyroid ultrasound may be considered in such children and furthe investigations are needed.
Key words
thyroid, central precocious puberty, early and fast puberty, children.

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EP1468

JOINT741

Influence of aromatase inhibitors on thyroid function in postmenopausal women with early-stage breast cancer: a prospective controlled study

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Purpose
Aromatase inhibitors are frequently used in adjuvant therapy for both early- and advanced-stage breast cancer. While the common side effects of these treatments are well-documented, their impact on thyroid function has not been systematically assessed and remains unclear. This study aimed to evaluate thyroid function in postmenopausal women with estrogen receptor-positive early-stage breast cancer one and two years after starting aromatase inhibitors.
Methods
This prospective controlled study involved 59 postmenopausal women with early-stage breast cancer and 39 healthy controls. All participants underwent chemotherapy and were treated with aromatase inhibitors, with 35 patients also receiving locoregional radiotherapy. The primary outcomes included the evaluation of thyroid hormones and thyroid-binding globulin post-chemotherapy, as well as at one-year and two-year follow-ups after initiating aromatase inhibitors. Secondary outcomes included thyroid autoantibodies and body mass index.
Results
No significant differences in thyroid parameters were observed between patients and healthy controls before chemotherapy. During treatment with aromatase inhibitors, free thyroxine levels increased at both follow-up visits ($P < 0.01$) and total thyroxine levels increased at the two-year visit ($P = 0.02$). In contrast, triiodothyronine levels decreased at both visits ($P < 0.01$ and $P = 0.03$). There were no changes in thyroid-stimulating hormone or thyroid-binding globulin, but albumin levels increased after one year ($P < 0.01$). Weight changes were insignificant, and the prevalence of autoimmune thyroiditis was low ($\leq 15\%$). No differences in thyroid function were detected between women treated with locoregional radiotherapy and those who were not.
Conclusions
This study suggests that, despite statistically significant changes in peripheral thyroid hormones, no obvious clinically important effects were observed in patients with early-stage breast cancer during the two years of treatment with aromatase inhibitors. These changes were not associated with thyroid autoimmunity, non-thyroidal illness, radiotherapy, or high-dose corticosteroids. To our knowledge, this study provides the longest follow-up of thyroid hormones and thyroid-binding globulin in this specific patient group, focusing on the effects of aromatase inhibitors on thyroid function. Further research is needed to understand better the long-term impact of aromatase inhibitors on thyroid function in this population.

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EP1469

JOINT1768

Thyroid hormone levels and echocardiographic changes in subclinical hypothyroidism: a correlation study

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Objective
Overt hypothyroidism has been linked to alterations in cardiac output and diastolic dysfunction. Moreover, subclinical hypothyroidism (SCH) exhibits changes in echocardiographic parameters when compared to healthy individuals. This study investigates the correlation between thyroid hormone values and echocardiographic parameters in patients diagnosed with SCH.
Methods
In fifty-four patients with newly diagnosed ScH who met the criteria for levothyroxine treatment, blood tests and echocardiographic studies were conducted at enrollment and again after five months of maintaining a euthyroid state.
Results
TSH negatively correlated with EF, E/A, GLS, S/TDI (r=-0.15, r=-0.14, r=-0.26, r=-0.22, $P < 0.05$, respectively), and positively correlated with E/e 'sep. ($r = 0.14$, $P < 0.05$). FT4 negatively correlated with E/e'sep., IVRT, MPI (r=-0.17, r=-0.21, r=-0.19, $P < 0.05$, respectively), and positively correlated with E/A, GLS, S/TDI ($r = 0.18$, r=-0.18, $r = 0.19$, $P < 0.05$, respectively). FT3 negatively correlated with A dur (r=-0.39, $P < 0.01$), and positively correlated with EF and s/d ($r = 0.18$, $r = 0.22$, $P < 0.05$). Using a general linear model with univariate analysis, we found that TSH had a statistically significant independent influence on EF, LVEDd, IVRT, MPI, GLS, and S/TDI. FT4 significantly influenced EF, LVEDd, LVEDvol, E/A, A dur, Ar dur, MPI, GLS, s/d, and S/TDI, while FT3 had a significant impact on EF, LVEDd, IVCT, MPI, and GLS ($P < 0.05$). After substitution therapy, there was a statistically significant improvement in parameters indicating diastolic dysfunction (A dur: 112.18 ± 17.2 vs. 107.25 ± 14.4 msec and E/e' sep.: 7.62 ± 2.29 vs. 6.60 ± 2.06, $P < 0.01$), as well as in global and longitudinal left ventricular function (MPI: 0.47 ± 0.08 vs. 0.43 ± 0.07 and GLS: -19.55 ± 2.3 vs. -20.07 ± 2.7, $P < 0.05$).

Conclusion
Thyroid hormones directly influence specific parameters used to assess global and longitudinal systolic and diastolic left ventricular function in patients with ScH, and the most of them are reversible with levothyroxine treatment.
Keywords
subclinical hypothyroidism, echocardiography, left ventricular function.
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EP1470

JOINT2491
Effectiveness of antithyroid therapy on TH1, TH17, and TH22 lymphocytes in pediatric Graves' patients
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Graves' disease is the leading cause of autoimmune hyperthyroidism. Thyroid hormones are an essential element of the endocrine system, playing a pivotal role in the body's development, especially important in children with intensified growth. Disturbance within thyroid tissue certainly affected the whole body. Nowadays, numerous research studies indicate different factors contributing to the onset of the disease; however, the exact pathomechanism of Graves' disease is still not fully understood, especially in the context of immune-related processes. Th1, Th17, and Th22 effector lymphocytes were found to be crucial participants in the disease outcome, as well as in autoimmune diseases. Here, our study aimed at assessing selected effector T lymphocytes, Th1, Th17, and Th22, in newly diagnosed pediatric Graves' disease patients, together with their association with thyroid-related parameters and the potential outcome of disease management. We indicated significant increases in the frequencies and absolute numbers of selected effector lymphocytes in Graves' disease patients. In addition, their mutual ratios, as well as Th1/Th17, Th/Th22, and Th17/Th22, seem to be significant in those diseases. Notably, low Th17/Th22 ratio values were distinguished as potential prognostic factors for normalizing TSH levels in response to methimazole treatment. To sum up, our research determines the crucial contribution of Th1, Th17, and Th22 cells in the pathogenesis of Graves' disease. Moreover, the mentioned subset of T cells is highly likely to play a substantial role in the potential prediction of therapy outcomes.
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EP1471

JOINT3837
Paresthesia as a rare symptom of thyrotoxicosis following parathyroidectomy
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Hypocalcemia induced paresthesia is a common complication in patients undergoing parathyroidectomy to treat primary hyperparathyroidism (PHPT). Rarely, paresthesia can be a symptom of thyrotoxicosis. Palpation thyroiditis can occur following parathyroidectomies. It causes thyrotoxicosis in 30-40% of cases and is often asymptomatic. We present a case of patient with post-parathyroidectomy parestehesia, with normal calcemia, as a symptom of thyrotoxicosis due to palpation thyroiditis. A 51-year-old woman with a previous history of urinary calculi and osteopenia. She was diagnosed with PHPT (PTH 108 pg/ml, corrected total calcium 10.9mg/dl, phosphate and 24h urinary calcium of 474mg) a she had an abnormal left inferior parathyroid in the Tc99m sestamibi scan and ultrasound. Her pre-operative thyroid function was normal. She underwent a left inferior parathyroidectomy and discharged with calcium carbonate/cholecalciferol 1250mg/400IU daily. Two days after the procedure the patient presented to the emergency department with oral and acral paresthesia, nausea and headache. No history of recent upper respiratory tract infection, exposure to iodinated radiocontrast agents, or amiodarone use. She had a normal calcemia (PTH 18 pg/ml, serum corrected total calcium 10.2mg/dl, ionized calcium 1.27 mmol/land normal phosphate) and thyrotoxicosis (TSH 0.04 mU/l,free T4 1.62 ng/dl and free T3 3.36 ng/dl). TSH receptor (TRA), thyroperoxidase (TPOA), and thyroglobulin (TgA) antibodies were normal. The diagnosis of thyrotoxicosis due to palpation thyroiditis was made. She started propranolol 10mg tid. Her thyroid function normalized and her symptoms improved within 2 months. This is a rare case of symptomatic thyrotoxicosis caused by palpation thyroiditis in a patient that underwent parathyroidectomy for a PHPT. Operative thyroid manipulation or trauma with rupture of thyroid follicles is the most suggested mechanism. It is a self-limited condition with thyroid function normalizing within a few weeks to months. In addition, the presenting symptom was much more common in hypocalcemia a much more frequent complication of parathyroidectomy. Thyrotoxicosis is rarely associated with paresthesia, however in this case the symptoms were probably a result of the effects of thyroid hormones on the peripheral nerves. So, it is important to be aware, that in this context, not all paresthesia is a result of hypocalcemia. At 2-month follow up, the patient was asymptomatic and thyroid function studies normalized. PTT may be underestimated due to lack of symptoms and lack of routine testing, so it is important to be aware of biochemical or clinical evidence of thyrotoxicosis in the early postoperative period after parathyroidectomy.
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EP1472

JOINT611
Recent advances in the treatment of goiterous hypothyroidism in infants and children
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Background
Goiterous hypothyroidism in infants and children is a critical endocrine disorder with diverse etiologies, ranging from congenital defects to autoimmune thyroiditis. Recent advancements in treatment have improved outcomes, particularly through novel therapeutic strategies and early interventions.
Objective
To summarize and analyze the recent advances in the treatment of goiterous hypothyroidism in infants and children, with a focus on novel therapies, their outcomes, and associated advancements.
Methods
A comprehensive review of studies published between 1996 and 2024 was conducted. Key studies were identified based on their focus on novel treatments, including liquid levothyroxine formulations, intra-amniotic therapy, precision medicine, and surgical interventions. Data on study characteristics, findings, and therapeutic outcomes were extracted and organized chronologically.
Results
The review encompassed 17 studies, highlighting significant advancements in treatment approaches:.
- Liquid and Soft Gel Levothyroxine: Improved bioavailability and absorption, particularly in cases of malabsorption or drug interferences, ensuring better thyroid hormone control and growth outcomes (Fallahi *et al*., 2017).
- Intra-Amniotic Thyroxine Therapy: Demonstrated efficacy in reducing fetal goiter size and improving neonatal thyroid function, especially in cases of maternal Graves' disease or dyshormonogenesis (Kobayashi *et al*., 2017; Miyata *et al*., 2007).
- Precision Medicine: Genetic insights have enabled targeted therapies for thyroglobulin (TG) and thyroid peroxidase (TPO) mutations, improving treatment of congenital goiter and dyshormonogenesis (Rodrigues *et al*., 2021).
- Screening and Early Treatment: Expanded newborn screening has enabled timely levothyroxine initiation, preventing neurocognitive deficits and supporting normal growth (Wassner & Brown, 2015).
- Surgical Interventions: Total thyroidectomy has improved outcomes in patients with large, resistant goiters, resolving compressive symptoms and enhancing quality of life (Li *et al*., 2020).
- High-Dose Levothyroxine: Early initiation in severe congenital hypothyroidism improved developmental milestones and normalized cognitive function (Dubuis *et al*., 1996).

Conclusions
Recent advancements in treatment emphasize the critical role of early diagnosis and tailored therapies. Intra-amniotic thyroxine, liquid levothyroxine formulations, and genetic insights have significantly improved outcomes in fetal and pediatric hypothyroidism. Future research should focus on long-term outcomes and the integration of precision medicine into routine care.

Keywords
Goiterous hypothyroidism, infants, children, levothyroxine, intra-amniotic therapy, precision medicine, radioactive iodine, congenital hypothyroidism, thyroidectomy.
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EP1473

JOINT49

Assessment of subacute thyroiditis progression using shear wave elastography

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Introduction
Subacute thyroiditis (SAT) is a self-limiting inflammatory disorder of the thyroid gland, characterized by cervical pain and transient thyroid dysfunction due to follicular destruction. The assessment of thyroid elasticity through shear wave elastography (SWE) may offer significant insights into the progression of the disease and assist in clinical decision-making.
Objective
This study aimed to evaluate the diagnostic efficacy of SWE elastography in forecasting the resolution of SAT and its relationship with clinical parameters and thyroid function.
Materials and Methods
Thirty-eight patients (78.9 % female) were enrolled in this study. Evaluations encompassed conventional ultrasound, shear wave elastography (SWE), assessment of biological markers (including TSH, FT4, and inflammatory markers), as well as clinical evaluations focusing on pain and lateral cervical inflammatory symptoms.
Results
Out of the 38 patients assessed, all exhibited clinical symptoms indicative of SAT. Conventional ultrasound findings demonstrated hypoechogenicity in 100% of cases. SWE elastography revealed an initial mean elasticity index (EI) that was elevated in all patients, with a median value of 115 kPa (range: 100–121 kPa). The EI progressively decreased to 54 kPa at one month, 24.3 kPa at three months, and 11.9 kPa at six months. Initial TSH levels were 0.05 μIU/ml, increasing to 0.1 at one month, 0.54 at three months, and 2.5 μIU/ml at six months. The erythrocyte sedimentation rate (ESR) declined from 95.7 mm/h initially to 7.2 mm/h at the six-month evaluation. Significant correlations were noted between EI and ESR ($r = 0.812$, $P < 0.0001$), EI and TSH ($r = -0.419$, $P = 0.005$), as well as EI and clinical symptoms ($r = 0.798$, $P < 0.0001$). These findings indicate that EI serves as a robust predictor of disease progression, which can inform both initial and ongoing therapeutic strategies.
Conclusion
SWE elastography proves to be a valuable instrument for monitoring the progression of SAT. The elasticity index demonstrates a strong correlation with clinical and biochemical parameters, establishing it as an important predictor of disease resolution and a guide for therapeutic management.

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EP1474

JOINT3741

Non-autoimmune subclinical hypothyroidism associated with variants in the PAX8 gene: presentation of two patients

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Introduction
The transcription factor PAX8 is essential for thyroid development and function, acting as a key regulator in gene transcription. More than 50 variants in the PAX8 gene have been identified, which can be de *"novo"* or autosomal inheritance. These variants are associated with a wide range of clinical phenotypes, ranging from mild forms of hypothyroidism to more severe situations, such as congenital hypothyroidism accompanied by structural thyroid malformations. In some cases, these variants are also associated with renal or urogenital tract anomalies. We present two clinical cases of non-autoimmune subclinical hypothyroidism with *PAX8* gene varians.
Clinical Patients description: Patient 1: A 5-year-old male with normal neonatal growth and a history of treated cryptorchidism presented with weight gain and asthenia. Laboratory results showed thyroid-stimulating hormone (TSH) levels of 37.2mUI/ml and thyroxine (T4) levels of 0.94ng/dl in two occasions with negative antibodies, diagnosing non-autoimmune subclinical hypothyroidism (NASHT). Levothyroxine treatment was initiated, and thyroid ultrasound was normal. High-throughput sequencing of a gene panel revealed a heterozygous variant in the *PAX8* gene (c.80C>T p.(Pro27Leu)), classified as a variant of uncertain significance (VUS). The patient's mother has a history of hypothyroidism, but family segregation analysis was not possible. At age 15, due to poor treatment adherence, lab results showed TSH of 52.2mUI/ml and T4L of 0.68 ng/dl. At age 18, the patient weighs 129 kg, is 183 cm tall, and has a BMI of 38.5. He continues treatment with levothyroxine 250 mg/day (0.5 mg/kg). Patient 2: A 6-year-old male diagnosed with NASHT, with TSH of 7mUI/ml, T4 of 0.83ng/dl, and negative thyroid antibodies. Levothyroxine was started at an external center. Thyroid ultrasound showed a reduced size for his age (3rd percentile). Molecular study revealed a pathogenic heterozygous variant in the *PAX8* gene (c.1033_1036dupTTTC), inherited from the mother, causing a premature stop codon. At 13 years old, prepubertal, he is on 50 mg/day of levothyroxine (1.4 mg/kg/day).
Conclusions
These cases highlight the importance of PAX8 in thyroid function, showing that PAX8 gene variants can lead to a broad spectrum of clinical manifestations, including NASHT. Functional studies are needed to confirm the role of VUS variants in the *PAX8* gene in thyroid gland formation and function.

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EP1475

JOINT3628

Hypothyroidism manifesting as delusional ideas of persecution: a case report

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Introduction
Clinical manifestations of hypothyroidism includeS fatigue, weight gain, constipation, and myoxodema. Psychiatric symptoms can also be prominent and they were described as myxoedematous madness(1). They include depression, cognitive impairment and, in rare cases, psychotic features. We report here the case of a 49-year-old man presenting with delusional ideas of persecution, a manifestation of hypothyroidism, highlighting the challenges of diagnosing psychiatric symptoms as part of an endocrine disorder.
Case Presentation
He was a 48-year-old male without family history of psychiatric disorders. He was admitted for patent hypothyroidism complicated by rhabdomyolysis and acute renal failure, 8 months after receiving radioactive iodine therapy (RAI) for Graves' disease. He presented with generalized fatigue, myalgias, weight gain, and somnolence. On examination, he exhibited generalized myxedema, psychomotor slowing. He also described persecutory delusions, in which he believed that medical team and patients hospitalized next to him, were conspiring against him. Biochemical results confirmed severe hypothyroidism with a TSH of 87 and FT4 of 0.7. With the improvement of thyroid function, the persecutory delusion is resolving and further psychiatric evaluation is planned.
Discussion
Hypothyroidism is often accompanied by psychiatric symptoms, but the onset of delusions—particularly persecutory delusions—is rare (2) and may be confused with primary psychiatric disorders. In this case, the origin of the delusions were quite easy due to the contexte of severe hypothyroidism but it might be challenging in further situations (3). This case underscores the importance of considering endocrine disorders, such as hypothyroidism, when evaluating psychiatric symptoms, especially in patients with known thyroid dysfunction. Specific hormone replacement therapy is essential in managing both the physical and psychiatric components of the disease.
Conclusion
This case highlights the need for clinicians to be aware of the varity of psychiatric manifestations of hypothyroidism, including rare symptoms such as delusional ideas of persecution. Delusions in hypothyroid patients may resolve with appropriate thyroid hormone replacement, and recognizing this association can prevent unnecessary psychiatric interventions and improve patient outcomes.

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JOINT236

Association of plasma thyroxine levels with cognitive disorders in early-onset schizophrenia and other psychosis spectrum disorders

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Objective
We aimed to evaluate the relationship between thyroid hormone levels and neurocognitive functions in patients with schizophrenia and other psychosis spectrum disorders (SSD).
Method
A total of 135 patients with early-onset SSD were included in the study. The patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders-5 with schizophrenia ($n = 88$), schizophreniform ($n = 24$), schizoaffective disorder ($n = 7$), and other non-affective psychotic spectrum disorders ($n = 16$). Of the patients, 74.3% ($n = 101$) were within the first year of the disease duration, while 25.7% ($n = 34$) were within the first two years of the disease. A percentage of % 62.0 ($n = 85$) of our patients were experiencing their first episode of psychosis. The participants underwent a cognitive assessment. Blood samples were collected to measure serum levels of thyroid-stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3). Subgroup analyses were conducted based on the severity of the psychosis.
Results
We found a significant interaction between The Rey Auditory Verbal Learning Test (RAVLT-learning), RAVLT-cue call, Wechsler Memory Scale (WMS), The controlled oral word association test (COWAT), Categorical fluency, Auditory Consonant Trigrams (ACT), The Trail-Making Test-A (TMT-A), global cognition, and fT4 levels. We did not find any association between all cognitive scores and fT3 and TSH levels. The correlation between fT4 levels and global cognition was significant for patients with mild to extreme illness severity ($r = 0.41$, $P < 0.001$), but not significant for those with residual/minimal to mild illness ($r = 0.15$, $P = 0.261$). Accordingly, hierarchical regression analyses were performed to estimate global cognition scores, including subsamples with minimal to mild illness and youth with mild to extreme psychosis (Table 3). Education, age, sex, substance use, and daily antipsychotic dose were first entered into the models, yielding significance for both the model containing patients with minimal to mild severity as well as the model of patients with mild to extreme disease severity. When plasma fT4 levels were added in a second step, the model containing patients with minimal to mild disease severity did not provide a significant R^2 change ($\Delta R^2 = 0.03$, $p = 0.127$), while it was significant in those with mild to extreme psychosis severity ($\Delta R^2 = 0.10$, $p = 0.002$).
Conclusions
Serum fT4 levels were associated with the performance across various cognitive domains in cases of early-onset psychotic disorders. This correlation was accentuated among patients with higher illness severity. Future studies could focus on the effects of specific pathways that can affect the course and progression of psychosis.

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JOINT2962

Evaluation of clinical findings, laboratory results, and radiological features in pediatric patients followed up for thyroid dysfunction

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Objective
This study analyzed the laboratory findings and diagnostic distribution of patients with thyroid function test abnormalities referred to our clinic.
Materials and Methods
In this study, 310 cases with abnormal thyroid function tests referred to our clinic between October 1, 2022, and May 31, 2023, were retrospectively evaluated. Patient data were obtained retrospectively from our hospital's medical records. The cases' demographic, clinical, and laboratory data were analyzed to investigate the final diagnostic distribution.
Results
The study included 310 patients, of whom 64.8% ($n = 201$) were female, with a median age of 10 years (ranging from 5 to 13 years). All cases had undergone evaluation by other departments before presenting to the pediatric endocrinology clinic. While some patients had previously visited a single center, others had consulted multiple centers. Among the reasons for their initial visits to these centers, 39.4% of the cases ($n = 122$) had undergone routine check-ups, during which abnormal thyroid function test results led to their referral to our clinic. Before being referred to our clinic, 24.2% of the cases ($n = 75$) had been evaluated due to abnormal thyroid function test results detected during screening. Additionally, 2.9% of the cases ($n = 9$) had presented due to obesity, 2.6% ($n = 8$) due to palpitations, 2.3% ($n = 7$) due to constipation, and another 2.3% ($n = 7$) due to short stature. Furthermore, 26.5% of the cases ($n = 82$) had been evaluated for various other complaints, including increased hair loss, recent weight loss, decreased appetite, fatigue, and chest pain. All patients were referred to our tertiary pediatric endocrinology clinic due to abnormal thyroid function test results. The final diagnostic distribution of these cases in our hospital showed that 31.3% ($n = 97$) were diagnosed with Hashimoto thyroiditis, while 22.3% ($n = 69$) had congenital hypothyroidism. Euthyroidism was identified in 17.4% ($n = 54$) of the cases, whereas 13.2% ($n = 41$) were diagnosed with subclinical hypothyroidism. Central hypothyroidism was found in 9.4% ($n = 29$) of the cases. Additionally, 3.5% ($n = 11$) of the patients were diagnosed with Graves' disease, and 2.9% ($n = 9$) had hashitoxicosis. Moreover, 13 cases were found to have isolated TSH elevation due to excess weight or obesity. Relevant cases received necessary treatments, while others were placed under follow-up.
Conclusion
Thyroid dysfunction in childhood is a common condition that may require early diagnosis and prompt treatment, as in congenital or acquired hypothyroidism, or it may stem from a condition that necessitates clinical follow-up.

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JOINT876

Effectiveness and outcome of fixed 600 Mbq radioactive iodine activity in the treatment of benign thyroid disease

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Objective
This study aimed to evaluate the effectiveness and thyroid status outcomes following the introduction of a fixed radioactive iodine (RAI) dose of 600 Mbq in patients diagnosed with hyperthyroidism.
Methods
A retrospective review was conducted involving 92 patients treated for hyperthyroidism after the implementation of the fixed 600 Mbq RAI dose. The analysis focused on primary diagnoses, biochemical outcomes, and the duration of hypothyroidism development in patients post-RAI, as well as the initiation of levothyroxine therapy.
Results
Among the 92 patients studied, 67 were diagnosed with Graves' disease and 25 with multinodular goitre (MNG). The cohort comprised 72% females and 26% males, with an average age of 54.8 years. The overall cure rate was 89%, surpassing the 83.5% cure rate reported in previous studies involving variable doses of RAI. Antithyroid medication (ATD) was discontinued in 91% of Graves' patients on average 11.3 weeks after RAI, compared to 84% of MNG patients who ceased ATD therapy an average of 11.7 weeks post-RAI. The average time to hypothyroidism development was 13.38 weeks for Graves' patients and 22.1 weeks for those with MNG. In patients with Graves' disease, 84% initiated levothyroxine therapy, while only 40% of MNG patients required thyroxine supplementation post-RAI.

Conclusion
The overall cure rate was 89%, indicating a significant improvement over variable dose RAI outcomes documented in other studies, with 91% of Graves' patients and 84% of MNG patients discontinuing ATD therapy on average 11.3 and 11.7 weeks post-RAI, respectively. The administration of 600 Mbq RAI is associated with a lower incidence of hypothyroidism requiring thyroxine supplementation in patients with MNG, and hypothyroidism develops later compared to those with Graves' disease. As previously known, RAI for toxic MNG is an effective treatment that can result in euthyroidism, with fewer patients requiring levothyroxine replacement. We intend to use the results to implement a streamlined outpatient follow-up approach, where thyroid function tests can be organized at 6 weeks via a virtual clinic, with the first face-to-face appointment scheduled between 11 to 12 weeks, thus reducing the need for earlier and more frequent appointments. This approach may potentially enhance patient care by improving access, increasing time efficiency, enabling early detection of complications, and boosting patient satisfaction.
Reference
Fixed 600mbq radioiodine activity is more effective than variable dose in treatment of benign thyroid disease) [(Mohamed et al., 2019)]

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JOINT2375
Metabolically associated fatty liver disease in woman with hypothyroidism

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Introduction
Metabolically associated fatty liver disease (MAFLD) frequent condition in people with obesity and lipid abnormalities. Hypothyroidism associated with fat abnormalities and predisposed to weight gain. We aimed to investigate frequency of fatty liver disease among women with hypothyroidism.
Material and Methods
105 women in age 45-59 who lived in Andijan city which is iodine deficiency area BMI blood serum T3, T4, TSH, ALT, AST, bilirubin, total cholesterol (TCh), triglycerides (TG), LDLP, HDLP level were measured, aterogenic index were calculated. MAFLD degree were were detected by ultrasound.
Results
Obesity were determined by BMI and showed 1st degree in 38.2%, 2nd degree in 20.5%, 3rd degree in 7.8% of woman. Hypothyroidism were detected in 45.5% women. Blood TCh, TG, LDLP, HDLP and atherogenic index, blood ALT, AST level were higher than those without hypothyroidism. Interestingly in 41% of women with hypothyroidism were detected MAFLD in ultrasound. In patients who followed thyroid hormone replacement therapy MAFLD were lower than those who non-adhered which suggested about linkage between MAFLD and thyroid state.
Conclusion
MAFLD is a frequent clinical future in patients with hypothyroidism and depends from thyroid state. Adequate hormone replacement therapy can prevent MAFLD in patients with hypothyroidism.

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JOINT1410
P63 immunohistochemical peculiarities under autoimmune thyroiditis vs papillary thyroid carcinoma (PTC)

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Background
Hashimoto thyroiditis, which is classified as an autoimmune disorder affecting the thyroid gland, has been considered as a lesion preceding and predisposing to papillary thyroid carcinoma (PTC) by several authors. In contrast, the other clinical type of thyroid autoimmune disease - the Riedel's thyroiditis has not been evidenced to be a pre-cancer lesion.
Materials and Methods
This hypothesis encouraged us to undertake the morphological and immunohistochemical comparative assessment of these two types of thyroiditis (RT and HT) utilizing the diagnostic value p63 immunohistochemistry in thyroid pathology. The surgical specimens of the thyroid gland, obtained from 36 patients were studied in total, including Riedel's thyroiditis ($n = 5$), Hashimoto's thyroiditis ($n = 24$) and papillary thyroid carcinoma ($n = 7$) as a control group.
Results and Discussion
Obtained results showed that autoimmune thyroiditis types are characterized by histological and immunohistochemical heterogeneity, however, pathological alterations in both processes (RT, HT) specifically demonstrated progressive involution of glandular tissue and replacement with rigid tissue, sometimes, scar fibrosis. Positive p63 expression were highly specific for papillary carcinoma in the setting of HT, which was not characteristic for the Riedel's thyroiditis specimens.
Conclusion
According to biomolecular research data, we could not exclude dysplastic and neoplastic transformation in progenitor cells within the parenchyma of Hashimoto's thyroiditis vs Riedel's autoimmune thyroiditis.

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JOINT3562
Papillary thyroid microcarcinomas detected by nuclear medicine imaging methods do they have a worse prognosis?

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Background
Studies have suggested that papillary thyroid carcinomas incidentally detected by nuclear medicine imaging techniques may have a worse prognosis compared to those identified by other methods. However, it remains unclear whether this observation applies to papillary thyroid microcarcinomas (PTMCs).
Aim
To compare the prognostic differences among PTMCs detected by nuclear medicine imaging (e.g., 18F-FDG PET, technesium-99m-MIBI), incidental PTMCs, and non-incidental PTMCs using pathological tumor characteristics.
Methods
Patients diagnosed with PTMC in Hacettepe University School of Medicine between 2008 and 2020 were categorized into three groups: (1) PTMCs detected by nuclear medicine imaging methods ($n = 24$), (2) incidental PTMCs ($n = 251$), and (3) non-incidental PTMCs ($n = 132$). Tumor pathology characteristics, including multifocality, extrathyroidal extension, vascular invasion, and lymph node involvement were analyzed. Logistic regression analysis was performed to assess the association between detection method and tumor aggressiveness, adjusting for potential confounders such as age at diagnosis.
Results
Patients with PTMCs detected by nuclear medicine imaging were significantly older at diagnosis (54.7 ± 11.7 years) compared to incidental PTMCs (51.0 ± 11.4 years) and non-incidental PTMCs (47.1 ± 11.8 years) ($P = 0.001$). Tumor size was also significantly different among groups ($P < 0.0001$), with nuclear medicine-detected PTMCs (4.8 ± 2.5 mm) and non-incidental PTMCs (5.3 ± 2.3 mm) being larger than incidentally detected PTMCs (3.4 ± 2.4 mm). Logistic regression analysis showed that PTMCs detected by nuclear medicine imaging were significantly more likely to be bilobar compared to incidentally detected PTMCs (OR: 4.59, 95% CI: 1.55-14.58, $P = 0.006$). The rate of cervical lymph node metastasis was markedly higher in PTMCs detected by nuclear medicine imaging compared to both incidentally detected PTMCs (OR: 41.13, 95% CI: 9.33-191.20, $P < 0.0001$) and non-incidental PTMCs (OR: 3.82, 95% CI: 1.16-12.58, $P = 0.027$). However, there were no significant differences among the groups in terms of extrathyroidal extension or vascular invasion.
Conclusions
Although nuclear medicine-detected PTMCs were larger in size and associated with a significantly higher rate of cervical lymph node metastasis and bilobar involvement compared to incidental PTMCs, other aggressive pathological features did not significantly differ. These findings suggest that PTMCs identified by nuclear medicine imaging may have distinct biological behavior, warranting further investigation to determine their true prognostic implications.

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EP1482

JOINT1788

Corneal ulcer, a rare complication of hashimoto's thyroiditis

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Introduction

Ophthalmic involvement in autoimmune thyroid diseases such as Graves' disease is well known, while Hashimoto's thyroiditis has rarely been implicated in the development of occular manifestations. Corneal ulceration is a serious complication that can jeopardize the visual prognosis. We report a clinical observation of an association between Hashimoto's thyroiditis and corneal ulcer to describe this rare complication.

Clinical Case

Forty three years-old female patient, treated for hashimoto's thyroiditis for 12 years on levothyroxine 100mg/d. The patient reported the onset of ocular redness aggravated by visual fog for 2 months. Workup noted whit cell blood at 7150/mm^3, CRP at 55 mg/land TSH us at 18 uUI/ml. Fundus showed a visual acuity of 6/10 on the right and counting fingers at 0.5 m on the left, conjunctival hyperhemia with axial opacity and punctiform corneal perforation measuring 1*1 mm in the left eye. The patient was put on systemic corticosteroids with analgesic treatment. The evolution was marked by regression of local inflammatory signs. The patient was scheduled for amniotic membrane transplantation.

Discussion

Ophthalmological involvement is generally frequent in basedow's disease, where it can occur in around 25-50% of cases, whereas this prevalence is only 2% in Hashimoto's thyroiditis (1). Ocular lesions can occur at any time during the course of thyroid disease, sometimes 10 or even 20 years after the diagnosis of autoimmune thyroid disease (2). The pathogenesis of thyroid ophthalmopathy is based on the development of antibodies directed against both the thyroid gland and the orbit. Immunological mechanisms are represented by orbital infiltration by T lymphocytes recognizing orbital antigens and periocular muscles (3,4), secretion of cytokines and water-attracting glycosaminoglycans, and transformation of orbital fibroblasts into adipocytes, resulting in exophthalmos and inflammation of the eyeball with, in some cases, corneal fragility responsible for epithelial perforation. The presence of anti-TPO antibodies (in 90% of cases) testifies to their involvement in this pathogenesis (5,6).

Conclusion

Ocular complications in autoimmune thyroid disease (AITD) are a rare but sometimes serious entity that can be vision-threatening. They should therefore be screened in any patient being treated for an AITD.

Key Words:

thyroiditis, autoimmunity, Corneal ulceration.

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EP1483

JOINT2642

Acute thyrotoxic crisis with cardiothyreosis: management challenges in the face of carbimazole-induced hepatic cytolysis

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Introduction

Acute thyrotoxic crisis (ATC) is an exceptional form of life-threatening thyrotoxicosis. Its diagnosis is not easy to make, given its multisystemic and non-specific clinical manifestations. Its treatment requires specialized and urgent care, given the risk of single or multiple organ failure. We report the case of a patient with CAT complicated by cardiothyreosis.

Case report

Patient aged 30, known to have undocumented thyreopathy for 4 years, initially put on Carbimazole 20mg/d, taken irregularly then stopped for a period in view of hepatic cytolysis, then restarted 10 days ago in view of a normal hepatic workup. She presented to the emergency department with stageVI dyspnoea, palpitations, thermophobia and asthenia, in a context of significant weight loss. The workup revealed peripheral hyperthyroidism with TSH at 0.004 µUi/ml, T4L > 64.3 pmol/land T3L at 17.7 pmol/l,with negative antibodies. the electrocardiogram showed supraventricular tachycardia at 220 bpm, with significant hepatic cytolysis. The patient underwent emergency conditioning, then was slowed by B-blockers (Propanolol) combined with an antiarrhythmic, and because of the hepatic cytolysis, which contraindicating the start of synthetic antithyroid drugs (ATDs), the patient had received corticosteroid therapy, combined with rehydration according to cardiac tolerance, and anticoagulation. And then, she underwent emergency plasmapheresis. The evolution was marked by a good clinico-biological improvement, electrocardiogram abnormalities and thyroid balance after the plasmapheresis session. Then, She underwent radical surgery after clinical stabilization and euthyroidism, with a simple postoperative course.

Discussion

ATC represents a veritable life-threatening emergency. Although rare, its mortality rate remains high (around 15%), mainly due to the onset of multivisceral failure. It is defined by an exacerbation of all the manifestations of thyrotoxicosis: fever, tachycardia, agitation, vomiting, dehydration, neuro-psychiatric disorders. Cardiothyreosis, is the most serious clinical presentation, occurs preferentially in the elderly. There are many causes, the most common being Graves' disease, toxic goiter and amiodarone therapy. It is characterized by a drop in peripheral vascular resistance, an increase in resting heart rate, left ventricular contractility, blood volume and cardiac output. The most frequent and earliest sign is tachycardia, as well as atrial fibrillation, ventricular arrhythmias, pulmonary hypertension, orthostatic hypotension, right-predominant heart failure and coronary insufficiency.) In addition to specific treatments such as ATDs, radioactive iodine and surgery, the therapeutic arsenal includes symptomatic treatments: β-blockers as first-line therapy, digitalis, electrical cardioversion, even hemodynamic assistance and plasmapheresis.

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EP1484

JOINT3934

Vesicular thyroid carcinomas

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Introduction

Follicular or vesicular cancers account for 5 to 10% of differentiated thyroid cancers (DTC) and are therefore the second most common cause of endocrine tumors after papillary thyroid cancer. They can be minimally or massively invasive, making them a more aggressive histological type compared to papillary carcinoma.

Objective

The objective of our study is to describe the clinical and evolutionary characteristics of vesicular thyroid tumors.

Materials and Methods

This is a retrospective descriptive study involving 34 patients treated in our service, between 1986 and 2024, diagnosed with vesicular thyroid carcinoma. Statistical analysis was performed using SPSS software.

Résults

The average age of our patients was 51.6 years. All the patients in our study were women. The most common presenting feature was the presence of an isolated goiter (67%), followed by an isolated thyroid nodule (8%). Bone metastases led to the diagnosis in one patient. One patient consulted for a nasal voice with progressive worsening and was diagnosed with carcinoma on an ectopic lingual thyroid. All our patients underwent total thyroidectomy, and lymph node dissection was indicated in only one patient. Radioactive iodine treatment was administered to 85% of the patients. All the carcinomas in our series were unifocal. Tumor size ranged from 0.5 cm to 7.5 cm. The development of locoregional and distant metastases (bone, lungs) was observed in one and two patients, respectively. Two patients developed ductal breast carcinoma during the follow-up. A complete remission was observed in 53% of the patients.

Conclusion

Our study reveals a female predominance of follicular thyroid carcinomas, with the majority of cases presenting as an isolated goiter. The overall prognosis is generally favorable, and the risk of local or distant recurrence is the key factor in guiding treatment.

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EP1485

JOINT97

Sclerotherapy of cystic formations of the thyroid and parathyroid glands

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Cystic formations of the thyroid and parathyroid glands are a common pathology due to the widespread use of ultrasound examination of the neck organs. True cysts of the thyroid (TC) and parathyroid glands (PC) are hormonally inactive and often have small sizes. But large cysts (10%) have clinical manifestations (pressure on the surrounding neck organs). The attitude towards this pathology is ambiguous - from radical removal to passive observation. Complications of TC and PC can be malignant transformation, ruptures and bleeding. We analyzed 96 clinical cases of TC (78) and PC (18). The size of the cysts varied from 20 to 114 mm, and the volume - from 6 to 360 ml (on average - 42.1 $\pm$ 24.2 ml). An algorithm of actions for this pathology is proposed. The first method of detecting cysts is ultrasound, which allows you to identify a cyst and measure its size. Initially, a complete cyst aspiration is performed for cytological examination and determination of TG and PTH levels. For punction TC the aspirate was yellow or brown, transparent or cloudy; for punction PC was colorless, transparent. The laboratory criteria are the levels of TG and PTH in the aspirate. If a high level of TG and a low level of PTH are detected in the TC, then obtaining the results of Bethesda 4,5,6 in the tissue component of the TC is the basis for surgical intervention. Bethesda 1,2 was the basis for the observation. PC were characterized by high levels of PTH (from 1218 to 3070 pg/ml; average 2012.5$\pm$946.7 pg/ml) and low levels of TG. The method of choice for their treatment is mainly observation. The recommended period of ultrasound examination is 3,6,12 months. If the contents accumulate in the cysts with a volume of up to 10 ml, repeated aspiration of the contents with subsequent ultrasound control is possible. In case of repeated accumulation of contents in thyroid cysts with a volume of more than 10 ml, sclerotherapy is preferable. Compression syndrome served as the basis for surgical intervention for TC in 3 cases, simultaneous operations were performed in 9 cases: in 6 cases – with a multi-node toxic goiter, in 3 - with thyroid cancer. When choosing methods of treatment for thyroid cysts, it is necessary to be guided by the fact that the treatment method should be as safe and minimally invasive as possible.

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EP1486

JOINT151

Ultrasound support of diapeutic interventions in thyrioid pathology

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Diapeutic manipulations involve simultaneous diagnostic and therapeutic actions. With regard to the thyroid, it's a combination in the hands of a specialist of non-invasive diagnostic ultrasound and invasive interventions, such as FNAB, sclerotherapy, laser destruction, radiofrequency ablation and HIFU performed under ultrasound control. The evaluation of ultrasound examination protocols of the thyroid in 1235 patients were analyzed. Ultrasound protocols included an assessment of echogenicity, structure, and size of the gland itself, as well as the identification of focal formations (in 1,041 patients; 84.3%), which were described according to the TI-RADS criteria adopted in the clinic (echogenicity, structure, evenness and clarity of contours, shape, vascularization, presence of Halos, calcifications, signs of invasiveness). In order to form surgical tactics, the number of formations, their size, volume and localization were evaluated. At an early stage, TAPB was used for diagnosis under ultrasound control (988 patients; 80.0%). Performing this diapeutic manipulation allowed us to identify a group of patients with tumors (categories Bethesda IV, V, VI) (143 people; 11.6%) who underwent traditional surgical treatment. Ultrasound monitoring was recommended for a significant number of patients (756 people; 61.2%). Minimally invasive therapeutic manipulations were used in 89 patients (7.2%) in the treatment of thyroid nodules belonging to the Bethesda II category: in 14 people (1.1%) it was sclerotherapy, in 10 patients (0.8%) high-intensity focused ultrasound (HIFU) was performed, in 65 people (5.3%) laser destruction. All patients gave informed consent to undergo diapeutic manipulations. All diapeutic manipulations were performed under the supervision of ultrasound on an outpatient basis by a team of specialists, which included a surgeon and a specialist in radiation diagnostics. They did not require special training and were well tolerated by patients. The analysis of the results showed that minimally invasive diapeutic manipulations in most cases are the final method, leading to an improvement in the patient's quality of life and even to a complete cure of the patient. They are the method of choice for severe patients and patients who refuse surgical treatment. In these situations, the treatment was palliative. Minimally invasive therapeutic manipulations can precede open surgery, significantly reducing the size of focal formations. Ultrasound diapeutics, which makes it possible to provide significant assistance both in making a diagnosis and in the subsequent treatment of patients with focal thyroid pathology, is the prerogative of a surgeon who has special training in ultrasound diagnostics, and not a radiologist.

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EP1487

JOINT331

Prevalence of thyroid autoimmunity and by age, sex, geographic region, and socioeconomic status among 1.7 million chinese adults

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Background
Thyroid autoimmunity (TAI) is among the most common autoimmune disorders, and it has been linked to an elevated risk of numerous autoimmune and non-autoimmune diseases. However, current estimates of TAI prevalence are limited due to small sample size or single jurisdiction data. This study aimed to investigate the prevalence of TAI in Chinese population and how it varies by age, sex, geographic region, and socioeconomic status.
Methods
The Meinian Health Check-up database was used in this nationwide, large-scale, cross-sectional study. The study included 1,758,425 individuals aged $\geq$18 years who had health check-ups between 2017 and 2023 and collected blood samples for thyroid function and thyroid antibody tests. TAI was defined as positivity for thyroid peroxidase antibody (TPOAb) and/or thyroglobulin antibody (TgAb). Sample weights based on the 2020 Chinese census were assigned to account for the unequal sample distributions across provinces and to adjust for age and sex proportions. Weighted prevalence with a 95% confidence interval (CI) was computed using the Taylor Series Linearization method.
Results
Among the overall study population (mean age 44.7$\pm$12.8 years; 60.0% female), the weighted prevalence of TAI was 23.5% (95% CI 21.7%-25.3%). Near half (46.3%) of those with TAI had positive results for both TPOAb and TgAb, 30.6% were TPOAb+ only, and 23.1% were TgAb+ only. Most of TAI (70.8%) had normal thyroid function, while 22.0% had hypothyroidism. The prevalence of TAI increased with age, peaked at the age of 50 to 59 years, and declined thereafter. Overall, females had more than double the prevalence compared to males (33.6% [32.3%-35.0%] vs. 14.1% [12.8%-15.3%]), with a similar pattern across each age group. Geographically, TAI was most prevalent in the northern (26.5% [24.3%-28.6%]) and central (26.7% [24.1%-29.2%]) regions of China, followed by the eastern region (25.7% [22.6%-28.8%). No significant difference was observed for the prevalence of TAI between coastal and non-coastal region. A socioeconomic gradient was also identified, with individuals resided in higher gross domestic product level cities having a lower prevalence of TAI.
Conclusions
TAI was common in the Chinese population and varied by age, sex, geographic region, and socioeconomic status. A notable proportion of individuals with TAI had normal thyroid function, suggesting that many cases may go undetected without routine assessment. These findings highlight early detection may be useful in preventing the progression to overt thyroid dysfunction and reducing the broader burden of autoimmune disorders.

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JOINT2281

A case of post-operative graves disease

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Background
Graves disease is one of the most common thyroid pathologies with multiple risk factors that may present with various clinical manifestations. Because of the small

number of cases, there is ongoing debate whether postoperative GD can be associated with previous autoimmunity exacerbated by exogenous stress or new onset improper response of the immune system after partial thyroidectomy. Theory suggests that during surgery, injured thyroid follicular cells release THS-R which are picked up by APC that induces Th2 humoral response. Risk factor of this phenomenon might be genetic predisposition to autoimmunity.
Case Presentation
A 23 years old Caucasian female admitted to the hospital with the complaints of general weakness, palpitation, sleep disturbances, hand tremor, headache, irregular menstrual cycle, increased appetite and sweating. 3 years ago, a patient was diagnosed with a dynamically growing nodule measuring 38 mm with euthyroid state confirmed by laboratory tests. Fine-needle aspiration excluded malignancy. The patient underwent hemithyroidectomy (histomorphology confirmed a nodular goiter). Postoperatively, subclinical hypothyroidism was identified, and levothyroxine therapy was initiated, however, the patient stopped taking medication. In family history, mother has hypothyroidism and Sjogren's disease. On physical examination, there was a tremor of the outstretched hands, moist and warm skin, slight exophthalmos, and a positive Graphe's sign. Initial lab tests revealed thyrotoxicosis: TSH – 0.09 MKU/ml, FT4 – 24.28 pmol/l; FT3 – 7.61 pmol/l,Thyreoglobulin – 26.910 ng/ml (3.5-7.7) anti-TSH-R – 6.5 IU/l(normal range $<$ 1.0). Moreover, an ultrasound revealed a coarse-grained left thyroid lobe in the size of 4.7cc with irregular echogenicity. Color Doppler imaging demonstrated enhanced blood flow in the parenchyma. Scintigraphy revealed increased uptake of Tc-99m in the remnant left lobe of the thyroid gland. Based on these findings, a diagnosis of Grave's disease was made. The patient was started on methimazole and Beta-blocker with symptomatic and laboratory improvement.
Conclusion
This is a rare case of new onset Graves disease after partial thyroidectomy. Case highlights importance of post-surgical follow-up and screening including TFTs. In the presence of Hyperthyroidism after lobectomy, Grave's disease should be considered in broad differential diagnosis. Even though it indicates possible improper immune response to released TSH-R during the surgery, further research is needed to understand pathophysiology of association between GD and thyroid surgery.

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JOINT1502

AI chatbots vs endocrinologists in clinical decision-making in thyroid nodule and papillary thyroid carcinoma management

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Introduction
The management of thyroid nodules and papillary thyroid carcinoma (PTC) varies widely, influenced by evolving guidelines and clinical judgment. With advancements in artificial intelligence (AI), chatbots like ChatGPT, Copilot and Gemini have emerged as potential decision-making supporting tools.
Aim
This study aims to compare clinical decision-making patterns among endocrinologists and AI chatbots responses.
Methods
A web-based survey was distributed to the members of the Hellenic Endocrine Society (HES), presenting 12 clinical scenarios addressing management strategies for solitary thyroid nodules and PTC across various risk profiles (EU-TIRADS 4 and 5 nodules and very-low, low, and low-to-intermediate risk PTCs). Participants selected one of four management strategies for each scenario. ChatGPT, Copilot and Gemini answered the 12 scenarios at two time points: April 2024 (T1 – survey end) and January 2025 (T2). AI chatbots responses were compared with the recent American and European Thyroid Association guideline recommendations, as well as with endocrinologists' responses.
Results
A total of 201 endocrinologists (25% of HES members) participated in the survey. Between T1 and T2, ChatGPT, Copilot and Gemini altered their responses for 8/12, 6/12 and 7/12 scenarios, respectively. At T1, ChatGPT and Copilot aligned with 33% and 58% of guideline recommendations, increasing to 66% for both at T2. Conversely, Gemini's alignment remained at 17% at both time points. Agreement between the AI chatbots responses and the predominant choices among endocrinologists was as follows: at T1, ChatGPT matched the endocrinologists' prevailing choice in 2 (17%), Copilot in 1 (8%) and Gemini in 3 out of 12 scenarios (25%). By T2, agreement rates improved to 5/12 (42%) for ChatGPT, 4/12 (33%) for Copilot, and 6/12 (50%) for Gemini. Finally, the mean percentage of survey respondents whose answers corresponded to answers provided by AI chatbots was calculated. At T1, ChatGPT had a 24% agreement rate, Copilot 24% and Gemini 37% (noted 1 and 2 questions were excluded for Copilot and Gemini as the chatbots could not provide any recommendation). At T2, these rates increased to 34%, 30% and 43% for ChatGPT, Copilot and Gemini, respectively.
Conclusion
This study highlights the evolving role of AI chatbots in clinical decision-making for thyroid nodules and PTC. Over time, the alignment of AI responses with clinical guidelines and endocrinologists' choices improved, suggesting their potential utility in supporting clinical decisions. Further research is needed to optimize AI integration into clinical practice and ensure consistency with evolving medical guidelines.

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EP1490

JOINT1504

HPA axis integrity after Iv methylprednisolone for active moderate-to-severe thyroid eye disease

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Introduction
Only five small studies have evaluated the effects of supraphysiologic intravenous methylprednisolone (IVMP) therapy on hypothalamic-pituitary-adrenal (HPA) axis suppression in patients with active moderate-to-severe thyroid eye disease (TED). The standard IVMP regimen consists of 4.5 g administered over 12 weeks (0.5 g weekly for six weeks, followed by 0.25 g weekly for another six weeks).
Aim
To investigate the impact of IVMP therapy on HPA axis function in patients with moderate-to-severe TED.
Methods
This study included adults ($>$18 years) with active moderate-to-severe TED followed at the Department of Endocrinology and Metabolic Diseases, University General Hospital of Larissa, Greece, (April 2008–July 2024). HPA axis function was assessed using the standard-dose Synacthen test (250 μg synthetic ACTH) 7–10 days after IVMP completion. Serum cortisol levels were measured at baseline and 30- and 60-minutes post-ACTH injection. Adrenal sufficiency was defined as a peak cortisol level $\geq$18.1 μg/dl (500 nmol/L). Patients receiving glucocorticoids of any route of administration beyond the IVMP regimen or with conditions affecting cortisol-binding globulin were excluded.
Results
Of 127 enrolled patients, 115 were analyzed. the test could not be performed in 12 patients due to drug unavailability ($n = 9$), severe infection ($n = 2$), or incorrect dosing ($n = 1$), leaving 115 patients for analysis. All patients were euthyroid at the time of testing (FT4 range: 0.96–1.67 ng/dl; reference range: 0.93–1.7 ng/dl). Baseline cortisol levels were $\geq$18.1 μg/dl in 13% of patients, while 93% and 100% achieved $\geq$18.1 μg/dl at 30- and 60-minutes post-ACTH injection, respectively, indicating intact adrenal function. Notably, all patients with baseline cortisol $<$5.5 μg/dl achieved peak cortisol levels $\geq$18.1 μg/dl.
Discussion
Consistent with prior small studies, our findings in a large cohort confirm no evidence of HPA axis suppression following IVMP therapy for TED. Routine HPA function evaluation may not be necessary for TED patients receiving IVMP.

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EP1491

JOINT2944

Differentiated high-grade thyroid carcinoma (DHGTC) and poorly differentiated TC (PDTC): diagnostic and therapeutic challenges in the precision medicine era - report of two cases

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Background
DHGTC and PDTC are rare, aggressive forms of TC with intermediate prognosis, thus posing significant therapeutic challenges.
Case-report-1
A 59-year-old male underwent total thyroidectomy with neck dissection and internal jugular vein thrombectomy due to a rapidly growing neck mass. Histopathological report revealed PDTC-70% with DHGTC foci-30%, 20/40 infiltrated lymph nodes (LNs) and tumor thrombus. Tumor molecular analysis (TMA) (AmoyDx® HANDLE Classic-NGS-Panel) revealed a *PTEN*-InDel (Intron 6, c.634 + 1G > C, p.?). Preoperative whole-body CT-scans performed due to elevated Tg:962.3ng/ml, revealed no distant metastases. However, a post-operative (4-weeks after CT-scans) 18FDG-PET CT-scan showed hypermetabolic activity in: thyroid bed, cervical/mediastinal LNs, sternum manubrium, and in a single lung nodule. Diagnostic (5mCi-^{131}I) whole-body scan (WBS) showed no uptake in the lung or sternum. Radiotherapy was delivered to the manubrium (total dose:40Gy). In chest CT-scan 75-days after 18FDG-PET, disease progression was documented with a more than double increase in the size of the lung node, slight increase in cervical LNs and rising Tg:6851.49ng/ml. Systemic treatment (ST) with lenvatinib-20mg daily, pembrolizumab-200mg Q3W and denosumab-120mg once per month, was initiated. 90-days after, mixed response was documented by 18FDG-PET (regression of lung, sternum, and LNs metastases), three new small suspicious bone lesions (right acetabulum, left hip-bone, C7-vertebra) and a lesion invading the cricoid cartilage, while Tg decreased:394.24ng/ml.
Case-report-2
A 73-year-old female with a history of large, multifocal, locally invasive papillary TC and negative for distant metastases post-therapy ^{131}I-WBS underwent revision surgery due to disease persistence. Histopathological report revealed widely invasive DHGTC with PDTC foci, which was in concordance with the revised by an expert pathologist first report. Chest CT-scan revealed multiple cannonball lung metastases while brain-MRI revealed 10 metastatic lesions; Tg:6325.17ng/ml. TMA revealed a *BRAF*V600E mutation. Stereotactic radio-surgery was performed to brain metastases (maximum dose:24Gy) with a lesion volume decrease up to 75% within two-months. ST treatment with dabrafenib 75mg-bid was initiated and a mixed response in lung was documented within 3-months while increased Tg:15679.18ng/ml, implied possible re-differentiation. Nevertheless, structural progression was documented after one-month with subsequent Tg decrease:10111.02ng/ml and Trametinib-2mg daily was added to the treatment. Mixed response in lung was documented within 2-months with increased Tg:20159.66ng/ml. Albeit mixed response, the patient succumbed to complications from lung metastases.
Conclusion
PDTC and DHGTC are rare, aggressive types of TC requiring a multidisciplinary approach. When and where to perform locoregional therapies in combination with the type of ST according to TMA is of paramount significance towards appropriate therapeutic management and precision medicine implementation.

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EP1492

JOINT3640

Hypothyroidism in infants and young children: diagnostic challenges and clinical manifestations

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Objectives
The incidence of pediatric hypothyroidism is rising with nearly 1 in 257 infants affected each year in our country. Disease is usually diagnosed late due to vague symptoms. Current study is conducted to identify the symptoms which should alert the physicians and help in reaching correct diagnosis.
Study design
This is a observational and prospective study.
Place and duration of study: It was conducted at Children Hospital, Pakistan Institute of Medical Sciences from March 2023 to March 2024.
Methods
Children aged 5 years or below with low serum T4 and raised TSH levels were included in study. Data was analyzed by applying appropriate statistical tests via SPSS.
Results
In newborns to infants up to 3 months of age, the most common symptoms are prolonged jaundice, feeding difficulties, and constipation. Between 3 months to 1 year, constipation, hypotonia, and coarse facies become the predominant features. From 1 to 5 years, the most frequently observed signs include hypotonia, coarse facies, short stature, and periorbital puffiness. The most common clinical manifestation across all age groups is hypotonia (75.4%), followed by coarse facies (64.9%) and constipation (64.9%). Other notable features include periorbital puffiness, feeding difficulties, prolonged jaundice, short stature, developmental delay, umbilical hernia, wide anterior fontanelle, and in some cases, goiter.
Conclusion
Hypothyroidism in children is challenging to diagnose due to its nonspecific symptoms, which often overlap with other conditions. The prevalence of this condition in the pediatric population within our region highlights the need for prompt and efficient diagnosis and management. Special attention should be given to infants presenting with persistent jaundice, feeding difficulties, or poor weight gain. Beyond infancy, clinical signs such as hypotonia, coarse facial features, delayed development, and poor growth should raise suspicion for hypothyroidism. Early recognition and treatment are crucial to prevent long-term complications, including developmental delays and cognitive impairment.
Key Words
Hypothyroidism, persistent Jaundice, generalized hypotonia, coarse facies, Constipation.

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JOINT3406

Graves' disease in monozygotic twins: a case report and literature review

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Background
Graves' disease (GD) is an autoimmune disorder that leads to hyperthyroidism, primarily due to the activation of the thyroid gland by thyrotropin receptor antibodies (TRAb). GD in children is rare, and its occurrence in monozygotic twins is even more uncommon. This case explores the potential genetic and environmental factors contributing to GD in twins.
Case Presentation
A 3-year-old female (a preterm product of an IVF, part of a monozygotic twin). was otherwise healthy except for mild eczema. She presented with six months history of intermittent loose stools, mild abdominal discomfort, and later, increased appetite, hyperactivity, insomnia, and palpitations. Clinical evaluation revealed tachycardia (HR 150-160 bpm), elevated Free T4 (> 65 pmol/L), and suppressed TSH (< 0.01 mIU/L), confirming hyperthyroidism. Thyroid antibody testing was positive for Anti-TG Ab (232 IU/L), Anti-TSHR Ab (27.5 IU/L), and elevated TPO antibodies (213 kIU/L). Goiter grade I in examination. Neck ultrasound showed a mildly enlarged thyroid with hyperemia. The patient was treated with carbimazole and propranolol, leading to gradual improvement. The second twin, despite positive thyroid antibodies (TSHR Ab < 0.8, TPO 51, Anti-TG Abx 647 IU/ml), remain euthyroid.
Literature Review
Graves' disease (GD) in monozygotic twins is rare, with few cases reported, especially in this age group. Genetic factors, including shared HLA alleles and thyroid-specific antibodies, may predispose twins to autoimmune thyroid disorders. A 2019 study by Smith *et al*. described a case where one twin developed GD while the other remained euthyroid, despite both having thyroid antibodies, highlighting the complex interaction between genetic predisposition and environmental factors like infections, stress, or maternal thyroid dysfunction. Del Giudice *et al*. (2018) found that monozygotic twins are at a higher risk for GD than dizygotic twins, emphasizing the role of genetics. However, environmental triggers may determine whether one twin develops the disease while the other stays asymptomatic.

Discussion
The presence of thyroid antibodies in the second twin, despite euthyroid status, suggests an increased future risk for GD. The published Literature supports the observation that elevated TRAb levels can precede clinical disease and may serve as a biomarker for early intervention. This case underscores the importance of monitoring for GD in siblings with positive thyroid antibodies, especially in the context of family history..
Conclusion
This case of monozygotic twins with divergent thyroid outcomes underscores the complex interplay of genetic and environmental factors in autoimmune thyroid disease. Early detection and monitoring of at-risk individuals are crucial.

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EP1494

JOINT703

The value of ultrasound features and elastography in the diagnosis of medullary thyroid carcinoma

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Introduction
Medullary thyroid carcinoma (MTC) is a rare thyroid malignancy with distinct histological characteristics, making its diagnosis via conventional ultrasound (US) challenging. Although malignancy risk stratification benefits from features like hypoechogenicity, irregular margins, and microcalcifications, their specificity for MTC remains under debate. This study evaluates the potential of combining elastographic stiffness measurements with US features to improve diagnostic accuracy in MTC.
Materials and Methods
This study analyzed 20 histopathologically confirmed MTC cases. Conventional US was used to assess nodule features indicative of malignancy, including hypoechogenicity, inhomogeneity, a taller-than-wide shape, irregular margins, microcalcifications, an interrupted thyroid capsule, and suspicious cervical lymphadenopathy. Shear Wave Elastography (SWE) (Aixplorer Mach 30) quantified nodule stiffness, with a mean elasticity index (EI) cut-off of 30 kPa used to suggest malignancy.
Results
The median patient age was 53.5 years, with a female predominance (70%, 14/20). The median nodule volume was 0.55 ml. All nodules were solid and hypoechoic, with 80% (16/20) showing inhomogeneous echotexture. Seven nodules had a taller-than-wide shape, and eight demonstrated irregular margins. No cases showed an interrupted capsule, while suspicious lymph nodes were detected in three cases on US. Microcalcifications were noted in 35% (7/20) of nodules, and 60% (12/20) were classified as high-risk according to TIRADS. SWE revealed increased stiffness in 75% (15/20) of nodules. The median EI was 35.5 kPa, with a maximum of 58.8 kPa. Coexisting autoimmune thyroiditis was present in 40% (8/20) of patients.
Conclusions
Integrating elastographic stiffness measurements with conventional US features enhances the diagnostic precision for MTC. SWE, in particular, serves as a reliable, non-invasive adjunct in differentiating malignant from benign thyroid nodules, emphasizing its clinical utility in routine practice.

Keywords
medullary thyroid carcinoma, ultrasound, elastography, shear wave elastography, diagnostic imaging.

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EP1495

JOINT733

The quest for reliable biomarkers: circulating free DNA in thyroid cancer

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Introduction
Thyroid cancer (TC) is the most common endocrine malignancy. The overall 5-year survival is in excess of 85%, especially in well-differentiated papillary type. Despite the very good prognosis, 20% of patients would have recurrence. Currently, surveillance consists of serial thyroglobulin, calcitonin and CEA, imaging and biopsies. All of which have limitations from poor sensitivity to risk of malignancy and invasiveness. Circulating Cell-free DNA (cfDNA) is a liquid biopsy that detects circulating DNA fragments in plasma. It is simple, non-invasive and has shown promising results in other cancers, such as breast and colon.
Aim and Objectives
We hypothesise that cfDNA can be used as a surveillance tool in TC, by plotting serial cfDNA levels against the clinical course of TC.
Methods
Eighty-two plasma samples were collected from 23 patients during follow up at different stages of TC (pre-op, post-op, post RI/chemo, remission, stable disease, residual disease, progression/mets). cfDNA was extracted using QIAamp® circulating NA kit (Qiagen). Total cfDNA and fragment length distribution was determined using 4200 TapeStation (Agilent Technologies).
Results
Participants characteristics are summarised in table 1. The lowest cfDNA concentration was 87ng/ml and the highest was 1430ng/ml. The mean value of cfDNA in each stage of the disease is shown in tablet 2. Papillary TC produced mean cfDNA concentration of 276.4ng/ml, compared to in 230.4ng/ml Follicular, 232.2ng/ml in Medulary and 298.2ng/ml in Anaplastic type. Interestingly, the highest cfDNA concentration was extracted from post-op plasma sample and the 2nd highest was from plasma sample taken during remission.
Discussion
Our results showed that cfDNA levels did not track disease activity although cfDNA was detected in patients with anaplastic and poorly-differentiated TC. The role of cfDNA in non-aggressive tumours without metastases is less clear and larger-scale studies are required to examine cfDNA role in surveillance of TC.

Table 1: Participants and tumour characteristics *TC: Thyroid Cancer.*

Gender	
Male	14
Female	9
Age at recruitment	*Average in years*
Male	55
Female	54
TC type	
Papillary TC	12
Follicular TC	5
Medullary TC	3
Anaplastic TC	3
Metastases at recruitment (Local and distant)	
Yes	13
No	*10*

Table 2: Average cfDNA concentration in various stages of TC.

Disease Stage	Number of cfDNA Samples	Average Concentration(ng/ml)
Pre-op	8	204.3
Post-op	16	256.3
Post RI/Chemo	14	203.5
Remission	17	286.7
Residual disease	8	251.3
Stable known disease	4	231.25
Progression/Mets	15	300.4

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EP1496

JOINT204

Autoimmune thyrogastric syndrome: clinical features, diagnosis, and management

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Introduction
Autoimmune thyrogastric syndrome is a rare condition characterized by the co-occurrence of autoimmune thyroid disease and gastric disorders, often associated with autoimmune gastritis. The syndrome can lead to both thyroid dysfunction and digestive symptoms, presenting diagnostic challenges due to the overlap of clinical manifestations. The aim of this study is to explore the clinical features, diagnostic approaches, and outcomes of patients diagnosed with autoimmune thyrogastric syndrome.
Methods
We conducted a retrospective analysis of patients diagnosed with autoimmune thyrogastric syndrome at our institution. Clinical data, including thyroid function tests, gastric biopsy results, and serological markers (such as anti-thyroid antibodies and anti-intrinsic factor antibodies), were collected. Additionally, we assessed patients' clinical outcomes following treatment with thyroid hormone replacement therapy and vitamin B12 injections. Gastroscopy was performed to assess the presence of autoimmune gastritis and other gastric abnormalities.
Results
A total of 12 patients (9 women, 3 men) were included in the study. The mean age at diagnosis was 48.5 years (range: 35-70 years). Of these patients, 10 had autoimmune hypothyroidism, 2 had hyperthyroidism, and 9 were diagnosed with autoimmune gastritis. Positive anti-thyroid peroxidase antibodies were found in 10 patients, and anti-intrinsic factor antibodies were present in 7 patients. Gastroscopy revealed signs of atrophic gastritis in 8 cases, with villous atrophy observed in 4 cases. After treatment with thyroid hormone replacement and vitamin B12 supplementation, 8 patients showed significant improvement in both thyroid function and gastrointestinal symptoms, while 3 patients had partial improvement. One patient did not show any significant clinical response.
Conclusion
Autoimmune thyrogastric syndrome is an uncommon but important condition that involves both thyroid and gastric autoimmune dysfunction. Early recognition and appropriate treatment, including thyroid hormone replacement and vitamin B12 supplementation, are essential for managing symptoms and improving patient outcomes. Clinicians should consider the possibility of this syndrome in patients presenting with symptoms of both thyroid and gastric disorders, particularly when autoimmune gastritis is suspected. Further studies are needed to better understand the pathophysiology and optimal management strategies for this syndrome.

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EP1497

JOINT2726

Dozens of doubts: a series of atypical presentations of medullary thyroid carcinoma running title: atypical presentations of medullary thyroid carcinoma

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Medullary thyroid carcinoma (MTC), originating from parafollicular C cells, accounts for 5- 10% of thyroid malignancies but is responsible for 15% of thyroid cancer-related mortality. This case series reviews 12 atypical presentations of MTC, highlighting significant diagnostic and therapeutic challenges. About 80% of MTC cases are sporadic, while 20% are hereditary, often linked to multiple endocrine neoplasia (MEN) syndromes. The predominant clinical manifestations include neck swelling, diarrhoea, and metastatic symptoms. In our cohort of 80 MTC patients, we identified 5 with considerable diagnostic ambiguity and with management complexities due to therapy-related complications. Notably, we observed cases with coexisting conditions such as chondrosarcoma, concurrent carcinoma prostrate, and ectopic Cushing's syndrome, complicating the clinical picture. We also had one female subject who have presented at the age of 16 years with negative RET mutation. One patient demonstrated a rare association with Marfanoid habitus linked to a RET mutation. One of them presented with metachronous VHL spectrum (Pheochromocytoma, pancreatic cysts and clear cell subtype of renal cell carcinoma) disease with MTC. one each presented with bowel perforation in an area uninvolved by metastatic process attributed to Lenvatinib treatment and glomerulonephritis due to tyrosine kinase inhibitor. This series underscores the necessity for comprehensive evaluation and individualized management strategies in MTC cases. Cases and figures will be elaborated during presentation. Given the potential for diverse clinical presentations and complications, our cases highlight the importance of awareness among healthcare providers regarding the varied manifestations of MTC, which can obscure diagnosis and complicate treatment.

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JOINT1873

Low risk of malignancy in thyroid nodules at our centre

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Objectives
To evaluate the results of cytology tests performed at our centre, correlate them with ultrasound characteristics and, in cases with surgical indication based on cytology results (Bethesda IV-VI), compare them with final pathological findings.
Patients and Methods
The EU-TIRADS classification was used for ultrasound characteristics, and the Bethesda system was used for cytology results. We analysed the results of 1,236 valid cytology samples recorded in our database from 20 June 2019 to 24 May 2024. Of the 93 nodules classified as Bethesda IV-VI, pathological findings were reviewed for the 87 that underwent surgery.
Results
The distribution of Bethesda categories was as follows: 938 nodules (75.9%) were Bethesda II, 202 (16.3%) Bethesda III, 26 (2.1%) Bethesda IV, 37 (3%) Bethesda V, and 33 (2.7%) Bethesda VI. Among EU-TIRADS 3 nodules, 19 out of 666 (2.9%) were Bethesda IV-VI; among EU-TIRADS 4, 36 out of 576 (6.3%); and among EU-TIRADS 5, 38 out of 257 (14.8%). Malignancy was confirmed in 62 out of 87 (71.3%) surgically treated cases: 5 out of 23 (21.7%) Bethesda IV nodules were malignant, 28 out of 36 (77.8%) Bethesda V nodules, and 32 out of 32 (100%) Bethesda VI nodules. For EU-TIRADS 3, 666 cytology tests were performed, with 5 (0.75%) confirmed malignancies; for EU-TIRADS 4, 576 tests with 25 (4.3%) malignancies; and for EU-TIRADS 5, 36 out of 257 (14%) malignancies.
Conclusions
The results indicate lower-than-expected rates of suspicious cytology and confirmed malignancy. Given the low malignancy rates across all ultrasound risk categories, we believe this may reflect a lower risk of malignancy in our population. The findings also support less aggressive surgical approaches or follow-up for nodules with Bethesda IV cytology in our patients.

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EP1499

JOINT481

Peculiarities of diagnostic gluten intolerance in ukrainian patients with autoimmune thyroiditis

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The prevalence of celiac disease (CD) in patients with chronic autoimmune thyroiditis (AIT) is estimated to be between 2 and 7.8%.
The aim of the study is to determining the frequency of combined autoimmune pathology - AIT and CD, including gluten intolerance without CD in Ukrainian patients.
Materials and methods
173 patients (three age groups: I – 5-20, II - 21-45, III – 46-60 yrs) with AIT and anti-thyroid peroxidase (ATPO) blood level exceeding 500 μIU/ml were examined: $n = 35$ M/138 F. Thyroid status was assessed using TSH and fT4 levels. Ultrasound diagnostics were also used to visualize the thyroid gland. Statistical processing of the results was performed using Package for Social Sciences v.16.0 (SPSS Inc, Chicago, Il, USA).
Results and discussion
It was found that 32.4% ($n = 56$) patients of all age had a high titer of anti-tissue transglutaminase antibody IgG (tTG) or anti-gliadin antibody IgG (AB AGA). In the I group a positive titer tTG IgG was in 14.3%, AGA IgG in 17.9%, in the II group – in 10.5% and 27.6%, respectively; in the III group – in 5.8% and 23.2%, respectively. Simultaneously positive titer of tTG and AGA IgG and IgA was only in 4 patients (2.3%), which in the presence of pronounced activity of antithyroid immunity, moderate hypothyroidism, as well as erased gastrointestinal symptoms and other nonspecific extraintestinal clinical signs, allows with a high degree of probability to establish the diagnosis of "CD" in these patients. In patients with only one elevated indicator - AGA IgG, it is possible to diagnose "Gluten intolerance without CD". Given the low frequency (2.9%) of high titer tTG IgA, the use of these indicators as a screening examination of patients with AIT is not advisable. Analysis of the dependence of the level of AGA IgG on the activity of thyroid autoimmunity revealed a positive correlation ($r = 0.83$, $P = 0.01$) with the level of ATPO, i.e., with high levels of ATPO, the frequency and severity of the immune response to the pathological effects of gluten increases.
Key words
autoimmune thyroiditis, celiac disease.
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EP1500

JOINT3624
Unusual presentation of hypothyroidism: pericardial effusion is not always due to cardiac cause
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Background
Pleural and pericardial effusion is a rare complication of severe hypothyroidism in children but can be present in 10 to 30 % of adults. Most pediatric cases have been in children with Down syndrome, Pericardial effusion in hypothyroidism is due to the increased capillary permeability, albumin distribution volume and reduced lymph drainage in pericardial cavity. Its presence in mild cases of hypothyroidism is uncommon although it can be seen in severe, long-standing hypothyroidism. The management of pericardial effusions is with thyroid replacement with or without an intervention to drain the fluid. Several studies have shown successful management of hypothyroid-induced pericardial effusion with echocardiographic tamponade physiology, but not clinical cardiac tamponade, to be treated effectively with levothyroxine alone.
Case presentation
A 12-year-old Down syndrome female, presented to our ER with complaints of dyspnea. The condition started one week before admission with orthopnea, the child started to sleep only on sitting 45 degrees position + progressively increasing dyspnea for 5 days at start on effort then one day before admission she developed dyspnea at rest. She is a known case of Down Syndrome karyotyping + echo showing VSD 8 mm at one month old with no follow up Her Examination: HR 100 bpm – BP 100/70 mmHg, RR 30 cycles/min Temp. 36.4°c, her anthropometric measurements: Height 150 cm (-0.68 SD), Weight 68 kg(+ 1.9 SD), BMI 30.2 (98th percentile), cardiac examination: Heart distant heart sound with murmur at mitral area, general examination: facial features of down syndrome, bilateral Lower limbs edema up to sacrum, Neck showed goiter with resonant sternum. She withdrew routine labs + TSH and freeT4 for screening of hypothyroidism. Till results revealed she did echocardiogram showed VSD 10 mm and moderate pericardial effusion with clear fluid.
TSH more than 1500 microIU/ml**, Free T4 0.6** ng/dl **The child received l troxin 50 mic/day + lasix IV + ACE Inhibitor**
Follow up after one week echocardiogram showed mild pericardial effusion + VSD
Follow up after 2 weeks: TSH 30 free T4 0.98, no pericardial effusion.
Conclusions
Hypothyroidism is one of the uncommon etiology causing pericardial effusion. Even though it occurs in long-standing myxedema, it can occur in mild cases too, which when unnoticed can be fatal. Since with early cardiac assessment and adequate thyroid replacement therapy, the pericardial effusion due to hypothyroidism can be reversible, it needs to be identified and managed early.
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EP1501

JOINT2759 Assessing sensitivity of thyroglobulin measurement in neck node fine needle washout for diagnosis of thyroid cancer metastasis: use of node dissection and 131I scintigraphy as reference standards
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Background
Detecting cervical node metastasis prior to surgery in patients with differentiated thyroid cancer is essential for guiding the extent of thyroid surgery and neck dissection. Guidelines recommend performing thyroglobulin measurement in fine needle washout to improve the sensitivity of ultrasound (US)-guided fine needle cytology for the diagnosis of neck node metastasis. The choice of 1 ng/ml of thyroglobulin as cut-off value for diagnosing metastasis remains controversial. Confirmation of the metastatic disease by node dissection is not feasible in many cases, thus leading to a risk of misclassifying the patients' status. In those cases, US node features are used to evidence patients' status at later stage. However, cervical lymph node metastases usually remain stable for years after thyroidectomy, and US node features suggestive of malignancy often lack sensitivity.
Objective
To assess sensitivity of thyroglobulin measurement in fine needle washout for the diagnosis of thyroid cancer node metastasis.
Methods
For this retrospective monocentric study, data on eligible patients attending our onco-endocrinology from 2011 to 2024 were collected using electronic records. Inclusion criteria were: completion of presurgical fine needle puncture of suspicious lymph nodes; subsequent thyroglobulin measurement in the needle washout; subsequent thyroidectomy; eligibility for 131I therapy after thyroidectomy. Diagnostic accuracy was assessed using a composite reference standard: histopathological lymph node examination if the node was dissected, or presence of 131I uptake on postablation scintigraphy if the node was not.
Results
A total of 537 patients were screened for eligibility. For 63 patients, metastatic status of punctured lymph node was confirmed by neck node dissection report or by 131I scintigraphy. For 14 patients, the punctured lymph node was free of metastasis. Area under the ROC curve (AUC) was 0.91 (95% confidence interval 0.85 - 0.98). Sensitivity of thyroglobulin measurement in needle washout was 87 % (95% confidence interval 76.9 - 93.4) for the threshold of 1 ng/ml.
Conclusions
Thyroglobulin measurement in fine needle washout efficiently detects neck node metastasis of differentiated thyroid cancer. We use 131I scintigraphy combined with histopathological records as a reference standard for assessing diagnostic accuracy. More studies estimating sensitivity of this diagnostic test are needed to help clinicians in the therapeutic choice. Local registration: DEC24-307
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EP1502

JOINT2614

Thyroid disease related to the SARS-CoV-2 virus

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The SARS-CoV-2 virus affects the respiratory system and causes pneumonia. However, it also affects other organ systems. As the COVID-19 pandemic swept over humanity it became apparent that it may affect the thyroid gland, as various cases of subacute thyroiditis started to emerge in relationship with the COVID-19 infection. The aim was to describe cases of thyroid disease observed and followed-up over a period of 4 years in a tertiary care facility.

Methods

Over a period of 4 years 6 cases of thyroid disease were diagnosed and follow-up in a tertiary care facility. These 2 cases of subacute thyroiditis, in 2 female patients, aged 45 and 48 years, respectively, 30 and 15 days after a mild COVID-19 infection, 1 case of subacute thyroiditis after the mRNA vaccine in a male patient aged 51 years, 1 case of Graves' disease after a COVID-19 infection in a female patient aged 33, 1 case of disease aggravation after a COVID-19 infection in a previously quiescent case of Graves' disease in a female patient aged 48 years and 1 case of hypothyroidism due to Hashimoto thyroiditis 6 weeks after a COVID-19 infection in a female patient aged 56 years.

Results

The patients who developed subacute thyroiditis after a SARS-CoV-2 infection were dealt with by prednisolone administration. However, in one of the patients the disease recurred, and steroids were administered. After remission the patient developed subclinical hypothyroidism and thyroxine was administered. Two years later both patients need 50 μg thyroxine daily to remain euthyroid. The patient who developed subacute thyroiditis following vaccination against COVID-19 received prednisolone and following tapering he is euthyroid. In the patient who developed Graves' disease and also developed thyroid ophthalmopathy, antithyroid medication was administered followed by subtotal thyroidectomy and ophthalmopathy is stable. The patient who had recurrence of Graves' disease is now stable on treatment with unimazole and thyroxine on a block and replace regimen. The patient who developed hypothyroidism is stable thyroxine. It appears that the SARS-CoV-2 virus affects the thyroid gland. It is related to the development of subacute thyroiditis, Hashimoto's thyroiditis, painless thyroiditis and Graves' disease as well as exacerbation of previously quiescent Graves' disease. It appears that thyroid cells express the ACE2 enzyme which acts as a receptor for the virus. However, as by now almost the entire population has been infected by COVID-19, thyroid disease in the context of the SARS-CoV-2 infection is relatively uncommon.

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EP1503

JOINT3805

Post-alemtuzumab thyroid autoimmunity remitting after commencement of ocrelizumab in patients with multiple sclerosis

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Objective

Immune reconstitution therapies (IRT), which include antibody-based cell-depleting therapies targeting CD52+ (alemtuzumab) or CD20+ (rituximab, ocrelizumab) leukocytes, are approved for the treatment of multiple sclerosis. Autoimmune thyroid disease (AITD) is the most common adverse effect of alemtuzumab treatment; Graves' disease (GD) being the most prevalent manifestation followed by Hashimoto Thyroiditis (HT).

Patients

We present nine clinical cases of secondary AITD induced by alemtuzumab (five cases of GD and four cases of HT) in which remission of thyroid autoimmunity was achieved after the initiation of ocrelizumab and in one case after commencement of rituximab and ocrelizumab subsequently.

Results

The five patients who developed GD post-alemtuzumab were initially treated with antithyroid drugs (ATD) and continued on "block and replace" treatment; two of them developed a fluctuating course between hyperthyroidism and hypothyroidism. Since the start of ocrelizumab all five patients have experienced an improvement in the course of GD with continuous decrease of thyroid-stimulating immunoglobulin (TSI) levels. In three patients GD resolved and ATD were stopped. The other two patients are currently under medical treatment in a dose reducing regimen. Similarly, thyroid autoimmunity with positive autoantibodies [anti-thyroglobulin (anti-Tg) and anti-thyroperoxidase (anti-TPO) antibodies] in all four patients who developed HT is under remission.

Conclusion

These cases highlight the possibility of remission of post alemtuzumab thyroid autoimmunity, especially GD, after ocrelizumab treatment with avoidance of further medical or surgical treatment.

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EP1504

JOINT3139

T cell gene expression differences between ATA+ infertile euthyroid and ATA+ hypothyroid patients

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Autoimmune thyroiditis – background

Hashimoto's thyroiditis is marked by the presence of autoantibodies (ATA) targeting thyroid peroxidase (anti-TPO) or thyroglobulin (anti-Tg), along with immune cell infiltration into the thyroid gland, resulting in chronic inflammation. Together with the impairment of central and peripheral tolerance, autoreactive $CD4^+$ and cytotoxic T cells play a crucial role in the pathogenesis and maintenance of the disease. Chronic inflammation ultimately leads to diminished thyroid function and an increase in thyroid-stimulating hormone (TSH) levels. ATA positivity does not necessarily result in hypothyroidism; yet, the clinically insignificant disease is a substantial risk factor for fertility and pregnancy complications even with a functionally intact thyroid gland and normal TSH levels.

How infertility is linked to autoimmune thyroiditis – hypotheses

Systemic immune disfunction affecting reproductive organs and maternal-fetal tolerance associated with ATAs present at reproductive sites. Relative insufficiency of the thyroid gland during pregnancy characterised by elevated TSH levels, as the thyroid gland fails to meet increasing hormonal demands.

Comparisons and results

We analyzed the gene expression patterns of total peripheral T cells (polyA, bulk mRNA) from ATA+ infertile euthyroid, ATA+ hypothyroid patients, and age-matched healthy controls (three individuals in each group). In the hypothyroid group, NF-κB, p53, TNF, cell proliferation, IL-17 signaling and migratory pathways were upregulated compared to both ATA+ euthyroid and healthy individuals, and members of the CXC chemokine subfamily exhibited elevated expression alongside inflammatory cytokines, such as IL-1α, IL-1β. Euthyroid ATA+ individuals showed no relevant alterations in their T cell gene expression profile relative to the healthy group, suggesting that discernible functional differences at the level of T cells emerge only when the thyroid gland is compromised, and fertility issues most likely have an underlying cause that is not necessarily present at T cell gene expression levels. Furthermore, while the impacted pathways were largely analogous in comparison of the hypothyroid vs. healthy, as well as between the hypothyroid vs. euthyroid ATA+ groups, minor differences were noticeable, including the HIF1 signaling pathway, indicating a transition to anaerobic metabolism only subsequent to thyroid dysfunction.

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EP1505

JOINT2320

Genetic testing in medulary thyroid cancer in a tertiary center in Romania

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This is a single-center study of 106 subjects who were tested for germline RET mutations at our center. Among those, 97 were diagnosed with MTC and 9 had genetically positive family history and underwent screening. A total of 74 patients underwent complete RET gene testing on exons 5, 8, 10, 11, 13, 14, 15, 16 and on the rest of 32 patients targeted analysis was performed. We identified a germline RET variant in 40 of 106 (37.7%) patients from 9 families; 8/40 (20%) were initially considered sporadic cases based on the negative family history for MTC or MEN2 related pathologies and from the 32 patients with positive family history, 9 were index cases and 23 relatives. Considering the identified mutations, when classified in ATA risk categories, 20/40 (50%) patients harboured a "high risk" (H) level mutation and 20/40 a "moderate risk" (MOD) level mutation. ATA H risk RET mutations: 20/20 (100%) with C634Trp/Phe/Arg mutations; 15/20 (75%) patients underwent thyroid surgery and were dignosed with MTC. Median (min-max) age at surgery was 37.4 (21-56) years. ATA MOD risk RET mutations: 8/20 (40%) patients with C618Arg mutation, 8/20 (40%) patients with C620Arg mutation and 4/20 (20%) with V804Met mutation; 16/20 (80%) patients had total tiroidectomy with median age (min-max) at surgery of 36 (10-68) years. As for genotype-phenotype correlation in MEN2 syndrome, 10/20 (50%) patients with a codon 634 mutation and 4/8 (50%) with a codon 618 mutation presented PHEO; in our cohort, no patient with codon 620 and 804 presented PHEO until the end of follow-up. Of all PHEO patients, 6/14 (42.8%) had bilateral disease with the median age of 9.6 years between left and right disease. Primary hyperparathyroidism (HPTH) was diagnosed in 6/20 patients, all with mutation in codon 634 and the median age was 43 years. Out of 66 cases tested negative for germline RET mutation, ten cases with advanced, metastatic MTC underwent RET somatic testing using fresh or formalin-fixed, paraffin-embedded primary tumor/metastasis tissue. From them, 8/10 (80%) patients tested positive for Met918Thr mutation and two cases harbored Cys634Arg mutation. Mutational screening is mandatory in all patients with extended MTC, being crucial in selecting targeted treatment with TKI inhibitors and predicting responsiveness to therapy.

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EP1506

JOINT2182

10 years of experience in providing surgical care to children with nodular and diffuse toxic goiter

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Aim
To study the structure of thyroid diseases in children who required surgical treatment, analysis of their gender and age distribution, features of the preoperative, intra- and postoperative course in case of thyroid nodules (TN) and diffuse toxic goiter (DTG), to determine the frequency of early and late complications, disease recurrences and their further treatment.
Materials and methods
This retrospective cohort study included 456 children (under 18 years of age) who underwent thyroidectomy at the Center between 2013-2022. According to the results of clinical and laboratory data and final pathohistological examination, all patients were divided into 3 groups: thyroid cancer ($n = 241$), TN ($n = 151$) and DTG ($n = 64$). In the preoperative period, the duration of the disease, patients' age, sex distribution, thyroid function, the results of instrumental examinations (thyroid ultrasound, FNAB with cytological assessment according to Bethesda) were investigated in patients with TN and DTG. In patients available for further postoperative follow up, the postoperative thyroid function, frequency of early and late complications and further treatment were studied.
Results
Among all thyroid diseases that required surgical intervention, thyroid cancer (52.8%) and female gender (75%) prevailed. The mean age of the operated children was 14.4 ± 2.5 years. TN were significantly more frequent in pubertal age group ($P < 0.05$). The mean duration of the disease before surgery in case of TN was shorter than in DTG ($P < 0.001$). Thyroidectomy was most often done in DTG, and hemithyroidectomy (HT) and/or HT+ lymphadenectomy (LD) in case of TN. In 21.3% of patients with TN after HT/HT+LD, euthyroidism was achieved. In patients with DTG in the late postoperative period, persistent hypoparathyroidism was the only and most frequent complication ($n = 2$, 12.5%). In contrast, in TN in the late postoperative period, 7 patients (10%) were diagnosed with a relapse of the disease, which occurred more often in younger children (13.0 [13.0; 14.0] years) compared to the group without relapse ($P = 0.01$). Treatment of relapse included follow-up in the majority of patients with TN (71.4%).
Conclusions
Thyroid cancer predominated in the structure of thyroid diseases requiring surgical intervention. Persistent hypoparathyroidism was the only complication in the treatment of patients with DTG. Considering the preservation of euthyroidism in 21.3% of patients with TN after HT/HT+LD, broader use of organ-preserving surgery should be considered, with further evaluation of postoperative hormone replacement therapy.

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EP1507

JOINT1727

Iratherapy and graves' disease: about 20 cases followed

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Introduction
Graves'disease is one of the usual indications of iratherapy in the Nuclear Medicine service whose main population followed to our service is young (20-40 years), addressed after failure of medical treatment (Carbimazol).
Objective
Highlight the effectiveness of Iratherapy as the most used therapeutic weapon in the young population.
Materiels and Methods
The files have been collected since 2021 and the information is transmitted on a sheet with the following criteria: Age/Number of cures/Recurrence/result (Hypothyroidism or euthyroidism) then statistical analysis of the sample.
Results
The majority of patients treated for Graves' disease by iratherapy in our department, had a remission of their pathology with hypothyroidism as major side effect, rarely an euthyroidism. Recurrence after the first treatment is $<10\%$, which required the administration of 2 to 3 additional treatments.
Discussion
The effectiveness of irathatherapy is no longer to be demonstrated in the literature and in current practice, and the results in our patients treated at our service confirm this trend. Resistance to iratherapy; requiring a 2nd, 3rd cure; is related to an increased volume of the thyroid gland at the time of administration of iodine 131; Patients with failed irathérapie are referred for surgery.
Conclusion
Iratherapy is an effective therapeutic weapon for Graves' disease, to be preferred among the young and professionally active population with a very low recurrence rate.

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EP1508

JOINT401

Hashimoto's thyroiditis or graves' disease? a case of thyroid autoimmune disease with oscillating thyroid function

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Introduction
Thyroid autoimmune diseases are characterized by a wide spectrum of clinical manifestations ranging from hypothyroidism to hyperthyroidism. This case highlights the diagnostic and therapeutic challenges of managing a patient with suspected overlapping autoimmune thyroid conditions.
Case Presentation
A 45-year-old woman was initially diagnosed with hyperthyroidism in 2008. Laboratory findings included TSH 0.004 μIU/ml (reference range: 0.35–4.94) and positive thyroid peroxidase antibodies (anti-TPO >600 U/ml). Thyroid

scintigraphy revealed a warm nodule in a normocaptating gland. Tapazole was prescribed but not initiated. She lost follow-up and returned one year later with hypothyroidism (TSH 5.208 µIU/ml). Levothyroxine therapy was initiated and titrated to 50 mg/day, achieving euthyroid status. During pregnancy, the levothyroxine dose was increased to 88 mg/day. The patient remained stable until 2019, when progressive thyroid function normalization allowed dose reduction, culminating in levothyroxine discontinuation in January 2020. Three months later, without levothyroxine, she developed hyperthyroidism symptoms, including tachycardia and insomnia. Laboratory tests showed TSH <0.02 µIU/ml, elevated free T4 (1.52 ng/dl), anti-TPO 692.59 U/ml, and TSH receptor antibodies (TRAb) 8.99 U/l (reference <0.55). Thyroid ultrasound revealed gland enlargement (volume: 11.8 cm^3) with an increased Doppler flow. An antithyroid medication was not initiated, and six months later, thyroid function spontaneously normalized (TSH 1.01 µIU/ml, free T4 0.75 ng/dl). The patient remains asymptomatic under regular follow-up.

Discussion

This case demonstrates the diagnostic complexity of thyroid autoimmune diseases, presenting features of both Hashimoto's thyroiditis and Graves' disease. The oscillation between hypothyroidism and hyperthyroidism, presence of positive anti-TPO, anti-TG, and TRAb, and the spontaneous normalization of thyroid function suggest a potential overlap syndrome. Factors contributing to disease variability, including immune modulation and external factors, need further investigation.

Conclusion

The clinical features underscores the importance of continuous follow-up and individualized management in patients with autoimmune thyroid disease. Oscillating thyroid function challenges the diagnosis and requires a multidisciplinary approach to optimize patient outcomes and prevent complications.

Keywords

Thyroid autoimmune disease, Hashimoto's thyroiditis, Graves' disease, hypothyroidism, hyperthyroidism, oscillating thyroid function

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EP1509

JOINT3409

Myxedema coma triggered by a urinary tract infection: a case report

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Introduction

Myxedema coma (MC) is a rare but severe endocrine emergency caused by a significant depletion of thyroid hormones, which can be triggered by various factors, including infections (1,2). Early diagnosis and prompt management are crucial for improving prognosis and reducing mortality (3). We report a case of MC precipitated by a severe urinary tract infection.

Case Report

A 78-year-old female with hypertension and chronic kidney failure (CKD) was admitted for septic shock of urinary origin. Upon admission, she presented with coma, hypothermia, bradycardia, hypoventilation, and generalized myxedema. The electrocardiogram showed right bundle branch block with diffuse low voltage. Laboratory tests revealed severe hypothyroidism (TSH $>$ 200 mU/l, FT4 $<$ 0.42 pmol/l, FT3 1.4 pg/ml), cortisol level of 155 ng/ml, and acute decompensation of CKD. Transthoracic echocardiography showed a mildly hypertrophied left ventricle with good kinetics. Management included continuous cardiorespiratory, hemodynamic, and thermal monitoring, along with antibiotic therapy, urgent hemodialysis, and thyroid hormone replacement with L-thyroxine (LT4) via nasogastric tube, starting with a loading dose followed by maintenance. Hydrocortisone hemisuccinate was also administered. The patient initially showed improvement in heart rate but died 2 days later due to multivisceral failure.

Discussion & Conclusion

MC is an acute decompensation of prolonged hypothyroidism, potentially fatal, characterized by cognitive impairment, hypothermia, bradycardia, hypoglycemia, and renal and respiratory insufficiency (1,4). It can be triggered by various factors such as cold exposure, infections, trauma, or anesthesia (1). Management requires continuous monitoring of vital signs and urgent administration of L-T4 (200 to 400 mg IV). Hydrocortisone is also administered to prevent adrenal crisis (1). T4-T3 combination therapy may be considered, as the conversion of FT4 to FT3 can be impaired in severely decompensated patients or those on steroid therapy, although this approach remains controversial (5).

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EP1510

JOINT3701

Toxic thyroid nodule and anterior pituitary insufficiency: a rare association

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Introduction

The association between a toxic thyroid nodule and anterior pituitary insufficiency is rare and presents a diagnostic challenge. We report a case illustrating this unusual clinical situation, characterized by thyrotropic insufficiency with suppressed TSH but low FT4, associated with corticotropic insufficiency due to granulomatous thickening of the pituitary stalk.

Case Report

A 75-year-old female with no significant medical history presented with symptoms of hyperthyroidism (palpitations, weight loss) for four years. Initial cervical ultrasound revealed a left sub-total lobar thyroid nodule measuring 25×9 mm (EU-TIRADS 3), with a benign cytology result. She was started on carbimazole (10 mg/day) and beta-blockers. Thyroid scintigraphy confirmed a left quasi-total lobar toxic nodule. However, thyroid function tests showed a suppressed TSH (0.24 µUI/ml) with paradoxically low FT4 (0.74 ng/dl), suggesting thyrotropic insufficiency. Pituitary MRI revealed thickening of the pituitary stalk of granulomatous origin. An anterior pituitary function assessment showed low 8 AM cortisol levels (98 ng/ml), requiring hydrocortisone replacement therapy (10 mg/day).

Discussion

The association between a toxic thyroid nodule and thyrotropic insufficiency is uncommon and poorly documented in the literature. Typically, a toxic nodule leads to primary hyperthyroidism, characterized by suppressed TSH with elevated FT4 and/or FT3. In this case, the hormonal discrepancy (suppressed TSH with low FT4) suggested thyrotropic insufficiency, confirming hypothalamic-pituitary involvement. Thyrotropic insufficiency is a rare condition (prevalence: 1/16,000 to 1/80,000). It can result from infiltrative pituitary lesions, such as granulomatous hypophysitis. Granulomatous hypophysitis, particularly in sarcoidosis or tuberculosis, can lead to multiple anterior pituitary deficiencies, notably corticotropic and thyrotropic insufficiency. In our case, the thickening of the pituitary stalk suggests a granulomatous disease, although initial investigations were negative. Further diagnostic workup, including salivary gland biopsy and angiotensin-converting enzyme dosage, is ongoing to assess for sarcoidosis. Regarding management, appropriate hormonal replacement therapy is crucial. The treatment of the toxic nodule relies on radioiodine therapy, which is particularly suitable for elderly patients refusing surgery.

Conclusion

This case highlights a rare association between a toxic thyroid nodule and thyrotropic insufficiency, altering the typical biochemical profile of a toxic nodule. It underscores the importance of investigating pituitary involvement in cases of hormonal discordance and considering a granulomatous etiology when structural abnormalities of the pituitary stalk are present.

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EP1511

JOINT4

Challenges in the diagnosis of thymic hyperplasia-associated myasthenia gravis in the setting of coexisting Graves' disease

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Background
Recognizing thymic hyperplasia secondary to Graves' disease (GD) is important for avoiding unnecessary investigations and surgeries. However, other causes of thymic hyperplasia or *de novo* thymic abnormalities after euthyroidism especially the presence of massive thymic hyperplasia should be investigated. The clinical features of myasthenia gravis (MG) and thyroid eye disease (TED) may be similar and thymic hyperplasia may occur in both conditions. This could be a diagnostic dilemma as to whether a conservative approach or investigations should be pursued. Thymectomy in patients with nonthymomatous MG could improve clinical outcomes and reduce the need for immunosuppressive therapy. Herein, we report an interesting case of the coexistence of severe TED and MG with the presence of thymic hyperplasia.
Clinical case
A 40-year-old Thai woman diagnosed with severe TED requiring orbital decompression and intravenous methylprednisolone presented with left eye ptosis and chewing weakness for 1 month. She denied limb muscle weakness, hoarse voice, or difficulty breathing. Her previous history included hypothyroidism after thyroidectomy for GD 18 months earlier. At the initial diagnosis of GD, laboratory tests were notable for highly elevated serum thyrotropin receptor antibody at 25.5 IU/l and then gradually declined to 13.2 IU/l at 6 months after thyroidectomy (reference range is 0 to 1.75 IU/l). Anti-acetylcholine receptor antibody was positive confirming the diagnosis of MG. A chest computed tomography scan showed a $10\times9\times1.6$ cm thymic enlargement. No mediastinal widening on previous chest X-ray (CXR) at the time of thyroidectomy was found. Therefore, thymic hyperplasia-associated MG was suspected and the patient underwent video-assisted thoracoscopic thymectomy. The pathologic results revealed non-neoplastic thymic tissue with focal thymic epithelial hyperplasia. At 1 year later, her symptoms have much improved and she was prescribed only oral azathioprine 50 mg/day without prednisolone. Strabismus and eyelid surgeries had been performed after inactive TED.
Conclusion
Our case highlighted a diagnostic dilemma as to whether a thymectomy is necessary for thymic enlargement in the setting of coexisting GD and MG. Previous CXR and clinical course of hyperthyroidism are important to differentiate between thymic hyperplasia secondary to GD and thymic hyperplasia-associated MG. While thymic hyperplasia secondary to GD is typically benign and improves with the regular treatment of GD, thymic hyperplasia-associated MG might need further investigations and treatments.

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EP1512

JOINT2009

Pre-operative lugol's iodine treatment in the management of patients undergoing thyroidectomy for graves' disease: is there an impact?

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Introduction
Graves' disease is a predominantly female autoimmune disorder of the thyroid gland. It is characterized by a diffuse goiter and biological hyperthyroidism, often accompanied by exophthalmos. Although medical treatments exist for Graves' disease, surgical excision of the thyroid gland offers a definitive treatment. Preoperative preparation with Lugol's iodine is still controversial. The aim of our study is to highlight the benefits of preoperative treatment with Lugol's iodine in the management of patients undergoing thyroidectomy for Graves' disease.
Patients and methods
This is a retrospective study that collected records of patients hospitalized for surgical management of Graves' disease over an eleven-year period.
Results
Our series included 51 patients, 38 women (75%) and 13 men (25%) with a mean age of 39.41 years and extremes of 14 to 69 years. The goiter was multi-nodular in 23 patients (45%), homogeneous in 22 cases (43%) and nodular only in 12% of patients. Surgery was indicated in cases of resistance to medical treatment (84%), poor compliance (8%) and associated thyroid carcinoma (6%). Forty-nine patients (96.1%) underwent preoperative preparation with potassium iodide (Lugol's solution 2%) at a dose of 07-10 drops*3/day (over a period of 07 to 10 days). All our patients underwent total thyroidectomy. The operative difficulties were mainly the dissection of the recurrent nerves and the parathyroid glands made difficult by the hypervascularization of the gland and the bleeding during the procedure. Postoperative complications included transient hypocalcemia in 21 patients (41.17%), transient dysphonia in 3 patients (5.88%), and hematoma in 2 patients (3.92%).
Conclusion
Total thyroidectomy is the procedure of choice for the definitive cure of Graves' disease. Postoperative complications are frequent and not negligible, hence the need for preoperative medical preparation. Both the American Thyroid Association and the European Thyroid Association recommend the use of Lugol's solution in the preparation of patients undergoing surgery, but their recommendations are based on low-quality evidence.

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EP1513

JOINT2130

Autoimmune thyroid disease: a continuum oscillating between hypothyroidism and hyperthyroidism: a case report

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Introduction
Autoimmune thyroid disorders can present atypical evolutions making their management complex. We report the case of a young patient presenting an unusual alternation between phases of hyperthyroidism and hypothyroidism.
Observation
A 26-year-old patient presented with primary hypothyroidism in the 4th month of her pregnancy, treated with L-thyroxine. She consulted 6 months after giving birth for asthenia, palpitations, and tremors. The biological assessments showed a suppressed TSH and elevated FT4. Anti Thyroid peroxidase antibodies and Anti-TSH receptor (ATSHR) antibodies were positive. L-thyroxine was interrupted and treatment with thiamazole was started. Three years later, biological hypothyroidism was objectified leading to the discontinuation of thiamazole. The patient presented at 12 weeks of pregnancy. She was still in clinical and biological euthyroidism. ATSHR antibodies had returned negative. Six months after delivery, a thyroid assessment revealed the reappearance of hyperthyroidism. A thyroid scintigraphy was performed, showing normal and homogeneous thyroid uptake. The diagnosis of autoimmune thyroid disease with swing antibodies was retained and the decision was to put the patient on low-dose thiamazole each time she presented a phase of hyperthyroidism.
Discussion
The initial positivity of ATSHR antibodies points towards Graves' disease, but a normal scintigraphy does not support this diagnosis, nor does the evolution with oscillation between hyperthyroidism and hypothyroidism. This oscillation could be related to a dynamic evolution of autoimmunity, with fluctuations of ATSHR antibodies between stimulating and blocking forms. There is also evidence that Graves' disease and Hashimoto's thyroiditis may be different manifestations of a continuous spectrum of autoimmune thyroid diseases.

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EP1514

JOINT2507

Thyroid disorders in autoimmune polyendocrinopathy

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Objective
To evaluate the characteristics of autoimmune thyroid diseases (AITD) occurring within the context of autoimmune polyendocrinopathy (APE).
Patients and Methods
This was a retrospective study including 41 patients diagnosed with APE involving AITD, hospitalized in the Endocrinology Department of Hedi Chaker University Hospital, Sfax, between 2009 and 2019.
Results
The mean age at diagnosis was 32.6 ± 15.3 years, with a female predominance. Hashimoto's thyroiditis was identified in 33 cases, while Graves' disease was present in 8 cases. The most common association was with type 1 diabetes (68.3%), followed by Addison's disease (36.6%). Other associated autoimmune conditions included primary ovarian insufficiency, autoimmune hypophysitis, celiac disease, chronic mucocutaneous candidiasis, myasthenia gravis, vitiligo,

and hypoparathyroidism, each occurring in one case. AITD was classified within APE type 3 in 22 cases, APE type 2 in 16 cases, and APE type1 in one case. Additionally, chromosomal anomalies, specifically trisomy 21, were observed in two cases. The first clinical manifestation was type 1 diabetes in 48.8% of cases, AITD in 29.3%, and Addison's disease in 14.6%.
Conclusion
AITD is an organ-specific autoimmune disorder that can coexist with systemic autoimmune diseases, suggesting a shared immune mechanism. This expands the spectrum of multiple autoimmune syndromes, necessitating vigilant clinical and biological monitoring, particularly for thyroid function.

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EP1515

JOINT3471

Optimizing thyroid surgery: the critical role of intraoperative histological examination

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Background
In thyroid nodular pathology, intraoperative histological examination is a crucial diagnostic tool that helps guide surgical decision-making.
Objectives
To assess the accuracy and effectiveness of intraoperative histological examination in the management of thyroid nodules and to highlight its benefits and limitations as a real-time diagnostic tool during surgery.
Methods
This retrospective cross-sectional study analyzed 333 intraoperative histological examinations performed on thyroidectomy specimens at our ENT Department over a five-year period (January 2018 – December 2022).
Results
I this study the mean age of 47.45 years, with a strong female predominance (male-to-female ratio of 1:5.8). The most common reason for discovery was a palpable cervical mass (57.35%), while incidental detection via ultrasound accounted for 15.6%. Ultrasound findings revealed that multinodular goiters were more prevalent (61.6%) than solitary nodules (38.4%). Malignant tumors were diagnosed in 21.3% of cases, with the majority being papillary carcinoma (87.3%), followed by follicular carcinoma (9.8%), medullary carcinoma (1.4%), and anaplastic carcinoma (1.4%). Intraoperative examination identified 61 malignant cases, 259 benign cases, and 13 uncertain cases. When compared to the final histopathological examination across all histological types, intraoperative examination demonstrated a diagnostic accuracy of 93%, with a sensitivity of 85.9%, specificity of 100%, positive predictive value (PPV) of 100%, and negative predictive value (NPV) of 96%. The Youden index was 0.86. The sensitivity of intraoperative examination varied by histological type. It showed strong concordance with the final pathology report in 90.3% of papillary carcinomas and 100% of medullary and anaplastic carcinomas, but only 42.8% of follicular carcinoma cases. The rate of secondary surgical interventions following final histological examination was 3% (10 cases).
Conclusion
Intraoperative histological examination plays a pivotal role in the surgical management of thyroid nodules, offering rapid and precise diagnosis that optimizes surgical decision-making and minimizes the need for reoperations. Its high specificity and sensitivity enhance patient care by ensuring appropriate surgical intervention.

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EP1516

JOINT3600

Secondary hyperparathyroidism and papillary carcinoma of the thyroid: about a case

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Introduction
Secondary hyperparathyroidism (SHPT) and coexisting papillary thyroid carcinoma (PTC) have been reported in sporadic cases and studies are scarce. The mechanism linking these two pathologies remains unclear. As a minimally invasive approach to parathyroidectomy has replaced bilateral neck exploration, a thorough preoperative thyroid evaluation is necessary to identify concomitant papillary carcinoma. We aim to report a case associating secondary hyperparathyroidism and thyroid papillary carcinoma.
Case report
This is a case of a 36-year-old woman with chronic renal failure, not on haemodialysis for IgA nephropathy, who was referred for hyperparathyroidism with a parathyroid hormone level of 334 pg/l and a calcemia of 2.08 mmol/l. Neck ultrasound showed a right lobar thyroid nodule of 19*13*10 mm, EUTIRADS 5 grade, with no pathological parathyroid gland. This was supplemented by a parathyroid scintigraphy, which showed no evidence of a pathological parathyroid gland. Fine needle aspiration of the thyroid nodule was inconclusive. The patient underwent a right thyroid lobectomy. Intraoperative frozen section analysis revealedtwo foci of papillary thyroid carcinomameasuring 1.4 cm and 1.7 cm, necessitating completion thyroidectomy and right recurrent mediastinal dissection. A subtotal parathyroidectomywas also performed. The final histopathological examination confirmed the PTC in the right lobe of thyroid, without lymph node involvement and parathyroid hyperplasia. The patient was therefore referred to nuclear medicine department for additional treatment with radioactive iodine.
Discussion/Conclusion
The prevalence of thyroid papillary carcinoma is high in patients with secondary hyperparathyroidism, compared with thyroidpapillary carcinoma in the general population. Most thyroid papillary carcinomas with SHPT are occult thyroid carcinomas and present no significant difference in terms of tumor pathological features and prognostic staging. It is necessary for surgeons to perform more adequate preoperative examination and be more careful during surgery to avoid missing the coexistence of thyroidpapillary carcinoma in patients with secondary hyperparathyroidism. Disclosure of interest: none declared

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EP1517

JOINT3882

Association of graves' disease and differentiated thyroid cancer: a report of two cases

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Introduction
The presence of hyperthyroidism is no longer considered a protective factor against the development of thyroid cancer. The coexistence of differentiated thyroid cancer and Graves' disease(GD) is a well-documented but rare phenomenon, with reported prevalence rates ranging from 0.1% to 9.8% in the literature. We present two cases of female patients with hyperthyroidism secondary to GD who were subsequently diagnosed with differentiated thyroid cancer.
Case Reports
Case 1: A 49-year-old female patient with a two-year history of GD was managed with antithyroid drugs (ATD). She developed drug-induced cholestasis as a side effect of ATD therapy. Clinical examination revealed bilateral firm cervical lymphadenopathies. Cervical ultrasound demonstrated a nodular thyroid structure, with the largest nodules located in the upper right lobe(14 mm)and the mid-left lobe, classified as EU-TIRADS IV. Due to ATD intolerance and the presence of cervical lymphadenopathies, the patient underwent total thyroidectomy with bilateral mediastino-recurrent lymph node dissection (MRLD). Histopathological analysis identified three foci of papillary thyroid carcinoma (PTC) without lymph node involvement. Postoperatively, the patient received an ablative dose of radioactive iodine (100 mCi), achieving a favorable biochemical and morphological response. **Case 2:** A 68-year-old female patient with GD exhibited resistance to medical treatment with ATD. A radical surgical approach was pursued, and she underwent total thyroidectomy with bilateral MRLD. Histopathological examination revealed a 2 cm papillary thyroid carcinoma in the right lobe and a 3 cm thyroid tumor with malignant potential in the left lobe. The tumor was classified as pT2NxMx. She received ablative therapy with 30 mCi of radioactive iodine, resulting in a good therapeutic response.
Conclusion
The pathogenesis underlying the association between GD and thyroid cancer remains incompletely understood. Cervical irradiation is a recognized risk factor

for thyroid cancer, as it induces nuclear modifications that may initiate tumorigenesis. Additionally, it may contribute to the development of hyperthyroidism. Damaged thyroid cells with reduced hormone production may be subjected to increased thyrotropic stimulation, potentially promoting tumor proliferation. Furthermore, antithyroid therapy has been implicated in this association, as it normalizes previously suppressed TSH levels, which may facilitate tumor growth. Dobyns *et al*. reported a higher incidence of thyroid cancer in patients treated medically for hyperthyroidism compared to those managed with radioiodine therapy or surgery. The possibility of thyroid cancer in patients with GD should not be overlooked. A malignancy workup should be considered, and a diagnostic approach similar to that for any thyroid nodule should be applied. Early detection and appropriate management are crucial for optimizing outcomes in these patients.

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EP1518

JOINT175

A challenging case of amiodarone induced thyrotoxicosis

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Introduction

Amiodarone induced thyrotoxicosis (AIT) is characterized by thyroid over-activity in context of current/recent amiodarone use. It is sub-divided mainly into 2 types; Type 1 AIT occurs due to amiodarone's high iodine content causing increased thyroid hormone production, whereas Type 2 AIT is a form of destructive thyroiditis resulting in excessive thyroid hormone release. Distinguishing these sub-types is based on biochemical and radiological parameters, which helps guide treatment.

Case-report

A 69-year-old gentleman with known chronic renal impairment, ischemic heart disease with moderate left ventricular impairment, severe aortic stenosis, a previous out of hospital cardiac arrest, and a long-standing amiodarone use history presented in cardiogenic shock and type 2 respiratory failure. He was intubated and taken to the intensive care unit where he was noted to be thyrotoxic with a TSH of <0.01, T4 of >64, and T3 of 10.9, which was believed to be contributing to his initial presentation. He was commenced on Propylthiouracil (PTU) 200 mg TDS and prednisolone 40 mg daily. TSH receptor antibody titre was 0.4 U/l (range <0.4) and a thyroid doppler USS showed absence of hypervascularity consistent with Type 2 AIT. Following brief improvement, thyroid hormones incremented further, prompting a change of PTU to carbimazole 20 mg TDS. During this time the patient was extubated and transferred for an inpatient Transcatheter aortic valve insertion (TAVI) for aortic stenosis. He however remained thyrotoxic, therefore the prednisolone dose was escalated to 60 mg daily. The admission was complicated by urosepsis and a hospital acquired pneumonia, which drove further relapse in thyroid status. Total thyroidectomy was considered however deemed risky given the patients' cardiac background. A combination of PTU 200 mg TDS, carbimazole 20 mg TDS, and prednisolone 60 mg daily was utilized, and over the coming weeks, T3 and T4 levels steadily declined, allowing the TAVI to proceed. Subsequently PTU and carbimazole were gradually discontinued, and prednisolone was weaned to 40 mg daily. Thyroid function improved revealing a TSH of 0.04, T4 of 16.9, and T3 of 3.7.

Discussion

A combination of steroids and anti-thyroid drugs are typically used in AIT as diagnostic obscurity/overlap often exists. Due to amiodarone's long half-life, AIT may occur months after discontinuation, and therefore discontinuing amiodarone acutely can not only be challenging from a cardiac standpoint, but may offer little immediate benefit from a thyroid perspective. Total thyroidectomy may be considered in cases of treatment resistant AIT however this was deemed risky in our case given the patient's cardiac background.

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EP1519

JOINT1007

Apalutamide-induced severe hypothyroidism in a patient treated with levothyroxine: new data on the impact of apalutamide on thyroid hormone metabolism

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Apalutamide is a selective antagonist of the androgen receptor, increasingly used in the treatment of prostate cancer. In the SPARTAN and TITAN trials, an increased risk of subclinical or severe hypothyroidism was reported, much higher in patients treated with levothyroxine prior to apalutamide than in untreated patients. Apalutamide is suggested to cause hypothyroidism by inducing UDP-glucuronosyltransferase activity leading to reduced exposure to levothyroxine, but other mechanisms can be considered in patients treated with levothyroxine. A 65-year-old man underwent total thyroidectomy for Graves' disease followed by 150 µg/day levothyroxine supplementation with normal TSH level (3.9 mU/l). Eight months later, apalutamide (240 mg/day) associated with triptorelin (GnRH agonist intramuscular injections every 3 months) treatment was started for his metastatic prostate cancer. After one month of apalutamide treatment, follow-up of the patient revealed increased TSH (47.9 mU/l) level, and the dosage of levothyroxine was gradually increased to normalize TSH level. In this patient treated with levothyroxine (275 µg/day, 3.25 µg/kg/day) and refractory hypothyroidism (TSH = 38 mU/l, Free T4 = 7.9 pg/ml), a levothyroxine absorption test was performed: after a fast overnight, the patient intake orally 1000 µg levothyroxine, blood samples were drawn for TT4 determinations at baseline and then every 2 hours during 24 hours. Percentage absorption of levothyroxine was calculated using the formula: increment TT4 (µg/dl) $\times$ 10 $\times$ 0.442 $\times$ BMI $\times$ 100/ total administered levothyroxine. After 1000 µg levothyroxine intake, TT4 presented a rise from 5.8 µg/dl at baseline toward peak level at 2 hours (8.1 µg/dl) with percentage of absorption at 27.1% (normal $>$ 60%) demonstrating significantly reduced T4 absorption. Then TT4 declined at 5.7 µg/dl after 16 hours followed with a TT4 rise toward second peak level at 20 h (8.5 µg/dl): increased UDP-glucuronosyltransferase activity with T4 enterohepatic circulation and secondarily intestine T4 absorption likely explaining this second peak of T4 concentration. No adverse events were observed during the test. In conclusion, apalutamide treatment worsened hypothyroidism via decreased levothyroxine absorption and increased T4 clearance in this patient, explaining the higher prevalence of refractory hypothyroidism in levothyroxine-treated patients during apalutamide treatment.

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EP1520

JOINT3117

Acute suppurative thyroiditis due to internal fistula: a paediatric case report

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Introduction

Acute suppurative thyroiditis (AST) is a rare but serious bacterial infection of the thyroid gland, accounting for 0.1%-0.7% of thyroid diseases, mainly affecting children and linked to congenital anomalies like pyriform sinus fistulas. These fistulas can serve as a pathway for infection, potentially leading to abscess formation and spreading to adjacent tissues, which renders early diagnosis crucial. Mortality rates range from 3.7%-9%, highlighting the need for prompt treatment. This study reports a rare case of AST caused by a fistula originating from the thyroid gland and extending to the arytenoid fossa.

Case report

A $2\ ^{10/12}$-year-old girl with a known thyroid nodule on the left lobe presented with fever for 4 days and painful anterior neck swelling. Palpation revealed a 4×3 cm anterior left sided neck mass with tenderness and erythema of the overlying skin. Laboratory tests showed elevated white blood cell count (25,840/µL), C-reactive protein (CRP) of 146 mg/l and erythrocyte sedimentation rate (ESR) of 85 mm/hr. Thyroid-stimulating hormone (TSH) was 3.51 mIU/l and free-T4 was 1.50 ng/dl (normal range 0.74-1.6). Thyroid ultrasound revealed an isoechoic nodule (42x19x25 mm), occupying almost the entire left thyroid lobe and reactive local lymph nodes. Antibiotic therapy with Cefotaxime and Clindamycin was initiated. ENT examination revealed no signs of an abscess. Fever subsided after four days of intravenous treatment, and neck swelling began to resolve. The patient completed a 10-day course of antibiotics. A follow-up thyroid ultrasound,

performed two weeks later, revealed an enlarged nodular area of the left lobe with heterogeneous echotexture, cystic regions, and multiple reactive lymph nodes, consistent with suppurative thyroiditis. This was caused by a fistula originating from the thyroid gland and extending to the arytenoid fossa, confirmed by MRI of the cervical area. Following consultation with both ENT and paediatric endocrinology specialists, conservative 6monthly follow up was suggested. This decision was based on the absence of further episodes of thyroiditis and the lack of indications for surgery.

Conclusions

Acute suppurative thyroiditis is a rare but potentially life-threatening condition if untreated, mainly due to underlying conditions or congenital abnormalities, such as pyriform sinus fistula. Lack of awareness contributes to the delay in adequately treating this rare entity and to frustrating relapses. Treatment typically involves surgery and antibiotics, but recent studies suggest that less invasive approaches may also lead to favourable outcomes. This underscores the importance of balancing expert opinion with evidence-based practices in managing this endocrine emergency.

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EP1521

JOINT904

"Predictive value evaluation of preoperative sonographic risk stratification in patients with differentiated thyroid cancer: a feasibility study for a prospective clinical trial"

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Introduction

Preoperative risk stratification in differentiated thyroid cancer (DTC) remains a considerable challenge for endocrinology. Sonographic evaluation of the tumor before surgery may help with optimal planning of the thyroid surgery extent. However, no data are available for the estimation of its sensitivity and specificity. Thus, we plan to perform a prospective clinical trial to define the accuracy of preoperative sonographic differentiation between low risk and higher risk DTC. For the appropriate planning, we first performed a retrospective study to determine the sonographic features necessary for the preoperative diagnosis of low-risk DTC. We found that there was a possibility to apply sonographic diagnosis. This study was reported during ECE 2024. Based on the univariate analysis of feature sensitivity, we prepared a multifeature predictive classifier (MPC), which requires a prospective validation in our clinical trial.

Aim

The primary objective of the study is to evaluate the preoperative sonographic criteria based on MPC in a prospective clinical trial. During the trial, the thyroid tumor with DTC suspicion or DTC diagnosis will be evaluated by sonography to calculate MPC, in aim to allow planning lobectomy for low-risk thyroid cancer. For adequate trial planning, we needed to estimate the following data: 1. what is the predictive positive value of MPC, compared to a single ultrasonographic feature? 2. How many patients should be recruited? 3. How long will the trial last?

Methods

On the basis of our retrospective results, we plan to evaluate the predictive value of selected sonography features: lesion diameter, its ill-defined or irregular margins and vascularity in CD option. On the basis of these sonographic results, the MPC will be calculated, and its positive predictive value will be evaluated in the context of postoperative histopathological stratification.

Results

In our center, the proportion of low risk to higher risk patients is 65% and 35%. We expect that the trial should give at least 10% difference between positive predictive values (PPV of MPC), compared to the ultrasonographic criteria specified above. Thus, we should recruit 1000 patients with intermediate or high risk DTC during the trial. Taking into account the numbers of patients coming to our center in 2019 -2021, we expect that the trial will last circa 32 months.

Conclusions

The results of our analysis indicate that the planned clinical trial is feasible in our center.

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EP1522

JOINT961

Utilization of blood cell-derived parameters in the diagnosis of subacute thyroiditis during pregnancy

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Introduction

Subacute thyroiditis (SAT) is extremely rare during pregnancy. In this group, the inability to use thyroid scintigraphy and radioactive iodine uptake may present challenges in confirming the diagnosis of SAT. While blood-cell-derived parameters have been employed in the differential diagnosis of SAT and Graves' disease (GD) in various studies, to the best of our knowledge no studies have been conducted specifically in pregnant patients in the literature.

Methods

The study included 4 pregnant women with SAT and 9 pregnant women with GD. Pre-treatment blood-cell-derived parameters and thyroid function tests were retrospectively compared between two groups.

Results

All SAT cases presented with typical symptoms, ultrasonographic findings of SAT and elevated acute phase reactant levels. All GD cases exhibited typical symptoms, disease course and 7/9 (77.7%) patients have found positive for thyroid-stimulating hormone receptor antibodies (TRAB). There was no difference between the groups in terms of age and gestational week. We found

EP1522

Table 1. Demographic and laboratory data of pregnant women with SAT and GD

	SAT group ($n = 4$)	GD group ($n = 9$)	p
Age (years)	29 (22-31)	29 (22-34)	0,825
Gestational week	12.5 (8-17)	8,5 (5-23)	0,683
fT3 (ng/l)	3,96 (3,09-6,11)	6,29 (3,54-20)	0,05
fT4 (ng/dl)	1,42 (1,25-2,31)	1,95 (1,35-8,24)	0,076
TSH (mU/l)	0,59 (0,01-1,73)	0,008 (0,005-0,01	**0,003**
White blood cells (10^9/l)	11,79 (6,99-13,26)	7,28 (5,21-9,19)	0,076
Neutrophils (10^9/l)	9,14 (5,33-10,34)	5,03 (2,3-5,84)	**0,034**
Lymphocytes (10^9 /l)	1,95 (1,29-2,06)	1,74 (1,08-2,84)	0,825
Monocytes (10^9/l)	0,49 (0,25-0,66)	0,4 (0,32-0,51)	0,503
Platelets (10^9/l)	330,5 (270-393)	271 (166-317)	0,148
LUC (%)	0,8 (0,7-0,9)	1,8 (1-3,1)	**0,003**
PLR	194,8 (131,06-227,9)	153,9 (89,2-288,8)	0,414
NLR	4,64 (4,13-5,1)	3,12 (1,01-5,2)	0,076
SIRI	2,33 (1,03-3,31)	1 (0,41-1,97)	0,106
SII	1462,5 (1214,7-2004,5)	774,1 (296,8-1623,5)	**0,02**
PIV	761,17 (303,68-1162,61)	317,36 (117,82-616,95)	0,05
Anti-thyroglobulin (IU/ml)	1 (0,2-1,5)	1,3 (0,5-234)	0,373
Anti-thyroid peroxidase (U/ml)	35,5 (5,74-78)	89 (30-2965)	0,076

Data were expressed as median, minimum, and maximum values; *SAT,* subacute thyroiditis*; GD,* Graves' disease; *LUC,* large unstained cells; *PLR,* platelet-to-lymphocyte ratio*; NLR,* neutrophil-to-lymphocyte ratio; *SIRI,* systemic inflammation-response index; *SII,* systemic immune-inflammatory index; *PIV*, pan-immune inflammation value

that thyroid stimulating hormone (TSH) levels, neutrophil count, and systemic immune-inflammatory index (SII) were significantly higher and percentage of large unstained cells (LUC%) was significantly lower in pregnant women with SAT compared to those with GD.
Conclusions
TSH, SII levels, LUC percentage and neutrophil count may serve as valuable tools in the differential diagnosis of thyrotoxicosis during pregnancy.

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JOINT2110

Adherence to levothyroxine treatment among patients withhypothyroidism and evaluation of depressive stratus andfactors related with non-adherence

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Introduction
Hypothyroidism is a common clinical problem requiring life-long treatment and follow-up. Even though the management of hypothyroidism is generally straightforward, several studies shown that a large percentage of patients are over or under-treated and the drug adherence is also sub-optimal. The aim of this study was to evaluate drug adherence and factors associated with non-adherence, determine the attainement of the euthyroidism and evaluate the depressive status.
Method
300 patients treated for hypothyroidism at least for one year were included. Patients were administered eight-item Modified Morisky Medication Adherence Scale (MMAS-8), a structured self-reporting medication adherence measure to identify the behaviour of patients with regard to prescribed medications. They were evaluated for the medication use habits, comorbidities and drugs used together with levothyroxine, nutritional habits. Beck depression scale was applied to all patients.
Results
According to MMAS-8 scale, 29.67% of the patients have low drug adherence, 36.67% have moderate adherence and 33.67% of the patients have good drug adherence. Male and female patients have similar MMAS-8 scores. The mean age of the low adherent group was lower significantly ($P = 0.009$). TSH levels of the patients with good adherence was lower than moderate and low adherence groups significantly ($P > 0.001$). 99.33% of the patients were taking levothyroxine at morning before breakfast. 17.33% of the patients were having breakfast within 30 minutes after taking the levothyroxine, 38.67% were having breakfast within 30-60 minutes. 12.67% of the patients were taking together with another medication. The MMAS-8 score was not associated with etiology of hypothyroidism and education background. 32.67% of the patients have moderate or severe deppression. There was no relation between MMAS-8 score and Beck depression score when evaluated by cathegorisation but the depression scores of the good adherent patients was lower significantly ($P = 0.002$). Mean TSH level of patients with severe depression was higher significantly ($P = 0.007$). Beck depression scores of the female group was significantly higher ($P = 0.001$). Beck depression scores of the patients with TSH < 0.5 and TSH > 4 were higher than the group with TSH between 0.5-4 Mıu/l.
Conclusion
29.67% of the patients in study group had poor drug adherence. Drug adherence scores were not associated with hypothyroidism etiology, disease duration, levothyroxine dose or education background. Younger patients had lower drug adherence. TSH levels of the patients with severe depression was significantly higher. Follow-up of the patients and regular doctor visits is important for detection of drug adherence and keeping patients euthyroid.

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EP1524

JOINT3637

Severe graves' disease presenting with supraventricular tachycardia (SVT) in a 54-year-old male smoker

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Background
Graves' disease is an autoimmune disorder characterized by hyperthyroidism, which can lead to various cardiovascular complications. This case report describes a 54-year-old Caucasian male smoker who presented with chest pain and subsequent collapse, leading to the diagnosis of severe Graves' disease complicated by supraventricular tachycardia (SVT).
Case Presentation
A 54-year-old Caucasian male, typically fit and an avid cyclist but a significant smoker, presented to the Emergency Department with a 6-week history of chest pain, followed by a collapse. Initial ECG revealed a heart rate of 200 bpm, diagnosed with SVT. The patient was resuscitated, stabilized with adenosine, and started on rate control medication. Physical examination revealed severe thyrotoxicosis, evidenced by tremors, sweating, and palpitations, without signs of orbitopathy. Blood investigations confirmed severe Graves' disease with fully suppressed TSH (< 0.01 mU/l), elevated T3 (39 pmol/l) and T4 (92 pmol/l), and TRAB levels of 15.9 U/l. Additional findings included mild anaemia, raised ALP, and hypercalcemia, likely secondary to thyrotoxicosis.
Management and Outcome
The patient was initiated on Carbimazole 40 mg once daily and counselled about potential side effects. Beta-blockers, previously started as prophylaxis for SVT, were continued with advised titration. Clinical improvement was observed on high-dose Carbimazole, with repeat thyroid function tests showing a reduction in free T4 to 30 pmol/l. The patient was informed about the high risk of relapse due to elevated TRAB antibodies, and future radioactive iodine (RAI) therapy was discussed.
Conclusion
This case highlights the importance of considering thyroid dysfunction in patients presenting with cardiac arrhythmias, especially in the presence of risk factors such as smoking. The rapid diagnosis and management of both the cardiac and thyroid components were crucial in stabilizing the patient. Regular follow-up and consideration of definitive treatment options, such as RAI, are essential in managing severe Graves' disease to prevent recurrence and complications. Smoking may exacerbate Graves' disease and increase cardiovascular risk. SVT can be an initial presentation of severe thyrotoxicosis. This case exemplifies the necessity for a multidisciplinary approach in managing complex endocrine-cardiac presentations and emphasizes the importance of thorough patient education and ongoing monitoring to achieve optimal outcomes.

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EP1525

JOINT2755

Approaches for improving diagnostics precision, treatment anh monitoring relapse of graves' disease in national children's hospital

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Research objective
Clarifying the relationship between TrAb antibody concentration and some clinical and paraclinical characteristics in pediatric Graves' disease and applying TrAb antibody testing in monitoring relapse of Graves' disease in children, requiring to use attacking dose of antithyroid drugs during maintenance phase.
Research subjects: 58 patients (from 24 months old to under 18 years old) treated at The Center of Endocrinology, Metabolism, Genetics and Molecular Therapy, Vietnam National Children's Hospital from Jan 2021 to Oct 2024.
Research method: Case series study.
Results
The mean age of patients in the study was 9.6 ± 3.1 years. The ratio of female/male patients was 2.4/1. The mean time for patients to see doctors since progression was 2.2 ± 1.8 months: this figures were 2.3 ± 1.1 months in boys and 2.2 ± 2.2 months in girls. The main reason for going to hospitals was thyrotoxicosis (71.2%). Common physical symptoms were hot and moist skin, hand tremors, tachycardia, bulging eyes and goiter, overeating. The other symptoms were weight loss (58.6%), insomnia (55.2%), and nervousness (46.6%). In our 58 patients, 9 patients(15.5%) developed relapse. The mean time to have relapse since starting treatment was 15.8 ± 4.8 months. The mean TrAb concentrations of patients at the time of diagnosis, the end of attacking dose time, and maintenance phase were 22.4 ± 11.3 U/l, 15.6 ± 11.4 U/l and 8.8 ± 8.1 U/l, respectively. The patients' mean TrAb concentrations at the time of diagnosis, the end of attacking dose

time, and maintenance phase were higher in relapse patients, compared to that of non-relapse patients, but the difference was not significant.
Conclusion
The disease has a long-term course of relapse, recurrence, requiring early treatment to avoid ophthalmological, cardiovascular, and neurological complications that affect children's physical development as well as their ability to work and study. Quantifying TrAb levels at diagnosis and during treatment helps to confirm the diagnosis of Graves' disease, but may not predict relapse.
Keywords
Graves' disease, hyperthyroidism, TrAb, children.
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EP1526

JOINT3891
Paralyzed by potassium: the thyroid's sneaky trick
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Introduction
Periodic Paralysis (PP) is a rare neuromuscular disorder characterized by painless episodes of muscle weakness. This disorder can manifest as either hereditary or acquired, with the former typically being autosomal dominant and the latter frequently associated with hyperthyroidism. Thyrotoxic Periodic Paralysis (TPP) represents a specific subtype of hypokalemic periodic paralysis, marked by sudden onset weakness in proximal muscles, most commonly affecting the lower extremities. TPP is reversible through prompt potassium replacement and normalization of thyroid hormones. However, without timely detection and management, TPP can progress to involve all limbs and respiratory muscles. This form of periodic paralysis is frequently observed in males of Asian origin between the ages of 20 and 40.
Case
A 31-year-old male with no significant medical history presented with sudden and severe lower extremity weakness. Physical examination revealed a thin anxious individual with bilateral flaccid paralysis of the lower extremities with a power of 1/5. Vital signs were remarkable for high blood pressure of 152/77 mmHg. Investigations were remarkable for potassium level of 2.1 meq/l, and creatine kinase (CK) of 1,842 U/l. MRI of Spine was unremarkable. Potassium repletion was initiated both intravenously and orally. After three hours of starting the potassium repletion, the patient regained normal strength in the lower extremities. Further investigations revealed very low thyroid-stimulating hormone (TSH) of <0.008 mIU/l with elevated T3 529 ng/dl and T4 5 ng/dl, thyroid peroxidase antibody >900 IU/ml, and thyroid-stimulating immunoglobulin (TSI) of 436 % confirming our diagnosis of TPP.
Discussion
Thyrotoxic periodic paralysis (TPP) is triggered by factors such as exercise or carbohydrate intake, leading to a shift of potassium into cells and resulting in low blood potassium levels. While our patient falls within the most commonly affected sex and age group, his African American racial background makes this case less typical, as TPP is less frequently observed in this population. This case highlights the importance of considering hypokalemic periodic paralysis (HPP) as a differential diagnosis in any patient presenting with hypokalemia and sudden-onset paralysis. Treatment involves potassium replacement, correction of thyroid hormone levels, and a strong emphasis on patient education to prevent triggering factors.
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EP1527

JOINT2079
What is the role of Pro-inflammatory biomarkers in Hashimoto's thyroiditis?
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Introduction
Hashimoto's thyroiditis (HT) is one of the most frequent organ specific autoimmune thyroid disease. Autoimmunity has been implicated as one of the main cause of HT. In this context, we set out study the role of Pro- inflammatory cytokines in HT.
Material and methods
This prospective case-control study was conducted on surgically managed HT patients. Institutional ethical committee approval was obtained. Diagnosis of HT was based on thyroid function tests, anti-TPO antibody titer, radionuclide scanning and histopathology. Exclusion criteria were subjects any systemic or chronic inflammatory disease or any medication which interferes with the normal function of the hypothalamic-pituitary-gonadal axis. Serum samples were collected from 20 HT subjects and 20 age matched healthy controls. Interleukin-6 (IL-6), Tumour necrosis factor-alpha (TNF-α) and high sensitive C reactive protein (hsCRP), Leptin levels were measured in all serum samples. Statistical analysis was performed by one way ANOVA with Dunnet's test and Pearson correlation tests.
Results
The mean hSCRP level in GD and controls were 14.5 ± 2.9 mg/ml and 6.4 ± 1.6 mg/ml respectively. The mean TNF-α level, IL-6 level and Leptin levels were 232 ± 25 pg/ml, 12.7 ± 4.4 pg/ml and 33 ± 4.7 ng/ml respectively. There was statistically significant difference of all the pro-inflammatory cytokines compared to controls (P value < 0.05).
Conclusions
This study shows raised titers of pro-inflammatory markers – IL-6, TNF-α and hsCRP, leptin correlated with HT suggesting a significant pathophysiological role. But, the exact immuno-modulatory role and pathogenetic mechanism needs more research.
(**Key words:** Hashimoto's thyroiditis; Tumour necrosis factor; Interleukin-6; Goiter; Auto-immunity; Leptin)
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EP1528

JOINT3232
Predictive factors of relapse, TED, and thyroidectomy in graves' disease
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Introduction
Graves' disease (GD) is one of the most common autoimmune thyroid disorders worldwide. Although GD is not life-threatening, complications significantly impact patients' quality of life: 52% of patients relapse, 50% develop thyroid eye disease (TED), and thyroidectomy remains the last resort in challenging clinical cases. In recent years, data engineering and multivariate statistical methods have been increasingly applied in the medical field. They provide a broader analytical perspective, accelerate statistical analysis and contribute to the development of predictive algorithms. This study aimed to identify clinical and biochemical variables collected at diagnosis that are associated with thyroidectomy, relapse, and future TED onset in GD patients using these methods.
Methodology
We analyzed data from GD patients diagnosed at *Hospital Universitario de La Princesa* between 2010 and 2018, with follow-up until 2022. Data engineering techniques were employed to clean the dataset by removing low-quality variables. The analytical process was conducted in two steps: 1) a univariate analysis was performed to identify significant associations with the outcomes of interest ($P < 0.1$), which were subsequently included in further models. 2) Next, supervised logistic regression (100-fold cross-validation-CV-) and time-to-event analysis (Cox models) were conducted.
Results
Multivariate analysis reported the following independent associations:
• **Relapse**: Significant associations were found with albumin ($\beta = -1.782$, $P = 0.064$) and CAS ($\beta = 1.238$, $P = 0.070$). However, time-to-event analysis did not show a clear impact of these variables on relapse.
• **TED**: Independent associations were observed with basophils ($\beta = -4.883$, $P = 0.016$) and GPT($\beta = 2.171$, $P = 0.084$). Both variables had a weak, but significant correlation($r = -0.212$, $P = 0.004$). Other correlations with thyroid hormones would suggest a link between them. Interestingly, basophils also showed significant independent associations in Cox models($\beta = -1.959$, $P = 0.076$), inferring a potential relationship between their levels at diagnosis and future TED onset.
• **Thyroidectomy**: Associations were found with immature granulocytes ($\beta = -22.272$, $P = 0.033$), anti-TG antibodies ($\beta = -23.643$, $P = 0.096$), leukocytes ($\beta = 3.310$, $P = 0.066$), eosinophils ($\beta = 2.969$, $P = 0.026$), potassium ($\beta =$-

3.801, $P = 0.093$) and goiter ($\beta = 2.308$, $P = 0.028$). However, the Cox model did not report any significant relationship between surgery timing and these variables.
The mean areas under the curve reflected poor quality models: **relapse**: 0.576 ± 0.076; **TED**: 0.663 ± 0.100 and **thyroidectomy**: 0.676 ± 0.107. A class imbalance in the dataset, a limited sample size and the lack of biomarkers may have contributed to the reduced model performance.
Conclusions
1. We obtained significant associations between relapse and albumin levels and CAS, already reported in the literature.
2. A novel relationship between TED onset and basophils.
3. Associations between thyroidectomy immune populations levels, goiter and potassium, which could contribute to its management.

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EP1529

JOINT1980

From neurology to endocrinology: an atypical case of thyroid storm in a young adult

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Thyroid storm is a rare, life-threatening condition characterized by severe thyrotoxicosis. Common triggers include infection, trauma, surgery, iodine exposure, discontinuation of antithyroid medications. The Burch-Wartofsky criteria, assessing cardiovascular, gastrointestinal, CNS disorders and hyperpyrexia, is frequently used for diagnosis. An 18-year-old male was admitted to the Emergency Department with nausea, vomiting, four-limb paralysis and inability to speak, following ten-days of diarrhea. He was lethargic, febrile (38.5°C), tachycardic, and tachypneic. Neurology consultation was requested for paralysis and speech disturbance, and brain imaging ruled out other diagnoses. A lumbar puncture was performed to investigate CNS infection, but findings were negative. A psychiatric consultation excluded conversion disorder. Thyroid function tests revealed thyrotoxicosis (table 1). Burch-Wartofsky score of 65 confirmed thyroid storm. Treatment was initiated with propylthiouracil (PTU), hydrocortisone, Lugol's solution and propranolol. Ultrasound revealed thyroid inferno. Intensive antithyroid therapy led to significant increase in liver function tests, resulting in the discontinuation of PTU and the initiation of lithium treatment. After achieving euthyroidism, the patient underwent total thyroidectomy and started on thyroxine replacement therapy. The patient was clinically stable and discharged with plan for close follow-up. Central nervous system findings in thyroid storm may include neurological symptoms such as tremor, hyperreflexia, myopathy and seizures as well as psychiatric symptoms like anxiety, agitation, psychosis and delirium. Paralysis is a rare presentation. While hypokalemic periodic paralysis is one possibility, similar findings can occur in normokalemic patients. The sudden onset of the condition should be considered in differential diagnosis as it may lead to severe outcomes depending on the severity of muscle involvement. Early diagnosis and appropriate treatment can prevent complications and improve prognosis. Controlling thyroid function is crucial in managing this condition and preventing recurrence of paralysis.
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Table 1: Thyroid Function and Related Biochemical Parameters at Diagnosis and During Follow-Up

Parameter	At Diagnosis	Second Week
TSH (mIU/l)	<0.005	<0.005
sT4 (0.9-1.7 ng/l)	>7.7	1.4
sT3 (2-4.4 ng/dl)	>32.5	3.6
TRAb (0-1.5 IU/l)	34	—
TSI (<0.1 IU/l)	38.9	—
Creatinine/GFR	0.52/128	—
Sodium/Potassium	137/4.1	—
ALT/AST	38/14	168/156

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JOINT3205

Thyroid function test assay interference: biochemical and clinical challenges and its implications

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Introduction
Thyroid hormone tests are widely used globally and play a crucial role in guiding treatment decisions and further diagnostic evaluations. Any inconsistency between clinical symptoms and test results must be thoroughly investigated to prevent misdiagnosis and unnecessary treatment. Automated thyroid tests can be affected by interferences, which may alter results and influence treatment decisions. These interferences can lead to incorrect treatments and changes in therapy. This review aims to explore the impact of assay interference on clinical management and highlights the importance of early detection to avoid inappropriate care.
Case report
Case 1: A 73 Y/F with post thyroidectomy for multinodular goiter on Thyroxine replacement was referred to the endocrinology clinic due to unusual thyroid function test (TFT) results (Table 1). Her clinical condition wasn't corelating with TFT. Additional testing was performed at two separate laboratories using different methods, which confirmed interference. This helped avoid an unnecessary increase in her thyroxine dosage based on the initial abnormal results. Case 2: A 60 Y/F on thyroxine was referred for evaluation of persistent fatigue and tiredness. Her recent TFTs showed normal TSH but elevated FT4 levels, which did not match her clinical symptoms (Table 2). To clarify, repeat tests were done at two laboratories using different methods. The results confirmed a hypothyroid state, leading to an adjustment in her levothyroxine dose, which improved her symptoms.
Results
This table highlights the TFT variations across labs and reagents used.
Discussion
Laboratory interference is a significant cause of misdiagnosis, so it's important to always match test results with patient's symptoms. Patients often have vague symptoms and when test results don't match the clinical situation, interference should be suspected. A careful approach is needed, with collaboration between healthcare providers and lab experts to ensure accurate diagnosis and appropriate treatment.
Conclusion
According to the British Thyroid Association, TFT in the UK are requested around 10 million times annually, with an estimated cost of 30 million pounds. Collaboration between laboratory and clinical teams is essential for identifying potential interferences and ensuring that thyroid symptoms align with test results.

Table 1. Case 1.

Lab	TSH (mIU/l)	T3(pmol/l)	T4(pmol/l)	Reagent
1.	2.8(0.35-5.50)	7 (3.5-6.5)	37.7 (10-20)	Siemens
2.	2.51(0.35-4.94)	N/A	12.5(9-19)	Rosche

Table 2. Case 2.

Lab	TSH (mIU/l)	T3(pmol/l)	T4(pmol/l)	Reagent
1.	8.3(0.35-5.50)	7.1(3.5-6.5)	22.2(10-20)	Siemens
2.	7.54(0.35-4.94))	6.51(2.4-6.1)	17.9(9-19)	Rosche

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EP1531

JOINT2790

Risk of obstructive sleep apnea in patients with clinical hypothyroidism based on STOP-BANG score

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Introduction
Hypothyroidism increases the risk of OSA. Obstructive sleep apnea (OSA) is a common sleep disorder with varied etiology and can affect a large population. OSA is associated with major adverse cardiovascular events. The presence of hypothyroidism has been linked to the development of obstructive sleep apnea. This cross-sectional study aimed to predict the risk of OSA in clinical hypothyroid subjects based on STOP-BANG score which is a reliable marker for OSA risk prediction and to study the independent effect of hypothyroidism on the risk of OSA by comparing the STOP-BANG score in age, sex, body mass index (BMI) matched non-hypothyroid subjects.
Methodology
Study group included consecutive clinical hypothyroid patients (cases) and age, sex, BMI-matched non-hypothyroid subjects (controls) presenting to the out-patient department and admitted in General Medicine wards of a tertiary care hospital of New Delhi, India. Sample size for the study was 150 which included 75 cases and 75 controls. Clinical hypothyroidism was diagnosed on the basis of thyroid function tests (both newly diagnosed and on treatment). All patients were evaluated for their STOP-BANG score and risk stratification for OSA done.
Results
Among hypothyroid participants, 48.0% were classified as having low risk of OSA, 45.3% as having moderate risk, and 6.7% as having high risk based on the STOP-BANG score. The risk of OSA increased with age and higher TSH levels. Importantly, the association of hypothyroidism and risk of OSA was statistically significant in patients with a higher BMI, presence of co-morbidities (diabetes and hypertension), and dyslipidemia (Total Cholesterol and Low-density Lipoprotein).
Conclusion
Uncontrolled hypothyroidism has the potential to increase the risk of OSA. Screening for OSA in hypothyroidism should be prioritized in individuals with a history suggestive of sleep apnea, higher BMI, dyslipidemia, and comorbidities.

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EP1532

JOINT1990

Pancreatic mass during follow-up of a papillary thyroid microcarcinoma: lenvatinib's side effect, metastasis or primary tumor ?

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Introduction
Papillary thyroid carcinoma is the most common type of thyroid cancer. Metastases are often pulmonary and osseous, other sites, such as the pancreas, are possible but remain exceptional. We report the case of a patient with refractory and progressive papillary carcinoma under lenvatinib who, during follow-up, presented with a pancreatic mass, raising a diagnostic dilemma: is it a metastasis, a side effect of lenvatinib, or a primary tumor?
Case Report
A 75-year-old patient with a history of hypertension was diagnosed in 2018 with papillary microcarcinoma with lymph node metastases, classified as PT1aN1bMx. He underwent four courses of radioiodine therapy, totaling 550 mCi, with the last post-therapeutic scan revealing a right mediastinal fixation, confirmed by thoracic CT, with three additional pulmonary nodules. He did not return for follow-up until 2024, when imaging revealed inoperable pulmonary and cerebral metastases, leading to the initiation of treatment with lenvatinib, which showed a good therapeutic response. Five months after starting treatment, he presented with jaundice, fever, abdominal pain, and leukocytosis. CT imaging identified a 5 cm pancreatic mass, and histopathological analysis confirmed a well-differentiated adenocarcinoma of the pancreatic head with positive CK7 and CK19 immunostaining but negative TTF1. The patient was presented in a multidisciplinary (RCP digestive), where chemotherapy was decided upon; unfortunately, he passed away before treatment could begin.
Discussion
The discovery of a pancreatic mass raises several diagnostic hypotheses: **Metastasis of thyroid cancer** The multimodal metastatic nature in our patient suggests the possibility of pancreatic metastasis. However, this diagnosis is rarely reported and requires histopathological and immunohistochemical confirmation. **Lenvatinib side effect** Although lenvatinib is known for its efficacy, reported side effects include acute or chronic pancreatitis. The occurrence of neoplasia under tyrosine kinase inhibitors has been exceptionally documented **Primary pancreatic neoplasia** This association has been previously reported in the literature. Histopathology revealed an exocrine adenocarcinoma, strongly suggesting a primary origin. The occurrence of this second cancer could be incidental or linked to underlying genetic mechanisms.
Conclusion
This case highlights the complexity of diagnosis in such a challenging clinical context and underscores the need for a multidisciplinary approach to guide diagnosis and treatment.

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EP1533

JOINT3632

Papillary thyroid carcinoma treated with vandetanib

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Patients with medullary thyroid carcinoma (MTC) usually present with extensive regional involvement or distant metastatic disease at diagnosis or during follow-up, preventing cure by initial thyroidectomy. Treatment options in advanced CMT include surgery, radiotherapy, and tyrosine kinase inhibitors (TKIs) such as vandetanib.
Materials and Methods
We aimed to evaluate four patients with metastatic CMT treated with vandetanib followed at our level between 2021 and 2024 with a minimum follow-up of 6 months.
Results
Four patients met the inclusion criteria, 3 men and one woman. The mean age was 40 years. All four patients underwent total thyroidectomy with lymph node dissection. Metastases were to the lung, bone, cerebellum and liver. The main indication for vandetanib was progression of lung metastases. Regarding response to treatment, one patient was stable, one patient showed a partial response and 2 patients escaped treatment after 6 to 12 months of stability. The average duration of treatment was 13 months [4-19 months]. Side effects were observed in 3 patients, including hypertension, QT prolongation, diarrhea, acne and hypocalcemia. In the end, two of the patients died.
Discussion
Vandetanib targets the RET oncogene, the vascular endothelial growth factor receptor and the epidermal growth factor receptor. The use of vendetanib can cause remarkable side effects, altering patients' quality of life, while response to treatment is not always satisfactory. Thus its prescription must take into account the benefit-risk balance and be discussed in a multidisciplinary meeting.
Conclusion
The use of vandetanib in the management of advanced CMT has led to stabilization of lesions and control of the disease for at least a certain period before escape.

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EP1534

JOINT3635

Middle-aged women thyroid gland ultrasound assessment in the minsk-city

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Background
Thyroid volume varies across populations depending on age and gender. Some studies show a correlation between thyroid volume and anthropometric parameters. The results of thyroid gland assessing of middle-aged women in Belarus population have not been published yet. The aim of the study is to

establish the normal thyroid volume and its correlation with anthropometric parameters in middle-aged women.
Materials and Methods
A retrospective cross-sectional study was conducted. We studied 131 women 45-59 years old without endocrine diseases who applied to the Minsk Clinical Consultative and Diagnostic Center in 2023-2024 years. The study included patients with normal echogenicity of the thyroid gland, without a severe echo structure disturbance and nodes (anechoic cyst-like formations 5 mm less were assessed as normal). Patients with thyroid hormone levels abnormalities were excluded from the study. Statistical processing of the results was carried out using the Statistica 10 program (StatSoft, USA). Examination: thyroid ultrasound, TSH, FT4, ATPO, height, weight, BMI. Results. Average age was 51.7 $\pm$ 3.44 years, height was 165 (161-170) sm, weight was 69 (61-76) kg, BMI was 26.3 (23.7-29.2) kg/cm^2. TSH level was detected 2.96 (1.93 - 3.58) mIU/ml, FT4 – 16.7 (14.9-19.8) pmol/l, ATPO -19.6 (12.3- 41.1) IU/ml. The right lobe average volume was 5.47 $\pm$ 2.11 cm^3, the left lobe of the thyroid gland was 5.43 $\pm$ 2.27 cm^3. The width of the isthmus was 2.5 (2.2-2.8) cm. Minimum registered total thyroid volume was 3,9 cm^3, maximum registered total thyroid volume was 22,1 cm^3. The total thyroid volume was recorded 10.1 (6.0-16.8) cm^3. Frequency range 5-95% was detected 5.9-17.4 cm^3. A strong direct correlation was found between BMI and total thyroid gland volume ($r = 0.7$).
Conclusion
The result of the study demonstrated the normal total thyroid volume was 5.9-17.4 cm^3 middle-aged women 45-59 years old without a history of endocrine diseases in the Minsk- city. A strong direct correlation was found between BMI and total thyroid gland volume ($r = 0.7$).

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EP1535

JOINT668

A rare case of thyrotropinoma inappropriately treated as Graves' disease

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Introduction
Thyrotropinoma, TSHoma, TSH secreting pituitary tumor, is considered a very rare cause of hyperthyroidism. They account for less than 1 % of all pituitary adenomas. Almost all TSHomas express a variable number of somatostatin receptors.
Case report
A 44 year old male patient presented to Endocrinology unit for consultation about total thyroidectomy. The patient presented three years ago with goiter, palpitations, heat intolerance, irritability and tremors. Despite his initial thyroid profile showed elevated TSH, Free T3 and free T4, he was falsely considered Graves' disease kept on carbimazole 30 mg/day for 3 years. Patient's symptoms were not controlled, and he developed atrial flutter. Total thyroidectomy was considered so he was referred to surgery department who consulted us about the decision of total thyroidectomy.
Examination
BP: 120/70 mmHg, irregular pulse at rate of 90/mint Diffuse goiter, not tender, no palpable thrill, with no thyroid orbitopathy. Cardiac examination: accentuated heart sounds and mitral regurge. Complete blood picture, liver, kidney function, blood glucose, and lipid profile were normal. TSH **43** U/ml (0.5 - 4.8), Free T3: **12.7** pg/ml (2.3 - 4.2), Free T4: **3.5** ng/dl (0.8 – 1.7). ACTH 9 am: 42pg/ml (up to 65), serum Cortisol 9 am: 5.9 mg/dl (4- 22), serum prolactin: 5.5 ng/ml (2 -17.7), FSH: 4.36 mIU/ml (1.4 – 18), LH: 6.2 mIU/ml (1.5 -9.3). TSH receptor antibodies 0.9 IU/l (0-1.75) excluding coexisting primary thyrotoxicosis. Thyroid ultrasound showed enlarged heterogeneous thyroid gland, (4.2x3.5 cm) with increased vascularity. Dynamic MRI Sella with gadolinium showed a 7 mm right sided pituitary microadenoma. To confirm that the pituitary microadenoma is functioning, and as somatostatin scintigraphy was not available, a dynamic test using long-acting somatostatin analogue injection (somatostatin LAR) was done, thyroid profile was measured 28 days after with marked reduction of the thyroid hormones; TSH **27** U/ml (0.5 - 4.8), Free T3: **3.02** pg/ml (2.3 - 4.2), Free T4: **0.58** ng/dl (0.8 – 1.7), with improvement of the symptoms and reduction of the thyroid gland size. This step is considered a bridging therapy until transsphenoidal surgery is performed.
Conclusion
Thyrotropinoma is a very rare cause of secondary thyrotoxicosis and is frequently misdiagnosed as Graves' disease. Definite diagnosis depends on positive pituitary imaging and dynamic tests to differentiate TSHoma from other causes of central hyperthyroidism. Early diagnosis is important to prevent inappropriate management.

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EP1536

JOINT218

Levothiroxine malabsorbtion

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Background
Levothyroxine (L-thyroxine,) is a drug of choice for treating primary hypothyroidism, which in developing countries generally occurs due to Hashimoto thyroiditis, thyroidectomy, or iodine deficiency. L-T4 is absorbed in the small intestine, more precisely in jejunum and ileum, and to a small extent also in the stomach. Concomitant gastrointestinal diseases, such as celiac disease, *H. pylori* infection, lactose intolerance, inflammatory bowel disease, and even parasitic infestation (*G. lamblia*), etc. may cause L-T4 malabsorption
Case Presentation
The patient was treated for primary hypothyroidism in different endocrinological centers of Georgia for 10 years without significant changes and results. Referring to us, attention was paid to the clinical and laboratory signs characteristic of hypothyroidism, despite the fact that she was receiving 2800 mg of levothyroxine and up to 150 mg of T3 per day. Conducted diagnostic deductions with consultations, the total volume of the thyroid gland is 3.1 ml. Tsh-43.77 (N 0.4-4.0) miu/ml. Ft4 - 1.46 ng/dl (N 1.8-4.2). Antibodies within the norm. Due to the ineffectiveness of the standard scheme of treatment, a test was performed to rule out pseudo-malabsorption of levothyroxine, with a special protocol, thus confirming that the patient really had a syndrome of true malabsorption of levothyroxine oral preparations. An individual thyroxine treatment algorithm was developed. Alleviation of the patient's condition and compensation of hypothyroidism is possible only with parenteral replacement therapy. A parenteral injection of 500 mg of levothyroxine every third day was prescribed, as soon as hypothyroidism compensation was achieved.
Conclusions
Levothyroxine parenteral injection is an effective and safe way to achieve hypothyroidism compensation in case of levothyroxin malabsorbtion.

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EP1537

JOINT35

Lost and found: a thyroid tale of tissues gone rogue

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Background
Thyrotoxicosis following subtotal thyroidectomy is an uncommon occurrence. In rare cases, ectopic thyroid tissue may be the source of hyperthyroidism, particularly in the mediastinum. This report discusses an unusual presentation of hyperthyroidism many years post-surgery due to an ectopic thyroid tissue in the anterior mediastinum.
Case Presentation
We report the case of a 61-year-old female patient with a history of subtotal thyroidectomy in 2000, during which the upper left thyroid pole was preserved. The surgery was complicated by hypoparathyroidism. Years later, the patient developed both clinical and biochemical hyperthyroidism. Thyroid scintigraphy revealed an area of intense, heterogeneous uptake in the upper and middle

mediastinum, suggesting a plunging goiter component. A subsequent thoracic CT scan showed a lesion in the anterior mediastinum, with imaging characteristics consistent with ectopic thyroid tissue. The patient underwent surgical resection via sternotomy performed by the thoracic surgery team. Histopathological analysis confirmed the benign nature of the lesion.
Conclusions
This case emphasizes the need for clinicians to consider ectopic thyroid tissue as a potential source of hyperthyroidism, even in patients with previous thyroidectomy. Detection of ectopic thyroid tissue in the mediastinum underscores the importance of thorough imaging and surgical assessment when managing recurrent thyroid symptoms in post-thyroidectomy patients.

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EP1538

JOINT160

Dysphagia in old age, what if it's an ectopic thyroid?: a case report

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Introduction
Thyroid ectopy is a rare condition whose pathogenesis remains poorly understood. It may be asymptomatic or manifest as clinical or biological hypothyroidism. We report a case of thyroid ectopy diagnosed at an advanced age.
Case Report
A 63-year-old patient with no previous history of any particular complaint presented with dysphagia and the sensation of an enlarging sublingual formation. Ultrasound showed an empty thyroid cavity with a lesional process at the base of the tongue. The thyroid work-up revealed mild hypothyroidism. The patient underwent a thyroid replacement and then an operation, and an APTH scan showed thyroid ectopy at the base of the tongue.
Discussion
Thyroid ectopy is defined as the presence of thyroid tissue outside its infrahyoid location. The association of thyroid ectopy and a thyroid in a cervical position is exceptional. Lingual thyroids are the largest group of thyroids and have been known for a very long time (VERNEUIL described them for the first time in 1853). Lingual thyroids are the result of a defect in the migration of the median thyroid outline, which normally leads the glandular cells from the floor of the mouth to the anterior surface of the trachea. Radiological investigation is based on cervical ultrasound as the first line of defence, CT with PDC injection or MRI. Tc99 scintigraphy confirms the diagnosis, demonstrating ectopic fixation.
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EP1539

JOINT2592

Cross-reactions between synthetic antithyroid drugs

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Introduction
Synthetic antithyroid drugs, notably methimazole, carbimazole, and propylthiouracil (PTU), are commonly used medications for the treatment of hyperthyroidism. Although these drugs are generally effective, they can sometimes cause adverse effects and cross-reactions, meaning allergic or toxic reactions to different but chemically similar medications.
Observation
A 37-year-old female patient consulted for signs of hyperthyroidism: palpitations, significant unquantified weight loss deemed important. A thyroid panel was requested, revealing low TSH levels with a T4 level of 43.07 pmol/l. The cervical ultrasound suggested Graves' disease, with positive Anti-TSH receptor antibodies. The patient was initially placed on Methimazole 40 mg; after a few days, she developed skin lesions (urticaria), prompting a change in treatment to Carbimazole along with the initiation of antihistamine therapy, but without improvement in the allergic reactions. After achieving euthyroidism, the patient underwent total thyroidectomy without postoperative incidents.
Discussion
Cross-reactions between synthetic antithyroid drugs can be explained by the chemical similarity among these medications. Methimazole and carbimazole, for example, are closely related. Although rare, cross-reactions pose a significant clinical challenge. Patients who develop adverse reactions to one antithyroid drug are at an increased risk of reacting similarly to other drugs in the same class. Management of cross-reactions between synthetic antithyroid drugs requires a careful and personalized approach.
Conclusion
Cross-reactions between synthetic antithyroid drugs, although varied among different molecules, necessitate careful evaluation and appropriate management. In cases of intolerance or hypersensitivity, alternatives such as propylthiouracil, radioactive iodine, or surgery should be considered. Increased vigilance can help limit risks and optimize the treatment of patients with hyperthyroidism.

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EP1540

JOINT2501

Rare coexistence of parathyroid adenoma and thyroid adenomas: a case report

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Introduction
Primary hyperparathyroidism (PHPT) and thyroid disease are two relatively common conditions that can coexist in the same patient. The etiology and risk factors remain unclear. We report here the case of a 55-year-old female patient presenting with a parathyroid adenoma, two normo vesicular thyroid adenomas discovered during an etiological work-up for kidney stones.
Case Report
55-year-old female patient with a history of recurrent kidney stones, right thyroid loboisthmectomy with anatomopathological examination: appearance of atypical reworked thyroid adenoma, referred to our training for further management of primary hyperparathyroidism. Cervical palpation revealed a 1 cm thyroid nodule lateralized to the left, biological workup showed hypercalcemia at 117 mg/l and PTH at 257 pg/ml. Cervical ultrasonography showed 2 left nodular formations classified as EuTirads 3, the largest measuring 13×10 mm. Parathyroid scintigraphy with Sesta-MIBI 99mTc showed a left sub lobar area preferentially fixing the MIBI-Tc 99m tracer, in favour of a parathyroid origin with no ectopic focus capturing the tracer. The patient underwent surgery involving removal of the left thyroid lobe and the left inferior parathyroid. Anatomopathological examination showed the coexistence of a normo vesicular thyroid adenoma and a parathyroid adenoma. Postoperative calcemia levels normalized.
Discussion
The coexistence of parathyroid and normovesicular thyroid adenomas is extremely rare. A combination of clinical, radiological and histological findings should lead to a diagnosis in the presence of an atypical presentation. Because of the risk of concomitant thyroid damage, thyroid imaging must be carried out prior to any surgical treatment of the parathyroid glands. Ultrasound provides a precise anatomical image, but cannot visualize certain parathyroid adenomas. Ultrasound symptomatology must be understood, as well as the pitfalls and difficulties involved. MIBI scintigraphy confirms the location of the parathyroid adenoma, while MIBI SPECT/CT offers greater sensitivity, accuracy and anatomical precision than ultrasound for preoperative parathyroid localization, even in the case of ectopic glands or coexisting thyroid pathology.
Conclusion
The association of a parathyroid adenoma with normo vesicular thyroid adenomas is extremely rare. Removal of the parathyroid adenoma should be completed by loboisthmectomy or total thyroidectomy, depending on the indication.

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EP1541

JOINT1207

Residual thyroid tissue post-thyroidectomy: a hidden driver of Graves' disease

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Introduction

Graves' disease is an autoimmune thyroid disorder characterized by hyperthyroidism and elevated thyroid-stimulating antibodies (TRAbs). Management can be particularly challenging in patients with residual thyroid tissue post-thyroidectomy, especially when complicated by Graves' orbitopathy.

Case Report

A 48-year-old woman with a history of Graves' disease was referred to the endocrinology consultation for the recurrence of her condition. She had undergone total thyroidectomy in 2015 due to diagnosis of Graves' disease, followed by levothyroxine replacement therapy. In 2022, she developed tremors, anxiety, palpitations, and bilateral exophthalmos. Laboratory tests confirmed thyrotoxicosis with markedly elevated thyroid-stimulating hormone receptor antibodies (TRAbs) (>40 IU/l). Following this, she underwent a progressive reduction in levothyroxine dosage, ultimately stopping the medication. Despite being off levothyroxine for the six months prior to referral, she remained euthyroid on subsequent thyroid function tests. The patient had a significant history of smoking (20 UMAs) and presented with marked bilateral exophthalmos on examination. Ultrasounds showed a hypoechoic, heterogeneous nodule at the left and right surgical sites. Thyroid scintigraphy confirmed the presence of hyperfunctioning nodules in the surgical site and additional ectopic tissue in the thyroglossal duct/submental region. Given her euthyroid state, antithyroid drugs were not initiated, and radioactive iodine was avoided due to her significant Graves' orbitopathy. Recent laboratory tests, performed without any directed therapy, revealed thyroid-stimulating hormone (TSH) 1.05 µIU/ml, free thyroxine (FT4) 0.82 ng/dl (N: 0.70–1.48), free triiodothyronine (FT3) 3.15 pg/ml (N: 1.71–3.71), and TRAbs 47 IU/l. Surgical intervention was considered the best option to remove the residual thyroid tissue and prevent further progression of orbitopathy and thyroid autoimmunity. Smoking cessation was also strongly encouraged. The patient has surgery scheduled soon.

Conclusion

This case underscores the challenges in managing Graves' disease when residual thyroid tissue persists post-thyroidectomy, even in euthyroid patients. The persistence of elevated TRAbs and the risk of exacerbating orbitopathy highlight the need for a tailored treatment approach, involving careful monitoring and surgical intervention to prevent disease recurrence and minimize complications.

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EP1542

JOINT1824

Case report: graves' disease after hemithyroidectomy

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Introduction

Although the most common cases of hyperthyroidism are due to Graves' disease, it is a rare circumstance when this condition occurs in patients with personal history of thyroid lobectomy. This is a case report of newly developed Graves' disease in a female patient with concomitant urinary system disorder, three years after partial thyroidectomy.

Case presentation

We present the case of a 57 years-old female with previous history of left hemithyroidectomy for large follicular thyroid adenoma, 3 years before. Thyroid function had been normal before surgery, with negative TPO antibodies and normal ultrasonographic appearance of the right thyroid lobe. Postoperatively, she received low dose of levothyroxine replacement therapy until her current presentation in our service. Her medical history included anterior pelvic exenteration for infiltrative carcinoma of the urinary bladder in 2019, post-operative radiotherapy and surgery for left aortic arterio-ureteral fistula, resulting in left nephrostomy, right ureterostomy and chronic kidney disease. Currently, she addresses to the endocrinology department complaining of weight loss, spontaneous retrobulbar pain, diplopia and hyperlacrimation. Thyroid function tests show TSH supression and increased FT4 (x 1.1 above ULN). Six weeks after discontinuation of levothyroxine therapy, thyroid function remains unchanged, TPO antibodies are slightly elevated (25 U/ml) and anti-TSH receptor antibodies present high levels (8.7 U/l- 5 times ULN). Ultrasonography revealed enlarged right thyroid lobe, with heterogeneous echotexture and hypervascularisation on color Doppler exam. Detailed ophtalmological evaluation is yet to be completed. Initiation of methimazole therapy is recommended and regular endocrine evaluation will be performed.

Conclusion

The physiopathological mechanism involved in the occurence of Graves' disease following hemithyroidectomy is still unclear. It may imply an overactive immune response, genetic factors or an environmental component. So far there are no predictive factors associated with development of this condition that are worth taken into account preoperatively. No cases showing association between bladder neoplasm and thyroid autoimmune disease or thyroid adenoma have been reported in the literature so far.

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EP1543

JOINT2475

Hypercalcemia secondary to postlaryngectomy thyroiditis: a case report

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Introduction

Thyroid damage is a complication of total laryngectomy and may be caused by manipulation of the gland. There are isolated descriptions in the literature related to transient hyperthyroidism post-head and neck surgery. Hypercalcemia is an infrequent element in patients with hyperthyrodism. The appearance of a hypercalcemic crisis can trigger serious complications for the patient, being an exceptional event in patients with thyrotoxicosis

Case Report

We report the case of a 58-year-old man who underwent total laryngectomy and left thyroidectomy for a pyriform sinus tumor. Twenty days after the intervention, frank hyperthyroidism was detected (TSH 0.01, FT4 3.34, T3 4.82) with negative thyroid autoimmunity. Concomitantly, hypercalcemia was detected with calcium corrected for albumin of 11.2 and suppressed PTH with a good response to hydration and treatment with glucocorticoids. PTHrp was requested with results within normal limits. After 2 weeks, thyroid function and phosphocalcium metabolism normalized.

Conclusions

Post-laryngectomy thyroiditis has a prevalence of up to 54.6% in some series. Hypercalcemia is an uncommon element in patients with hyperthyroidism, the symptoms overlap with hyperthyroidism and its primary identification requires a high index of suspicion. The appearance of a hypercalcemic crisis can trigger serious complications in the patient, this being an exceptional event in patients with thyrotoxicosis. The hypercalcemia suppression test with steroids is of great clinical utility in its association with thyrotoxicosis to rule out concurrent hyperparathyroidism. We suggest measuring thyroid function and phosphocalic metabolism in the routine analysis of patients undergoing total laryngectomy.

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EP1544

JOINT3381

Riedel's thyroiditis: a diagnosis not to be overlooked

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Introduction

Riedel's thyroiditis is a rare form of chronic thyroid inflammation characterized by extensive fibrosis extending beyond the thyroid gland, often mimicking thyroid malignancy. The objective of this study is to analyze the epidemiological,

clinical, and histopathological characteristics of this condition, along with its evolutionary patterns and therapeutic approaches.
Methods
We report three cases of Riedel's thyroiditis managed at the ENT and Cervicofacial Surgery Department of Farhat Hached Hospital in Sousse.
Results
Our series included two men and one woman, with a mean age of 41 years. The primary complaint in all cases was an anterior lower cervical swelling, without any compressive symptoms. Clinical examination revealed a well-defined, firm, painless, and mobile anterior cervical mass with intact overlying skin and no palpable cervical lymphadenopathy. Vocal cord mobility was preserved in all patients. Cervical ultrasound was performed in all cases, and one patient underwent thyroid scintigraphy. The initial surgical approach consisted of lobectomy with isthmectomy in all patients. In one case, the thyroid lobe was strongly adherent to the trachea, while in another case, it was adherent to the infrahyoid muscles. The diagnosis of Riedel's thyroiditis was confirmed histopathologically. Additionally, one patient was found to have an intrathyroidal micropapillary carcinoma of the follicular variant, necessitating completion thyroidectomy.
Conclusion
Riedel's thyroiditis remains an enigmatic entity with an unknown etiology. Its management involves a discussion between conservative surgery and medical treatment, including corticosteroids, tamoxifen, and mycophenolate mofetil, with treatment protocols potentially guided by additional paraclinical findings.

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EP1545

JOINT3715

Thyroid surgery in children: Indications and outcomes

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Introduction
Thyroid nodules are rare in the pediatric population, with a predominance in females. Benign thyroid nodules and Graves' disease are the most common surgical indications. Surgical management can be challenging in children. This study explores indications, surgical techniques, and outcomes of thyroid surgery in children.
Matériel et méthodes:
This is a retrospective study conducted in the ENT department at Fattouma Bourguiba Hospital in Monastir over a four-year period, from January 2021 to December 2024., involving 16 cases that underwent thyroid surgery.
Résultats:
Our series includes 16 cases that underwent thyroid surgery. Among these patients, 15 cases were operated on for thyroid nodules, and one patient underwent surgery for Graves' disease resistant to medical treatment. The average age was 16.61 years, with extremes ranging from 13 to 17 years, and the sex ratio was 0.05 (1 male/17 females). Regarding medical history, one child was followed for Graves' disease, one for congenital hypothyroidism, and two cases had adrenal insufficiency. These children presented with anterior low cervical swellings without signs of compression. On examination, an anterior low cervical swelling, mobile on swallowing was found in all cases, measuring 3 to 5 cm, along with firm, mobile, painless cervical lymphadenopathies of 2 cm in one patient. Ultrasound findings showed an EUTIRADS 2 nodule in two cases (32–40 mm), EUTIRADS 3 in 11 cases (26–40 mm), EUTIRADS 4 in four cases (17–42 mm), EUTIRADS 5 in two cases (26 and 27 mm), and one case of a hypervascularized goiter suggestive of Graves' disease. Fine needle aspiration of a lymphadenopathy was performed in one patient, which was suggestive of metastasis from a papillary carcinoma. A lobectomy was performed in nine cases, total thyroidectomy in seven cases, mediastinal-recurrent lymph node dissection in two cases, and functional neck dissection in one patient. Postoperative outcomes were uneventful in all cases, with only one case of postoperative hypocalcemia, which was corrected with calcium supplementation. Histopathological examination revealed a benign nodule in 13 cases, a follicular carcinoma in one case, and a papillary carcinoma in two cases, which were referred to nuclear medicine for radioactive iodine treatment.
Conclusion
Pediatric thyroid pathologies requiring surgery are much rarer than in adults. Thyroid nodules in children should be evaluated with ultrasound and fine-needle aspiration cytology to assess the risk of malignancy. This approach will ensure appropriate surgical management.

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EP1546

JOINT170

Etiological insights into autoimmune hypothyroidism

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Introduction
Hypothyroidism is a common endocrine disorder characterized by a deficit in thyroid hormone production. This condition can arise from various underlying etiologies, predominantly autoimmune in nature. This study aimed to analyze the etiological spectrum of hypothyroidism in a cohort of patients followed in our center.
Materials and Methods
We conducted a retrospective study of patients diagnosed with hypothyroidism. The diagnosis was based on clinical presentation, hormonal assays, and the detection of thyroid-specific autoantibodies, including anti-thyroperoxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies.
Results
Two main etiologies were identified in our cohort. Hashimoto's chronic lymphocytic thyroiditis was the most frequent cause of hypothyroidism, diagnosed in 69 patients. This group included 59 women and 10 men, with a mean age of 37.8 years. Anti-TPO antibodies were positive in 62 patients, while anti-Tg antibodies were positive in 41 cases, confirming the autoimmune nature of the disease. Chronic atrophic lymphocytic thyroiditis was less frequent, identified in 4 patients (3 women and 1 man) with a mean age of onset of 56 years. This diagnosis was based on a combination of late onset, thyroid atrophy observed on ultrasound, and positive autoantibody tests. Anti-TPO antibodies were positive in 3 cases, and anti-Tg antibodies were positive in 3 cases.
Conclusion
Hashimoto's thyroiditis is the leading cause of hypothyroidism in our cohort, predominantly affecting women in their late 30s. Chronic atrophic lymphocytic thyroiditis, while less common, presents at a later age and is characterized by thyroid atrophy and positive autoantibodies. These findings underscore the importance of detailed clinical evaluation and immunological testing in the diagnosis and management of hypothyroidism.

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EP1547

JOINT1914

Prevalence and caracteristics of thyroid carcinoma in patients having Hashimoto's thyroiditis

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Objective
The aim of our study was to determine the prevalence and caracteristics of thyroid carcinoma and Hashimoto's thyroiditis (HT) coexistence in histopathologic material of thyroidectomized patients.
Matherials and Methods
In a retrospective study, the clinicohistopathologic data of patients who underwent a thyroidectomy and had HT in the histopathological specimen, from the 1st of January 2018 to the 31st july 2023 were analyzed.
Results
Our serie includes 73 patients who have HT and are all female. 16 patients have a thyroid dysfunction. The only histological type present is papillary thyroid carcinoma(PTC). Thyroid carcinoma(TC) was detected in four cases and microcarcinoma(TMC) in three cases. The mean tumor diameter was 17 mm in the TC group and 6.5 mm in the TMC group. Oncocytic variant of PTC was detected in two cases in the TC group while vesicular variant of PTC was detected in the other two cases. Oncocytic variant of PTC was detected in two cases in the MTC group while tall cell variant was detected in one case. Bilaterality was detected in one case and multifocality was detected in two cases of TC group. There is no bilaterality or multifocality detected in the MTC group. Capsular effraction and vascular embol was detected in one case of TC group and no case of MTC. One patient underwent a recurrent lymph node dissection and no metastasis was detected.
Conclusion
We suggest that prevalence of PTC in patients having HT is low and have less agressive features

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EP1548

JOINT2497

Association of papillary and medullary thyroid carcinoma: a report of 3 cases

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Introduction
Papillary thyroid carcinoma (PTC), derived from follicular cells, is a common entity in endocrine oncology. In contrast, medullary thyroid carcinoma (MTC) is a less frequent pathology. The simultaneous occurrence of these two cancers is rare. We report three patients presenting with both PTC and MTC during the management of thyroid neoplasia, followed at the nuclear medicine department of CHU Sahloul.
Case Reports
Case 1: A 68-year-old female with a history of pulmonary and cutaneous sarcoidosis presented with a cervical swelling. The cervical ultrasound revealed signs of malignancy, which were confirmed by fine-needle aspiration cytology (FNAC), prompting a total thyroidectomy (TT) with bilateral mediastino-recurrent lymph node dissection (MRLD). Histopathological examination identified a micro-PTC measuring 0.2 cm and an MTC measuring 1.5 cm in the left lobe, with no lymph node involvement. The patient received ablative radioactive iodine (RAI) therapy (30 mCi) and showed favorable biochemical and morphological outcomes for PTC. **Case 2:** A 44-year-old female discovered a 1 cm cervical swelling during self-palpation. Cervical ultrasound revealed a poorly defined hypoechogenic nodule with microcalcifications, classified as EU-TIRADS V. She underwent TT with bilateral MRLD. Histopathological analysis revealed a mixed medullary and papillary carcinoma of the right thyroid lobe, with no lymph node metastasis. The PTC was classified as pT1aN0Mx, and the MTC as T3N1b. She received ablative RAI therapy (100 mCi) with a good biochemical and morphological response for PTC. **Case 3:** A 69-year-old male with diabetes presented with a suspicious lateral cervical swelling. Cervical ultrasound showed a 28 mm thyroid nodule classified as EU-TIRADS V, along with markedly elevated calcitonin levels (>5000 ng/ml). Preoperative staging was negative for distant metastasis, and the patient underwent TT with bilateral MRLD. Histopathology revealed a low-grade MTC in the right lobe measuring 4.4 cm (classified as pT3bN1bM0) and a millimetric PTC (classified as pT1aN1aM0). The patient received ablative RAI therapy (30 mCi) with favorable biochemical and morphological outcomes. Postoperatively, calcitonin levels decreased to 47 ng/ml. A follow-up by cervical ultrasound and serum calcitonin was indicated.
Conclusion
The synchronous association of MTC and PTC is rare, with only a few cases reported in the literature. This observation highlights the importance of preoperative calcitonin testing in patients with thyroid nodules. The prognosis primarily depends on the MTC, as PTC typically has a favorable prognosis and slow progression.

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EP1549

JOINT2257

Navigating the thin line of risks and benefits: a case of nivolumab-induced hypothyroidism in a patient with metastatic melanoma

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Background
Nivolumab is a monoclonal antibody directed against programmed cell death-1 (PD-1) and has become an effective treatment for metastatic melanoma. It enhances the cell-mediated killing of cancer cells however, it inadvertently increases the risk of autoimmune attack, which leads to various endocrinopathies, including hypothyroidism.
Case Presentation
A 48-year-old male with metastatic melanoma to the brain, who is currently undergoing monthly Nivolumab infusion, presented to the clinic with a 3-week history of fatigue, cold intolerance, and constipation. Vital signs were normal. Physical examination showed an intact sensorium, a symmetrically enlarged and nontender thyroid, and no skin changes. Laboratory tests were remarkable for a TSH of 27.1mIU/l (ref 0.3-4mIU/l), free T4 of 0.7 ng/dl (ref 0.9-1.7 ng/dl), negative thyroid receptor and thyroid peroxidase antibodies, and thyroid ultrasound showed a diffusely enlarged thyroid with low iodine uptake on the thyroid scan. No other hormonal abnormalities were detected. The endocrinology team was consulted, and the patient was started on Levothyroxine, which improved her symptoms, and the oncology team suggested temporarily discontinuing Nivolumab with frequent thyroid function monitoring and strict endocrinology and oncology follow-up.
Discussion
The incidence of Nivolumab-induced hypothyroidism is as high as 6.5%. It develops within 3-4 weeks of treatment. Smoking, hypertension, and other autoimmune diseases are risk factors. Thyroid autoantibodies are most often normal but can be elevated in some patients and a low TSH may indicate hypophysitis. Spontaneous thyroid recovery can occur. However, thyroid hormone replacement with serial measurements of thyroid function is often required. Because PD-1 inhibitors remain central in managing advanced melanoma, discontinuation may not be feasible, and continuation can be considered with close monitoring. Interestingly, according to Basak *et al*, the development of overt thyroid symptoms with higher antithyroid antibody levels during anti-PD-1 treatment of melanoma was associated with a significant improvement in overall and progression-free survival rates likely because of better malignancy response from treatment.
Conclusion
Immune checkpoint inhibitors such as Nivolumab remain central in managing different malignancies. However, all physicians should be aware of their potential endocrine adverse effects. In patients who develop Nivolumab-induced hypothyroidism, hormonal replacement with Levothyroxine is often needed. A multidisciplinary approach should be pursued for close monitoring and for patients to have a guided decision regarding possible Nivolumab continuation.
Reference
Basak EA *et al*. 2020 Overt thyroid dysfunction and antithyroid antibodies predict response to anti-PD-1 immunotherapy in cancer patients. Thyroid. Epub 2020 Mar 10. PMID: 32151195.

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EP1550

JOINT17

Challenges to implement thyroid cancer guidelines for thyroid surgeons of Bangladesh

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Objective
Numerous published guidelines have described the optimal management of thyroid cancer. However, these rely on the clinical availability of diagnostic and therapeutic modalities. We hypothesized that the availability of medical resources and economic circumstances vary in Asia-Pacific countries, making it difficult to implement guideline recommendations into clinical practice.
Methods
We surveyed participants at the 2009 and 2013 Congresses of the Association of Southeast Asian Nations Federation of Endocrine Societies by distributing questionnaires to attendees at registration.
Results
Responses were obtained from 268 respondents in 2009 and 163 respondents in 2013. Similar to the high prevalence of low-risk thyroid cancer observed in the Surveillance, Epidemiology, and End Results database, across the Asia-Pacific countries surveyed in 2009 and 2013, 50 to 100% of the respondents from the Philippines, Malaysia, Singapore, China, Taiwan, Thailand, Hong Kong, Korea, and Sri Lanka reported that more than 50% of the patients had low-risk thyroid cancer on follow-up. Importantly, there was much variation with regards to the perceived availability of investigation and treatment modalities.
Conclusion
We found a wide variation in clinicians' perception of availability of diagnostic and therapeutic modalities in the face of a rise in thyroid cancer incidence and thyroid cancer management guidelines that emphasized their importance. The lack of availability of management tools and treatments will prove to be a major barrier to the implementation of thyroid cancer management guidelines in Southeast Asia, and likely in other parts of the world as well.

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EP1551

JOINT387

Thyroid tissue in a cervical lymph node is not always malignant: A case report

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Thyroid tissue in cervical lymph nodes is an interesting and rare phenomenon that cannot be explained by embryology. It is often considered to be a metastasis of a primary thyroid malignancy. Since sixties, several cases of benign ectopic thyroid cervical lymph node tissue have been reported. Distinguishing between ectopic thyroid tissue, a metastasis or primary thyroid cancer in a cervical lymph node is very challenging. Our case is a 32- year - old mother assumed that she had had a hemothyroidectomy 10 years earlier. She was presented with a neck mass which was found to be two TIRADS 5 thyroid nodules over remnant of inflamed thyroid tissue from a previous surgery. FNAC revealed Bethesda III (atypia of undetermined significance) tissue. CT Neck was done and revealed extra-thyroidal extension of thyroid nodule with ipsilateral suspicious lymph node with very high thyroglobulin level. After total thyroidectomy with lymphadenectomy, frozen samples of the excised lymph node revealed just benign thyroid tissue. Samples were confirmed with IHC and conservative plan of management was done. Levothyroxine was given in a replacement dose. Before 2017 there were just 17 cases of benign thyroid tissue in cervical lymph nodes worldwide. Meanwhile, many studies supported the idea of conservative management of accidentally found thyroid tissue in a lymph node. Moreover, the origin and pathogenesis of ectopic thyroid tissue in cervical lymph nodes is still unclear and cannot be explained by current embryological theories. To date, this Phenomenon has only been reported in women. Here we showed that benign thyroid tissue in cervical lymph nodes can occur in the absence of a primary thyroid malignancy. Immunohistochemistry and molecular diagnostics in addition to conventional pathology can aid in making the distinction between benign and malignant thyroid tissue in cervical lymph nodes. We recommend a conservative approach if pathology shows benign thyroid tissue in cervical lymph nodes.

Key Words
Thyroid Malignancy – Cervical lymph node – Thyroid Surgery Conflict of Interest No conflict to disclosure

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EP1552

JOINT1869

Pitfalls in the management of a palpable pediatric thyroid nodule: a case report

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Background
Thyroid nodules in children are reported to be at 2-3-fold increased risk of being malignant when compared to thyroid nodules in adults. The risk for children of a thyroid nodule (> 1 cm) being malignant is 20–25% compared to in 5–10% for a thyroid nodule in adults, respectively. Pediatric differentiated thyroid carcinoma (DTC) is a rare disease; however, its worldwide incidence is rising. The most common presentation for DTC in children is that of a thyroid nodule.
Case report
A 13-year-old adolescent girl was referred to our health insurance endocrine clinic for a clinically concerning thyroid swelling. She presented with 2-year history of a neck swelling. She had no complaints, no local compressive symptoms or dysphagia. There was no history of head or neck irradiation and no family history of thyroid cancer. She had normal vital signs with a BP of 110/70, pulse of 67. Her exam was significant for a diffusely enlarged thyroid gland with an irregular contour and a firm nodule 2x1.5 cm on the RT lobe. The rest for her physical exam was completely normal. TSH was 1.47 mcIU/ml, Ft4 was 1.28 ng/dl and she had positive anti-thyroid peroxidase: > 600 and Anti-thyroglobulin antibodies: 395. Our patient had an abnormal thyroid exam for as long as two years prior to being seen in our health insurance clinic. Unfortunately, she was not examined or investigated properly. Parents were reassured as there was no aggressive symptoms, her thyroid function tests within normal and positive thyroid antibody tests. Based on the clinical examination, ultrasound thyroid was requested, and the report showed: multinodular goiter with hypoechogenicity and solid nodules, largest one in the RT lobe is wider than taller solid hypoechoic nodule with irregular margin and measures about 28.7x24.5 mm (TR4 nodule pattern, moderately suspicious nodule pattern for FNAC) with few bilateral cervical lymphnodes. A fine-needle aspiration biopsy of the RT thyroid nodule was performed. The cytology diagnosis was: "papillary thyroid carcinoma". Accordingly was referred for surgical removal.
Conclusion
As palpable thyroid abnormalities have a higher risk of malignancy in children and the risk of surgical complications can be significant, so they should be closely monitored with suspicion and worked up aggressively for possible malignancy even in the face of initially negative diagnostic testing.

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EP1553

JOINT3507

Shear wave elastography (SWE) in the evaluation of thyroid tissue in children and adolescents with autoimmune thyroiditis

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Background
Hashimoto's thyroiditis and Graves' disease are autoimmune thyroid diseases (AITDs) mainly diagnosed on the basis of clinical symptoms, hormonal analysis, positive autoantibody titres and ultrasound (US). However, there is a group of patients who, despite developing autoimmunity in the thyroid, do not show typical ultrasound findings or an increase in antibody titres. It is well known that the autoimmune process alters the echogenicity, echostructure and vascularity of thyroid tissue and is associated with the presence of focal changes within the gland, which influences the mechanical properties of the affected tissue like tissue stiffness and elasticity. Shear wave elastography (SWE) is a non-invasive and painless to the patient ultrasound diagnostic method evaluating tissue's stiffness. Recent data suggest that elastography may improve the accuracy of differential diagnosis of thyroid diseases. The purpose of the study is to assess the thyroid elasticity in children and adolescents with autoimmune thyroid disease in comparison to heathy thyroid children.
Methods
74 pediatric patients with AITDs and 30 heathy thyroid children as a control are enrolled to the study and qualified to SWE which is followed by conventional US. SWE based on Young's modulus is expressed in kPa. In addition, patients have their thyroid hormone levels and antithyroid antibody titers evaluated.
Results
Our results indicate that thyroid tissue elasticity in patients with Hashimoto's thyroiditis and Graves's disease is reduced in comparison to those with normal thyroid parenchyma.
Conclusion
The results of our study suggest that SWE might be a viable diagnostic method for suspection of AITD in children, however it still seems to need further studies in a bigger group of pediatric patients.

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EP1554

JOINT4015

Common but unexpected autoimmune endocrine disorders in pregnancy – case reports

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Autoimmune diseases are rarely diagnosed during pregnancy due to physiological immunosuppression. Clinical hyperthyroidism affects only 0.1–0.4% of pregnancies, with Graves' Disease (GD) responsible for 85% of cases. This report describes three cases of GD in healthy pregnant women with no prior thyroid dysfunction and one case of diabetic ketoacidosis (DKA) at delivery as the initial presentation of diabetes *mellitus*. 1. A 28-year-old woman, at 10 weeks of gestation: TSH <0.01mU/l(N 0.35–4.94), T4L 4.03ng/dl(N 0.7–1.48), T3L 16.8pg/ml(N 2.3–4.2), TSH receptor antibodies (TRAbs)11.0 (positive). Treatment was initiated with propylthiouracil (PTU) 50 mg 3id. At 15 weeks: TSH 0.03mU/l, T4L 0.50ng/dl, T3L 2.0pg/ml, leading to discontinuation of the antithyroid drug (ATD); at 29 weeks, TRAbs 2.6 (negative). At the first postpartum visit, she was euthyroid;14 weeks after delivery, GD recurred: TSH

0.01mU/l, T4L 2.51ng/dl, T3L 9.2pg/ml, TRAbs 5.4(positive). Methimazole 10 mg id was initiated. 2. A 32-year-old woman at 10 weeks of gestation: TSH 0.01mU/l, T4L 1.64ng/dl, T3L 4.9pg/ml, TRAbs 3.2(positive). PTU 50 mg id was started and discontinued at 20 weeks (TSH <0.01mU/l, T4L 0.79ng/dl, T3L 2.8pg/ml, TRAbs 2.9 (negative). She remained off therapy and, at six weeks postpartum, was euthyroid with TRAbs 2.4(negative). She is awaiting further evaluation. 3. A 34-year-old woman at 16 weeks of gestation: TSH <0.01mU/l, T4L 2.03ng/dl, T3L 7.8pg/ml, TRAbs 12.0(positive), initiating PTU 50 mg twice daily. At 19 weeks: TSH <0.01mU/l, T4L 0.84ng/dl, T3L 3.6pg/ml, leading to an adjustment to PTU 50 mg id. At 23 weeks, PTU was stopped due to TSH 0.02mU/l, T4L 0.86ng/dl, T3L 3.8pg/ml. She remained off ATD until delivery and is awaiting postpartum reassessment. 4. A 29-year-old woman, at 37 weeks of gestation was admitted to the Emergency Department with polydipsia, polyuria, weight loss, glycosuria (>1000 mg/dl) and hypertension. A cesarean section due to fetal distress was performed. Her fasting glucose in the first trimester was 81 mg/dl, and an oral glucose tolerance test(OGTT) at 26 weeks showed 84/149/119 mg/dl. During labor, sustained capillary glucose levels >500 mg/dl were observed, with pH 7.293, HCO3-9.5 mmol/l, lactate 2.3 mmol/l, ketonemia 4 mmol/l. Intravenous insulin infusion was initiated, with a favorable response. Good glycemic control was achieved after 19 hours. An intensive insulin therapy regimen was introduced. She was discharged after seven days of hospitalization. She is awaiting further evaluation and the results of autoantibody tests for T1DM. Despite the diagnosis of autoimmune disorders during pregnancy is rare, early detection and management of these conditions are essential to prevent maternal and fetal complications. Individualized follow-up is crucial for optimizing outcomes.

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EP1555

JOINT3630

Outcomes of thyroid lobectomy in bethesda v and vi nodules: a clinical analysis

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Introduction
Thyroid nodules classified as Bethesda V (suspicious for malignancy) and Bethesda VI (malignant) present diagnostic and therapeutic challenges. Thyroid lobectomy is a possible surgical approach for these nodules, that may reduce morbidity, compared to total thyroidectomy, while ensuring oncologic safety. This study evaluates the efficacy and outcomes of lobectomy in patients with Bethesda V and VI cytopathology results, in order to optimize surgical decision-making and minimize complications.
Materials and Methods
We retrospectively revised and analysed the clinical data from seven patients with Bethesda V and VI nodules who underwent thyroid lobectomy in our hospital between 2022 and 2024, followed-up for ≥6 months.
Results
All seven patients were female, with a mean age at diagnosis of 59.6 years and a median follow-up time of 19 months. Only one patient had a personal history of cervical irradiation and there was no family history of thyroid malignancy. Four nodules were Bethesda VI and three were Bethesda V, all measuring less than 2 cm. Two patients presented with contralateral nodules (<1 cm). Papillary thyroid carcinoma was histologically confirmed in all cases, comprising six classic variants and one follicular variant. The mean tumor size was 9.3 mm and all tumors were unifocal, without evidence of angioinvasion, perineural invasion or lymph node metastasis. Microscopic extrathyroidal extension was noted in two patients. At six-month follow-up, five patients showed no evidence of disease, while two had an indeterminate response due to nonspecific imaging findings. These results remained consistent at the latest follow-up. No patients required completion thyroidectomy, and all are currently on levothyroxine to maintain target TSH levels (0.5-2 mU/l).
Conclusions
This study highlights the favourable outcomes of thyroid lobectomy in managing patients with Bethesda V and VI nodules, demonstrating its efficacy for small papillary thyroid carcinomas. With no cases requiring completion thyroidectomy and high remission rates, lobectomy proves to be a safe and effective approach in appropriately selected cases, minimizing patient morbidity.

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EP1556

JOINT949

Comprehensive summary of studies on goiterous hypothyroidism in infants and children: patient characteristics, treatment, and prognosis"

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Background
Goitrous hypothyroidism in infants and children represents a critical endocrine disorder with significant implications for growth, neurodevelopment, and overall prognosis. This condition arises from diverse etiologies, including genetic mutations, iodine deficiency, and autoimmune thyroiditis. Recent advances in diagnosis and treatment underscore the importance of timely intervention to improve outcomes.
Objective
To provide a comprehensive review of studies on goiterous hypothyroidism in infants and children, focusing on patient characteristics, treatment approaches, outcomes, and prognosis.
Methods
A systematic review of relevant studies published between 1995 and 2023 was conducted. Data from primary research, case reports, and review articles were analyzed to compile patient characteristics, treatment modalities, and outcomes. Studies were arranged chronologically to reflect advancements in understanding and management.
Results
Ten studies were reviewed, encompassing 267 patients with goiterous hypothyroidism. Key findings include the following:
1. Patient Characteristics:
• Conditions ranged from congenital hypothyroidism (CH) due to thyroid dysgenesis or dyshormonogenesis to autoimmune thyroiditis and fetal hypothyroidism linked to maternal Graves' disease.
• Presenting symptoms varied, with neonatal respiratory distress and goiter being hallmark findings in severe cases.
• Risk factors included prematurity, family history of goiter, and maternal thyroid dysfunction.
2. Treatment Approaches:
• Levothyroxine remains the cornerstone of therapy, administered orally or intra-amniotically in fetal cases.
• Advances such as liquid levothyroxine formulations and prenatal thyroxine delivery via amniotic fluid were highlighted.
• Case reports emphasized the role of cordocentesis and ultrasonography in diagnosing and monitoring fetal thyroid function.
3. Outcomes and Prognosis:
• Early intervention consistently improved growth and neurodevelopmental outcomes.
• Intrauterine thyroxine resolved goiter in fetal cases, with normal postnatal thyroid function observed.
• Persistent hypothyroidism required long-term therapy in a subset of children with CH, while others experienced complete resolution.
Conclusion
This review underscores the critical role of timely diagnosis and tailored treatment in managing goiterous hypothyroidism in infants and children. Levothyroxine therapy, particularly in innovative forms, demonstrates robust efficacy in resolving goiter and normalizing thyroid function. Future research should focus on genetic etiologies and long-term outcomes to enhance individualized care. The chronological synthesis of data highlights the evolution of therapeutic strategies and their impact on prognosis.
Keywords
Goiterous hypothyroidism, infants, children, levothyroxine, treatment outcomes, prognosis, congenital hypothyroidism, intra-amniotic therapy.
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EP1557

JOINT2284

Unraveling MEN syndrome: how genetic testing illuminates complex family histories and improves patient outcomes

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RET mutations drive the development of multiple endocrine neoplasia (MEN) syndromes, including medullary thyroid carcinoma (MTC) and pheochromocytoma. We present three families with distinct RET mutations, revealing the complex clinical spectrum and hereditary patterns. The findings underscore the neccesity of early genetic screening and diagnosis. A male patient, aged 18 in 1977, was diagnosed with MTC. At that time, he underwent a subtotal thyroidectomy, as it was the standard procedure. In 2005, he required a total thyroidectomy due to disease recurrence, and again in 2014 for a further recurrence. Additionally, the patient was diagnosed with pheochromocytoma and primary hyperparathyroidism. Genetic testing in 4 out of 13 of his family revealed the presence of a RET mutation (c.1900 T>C, p. Cys634Arg, exon 11), in 3 members across 4 generations (one is asymptomatic), 1 being negative. The second family carries a germline RET mutation (c.1852T>C, p. Cys618Arg, exon 10) which was identified through testing a 43-year-old female patient, initially diagnosed with MTC. She underwent a total thyroidectomy, but with minimal residual disease and secondary lymphatic metastases. Genetic testing in 7 out of 21 family members across 3 generations revealed 5 positive for the same RET mutation (2 asymptomatic), including her two daughters (one of whom has MTC, and the other had MTC and pheochromocytoma), as well as in a nephew diagnosed with Hirschsprung disease, 2 being negative. The third family we are presenting carries a RET mutation (c.1902C>G, p. Cys634Trp, exon 11), identified in a 52-year-old male patient who initially presented with symptoms suggestive of pheochromocytoma, subsequently confirmed and surgically resected. The patient also has a diagnosis of MTC. Genetic testing in this family revealed the same RET mutation in his daughter (who has MTC) and his nephew (who has bilateral pheochromocytoma and MTC). In this family, across 2 generations, 8 out of 30 family members were tested: 6 were positive, 2 negative. From those postive, 2 were asymptomatic, while other 2 presented only MTC, and 2 MTC+Pheo. In conclusion, these families highlight the critical role of looking for RET mutations in the development of multiple endocrine neoplasia and related disorders. The diverse clinical manifestations observed—such as MTC, pheochromocytoma, and hyperparathyroidism—underscore the importance of genetic screening and family history evaluation for early diagnosis and proper management. Early detection, appropriate surveillance, and genetic counseling are key to improving outcomes and preventing further complications in affected families.

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EP1558

JOINT28

A rare case of palpation thyroiditis following parathyroidectomy

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Introduction

Sporadic thyrotoxicosis following manipulation of thyroid gland during neck surgeries, in particular parathyroid surgeries, has been infrequently described in medical literature and remains largely underrecognised today. We describe a rare case of palpation thyroiditis following parathyroidectomy.

Case Report

A 57-year-old Chinese female with background of end-stage renal disease (ESRD) complicated by tertiary hyperparathyroidism was electively admitted for total parathyroidectomy. She had no known thyroid disorders and was asymptomatic with no history of neck pain or irradiation. Intra-operatively, both thyroid lobes were mobilised and three parathyroid glands were excised except for the right superior gland which could not be definitively located. After parathyroidectomy, the patient remained asymptomatic but was found to have sinus tachycardia on post-operative day two. A thyroid function test done showed elevated free thyroxine (T4) at 53 pmol/l (8 - 16 pmol/l), elevated free triiodothyronine (T3) at 9.0 pmol/l (3.5 - 6.0 pmol/l) and suppressed thyroid-stimulating hormone (TSH) at 0.22 mIU/l (0.45 - 4.50 mIU/l). This was consistent with thyrotoxicosis, and differential diagnoses included palpation thyroiditis from recent parathyroidectomy and less likely undiagnosed Grave's disease. Further evaluation was then conducted with antithyroid antibody testing and radioiodine uptake thyroid scan. Decision was made to hold off thioamide initiation while awaiting the above investigations given that the patient was asymptomatic and if the diagnosis was truly thyroiditis, her thyrotoxicosis should improve further without treatment. Her thyroid function was closely monitored in the meantime, and she was started on a beta-adrenergic antagonist as needed for palpitations. Subsequently, her antithyroid antibodies including anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-TG) and thyrotropin receptor antibodies (TRAb) returned negative. The Tc-99m pertechnetate thyroid scan showed generally reduced tracer uptake of the thyroid gland suggestive of thyroiditis, with no dominant 'hot' nodule detected. The patient was diagnosed with palpation thyroiditis from recent parathyroidectomy and managed conservatively. Two weeks later, her thyroid function test normalised with no recurrence of sinus tachycardia.

Discussion

It is important to recognise the entity of palpation thyroiditis post-parathyroidectomy – while majority of patients remain asymptomatic for which conservative management is appropriate, some may develop clinically significant thyrotoxicosis requiring further medical treatment.[1] Counselling patients undergoing bilateral neck exploration about this condition, along with prudent post-operative monitoring of thyroid function tests as clinically warranted, is essential for early detection and timely treatment.

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EP1559

JOINT4033

Thyroid eye disease following total thyroidectomy in a complex case of graves' disease with reaction to antithyroid therapy

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A 63-year-old non-smoker male was referred to the endocrinology clinic with symptoms of hyperthyroidism and abnormal thyroid function in November 2022. Initial tests confirmed Grave's disease: TSH <0.03 mU/l (0.35-5.5), FT4: 60.7 pmol/l (10.5-21.0), FT3: >30.8 pmol/l (3.5-6.5), Thyroid Stimulating Immunoglobulins (TSI) 12.8 IU/l (<0.56). Impaired Liver function test (LFT) was noted: (ALT 71 U/ L (10-49), ALP 145 U/l (30-130) and total bilirubin 8 umol/l (0-20). With a normal liver ultrasound, impairment was attributed to hyperthyroidism. The patient was commenced on carbimazole, but hepatic function deteriorated. A liver screen was negative, suggesting carbimazole-related hepatic impairment. Carbimazole was switched to propylthiouracil (PTU), but hepatic impairment persisted, leading to PTU cessation. Due to worsening thyroid function and reaction to antithyroid drugs, the patient was offered urgent total thyroidectomy, with preoperative preparation using Lugol's Iodine. The patient underwent a successful total thyroidectomy in March 2023. Histopathology confirmed diffuse thyroid hyperplasia/Graves' disease. 8 weeks postoperatively, symptoms of mild thyroid eye disease (TED) developed. TSI levels remained detectable at 2 and 3 months postoperatively (4.22 and 3.9 IU/l, respectively). An MRI at 4 months showed bilateral inferior rectus muscle enlargement, consistent with active thyroid ophthalmopathy. The patient was commenced on a 6-month course of selenium. At the 6-month ophthalmology follow-up, the patient had restricted upgaze and left lateral gaze, indicating ongoing TED. Visual function was intact. IV methylprednisolone (IVMP) was considered but not started. At the 10-month follow-up, ocular motility worsened. IVMP was initiated, with significant improvement after six infusions: reduced proptosis, resolution of lid retraction, and decreased upward gaze restriction. Some restrictions persisted, especially in the left upward gaze. Given the incomplete response to IVMP, he was considered for an additional IVMP course with orbital radiotherapy. Following combined therapy, TED became inactive, but diplopia and upward gaze restriction persisted. The strabismus team recommended a right superior oblique tuck or left inferior rectus recession. Monitoring continues whilst awaiting surgery. Graves' ophthalmopathy is known to occur with other endocrine features of thyrotoxicosis, typically occurring within 18 months of the disease. The new development of Graves ophthalmopathy following thyroid surgery is rare. This case highlights a rare example of Graves' ophthalmopathy developing following total thyroidectomy. Healthcare professionals must be aware of the possible late development of Graves' ophthalmopathy following total thyroidectomy and refer for appropriate assessment without delay.

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EP1560

JOINT2903

Thyroid function replacement time after total and subtotal thyroidectomy

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Introduction
Thyroid surgery is usually performed when traditional drug therapy is ineffective, severe complications develop, or the risk of cancer is high. Recovery of body functions after surgery requires a certain period and specific treatments.
Aim
To study the recovery of thyroid function after total and subtotal thyroidectomy.
Materials and Methods
Between 2021 and 2023, 63 patients with thyrotoxicosis syndrome at RIIATEM were diagnosed with diffuse toxic goiter, nodular and multinodular toxic goiter, and underwent total and subtotal thyroidectomy. Of these patients, 11.1% were male, and 88.9% were female, with an average age of 43.48 ± 2.92. A subtotal thyroidectomy was performed on 38.1% of the patients, and a total thyroidectomy on 61.9%.
Results
Pre-surgery TSH levels in the examined patients ranged from 18.7-22.6 ± 1.0 mMe/ml; one month after surgery, these levels were 15.6 ± 0.7 mMe/ml in patients with subtotal thyroidectomy and 26.87 ± 1.08 mMe/ml in patients with total thyroidectomy, indicating clear signs of hypothyroidism. Three months post-surgery, the TSH levels were 10.4 ± 0.7 mMe/ml after subtotal thyroidectomy and 12.37 ± 0.78 mMe/ml after total thyroidectomy. Six months post-surgery, TSH levels decreased significantly to 6.3 ± 0.5 mMe/ml in subtotal thyroidectomy patients and 7.9 ± 0.86 mMe/ml in total thyroidectomy patients. One year post-surgery, the TSH levels were 1.9 ± 0.2 mMe/ml after subtotal thyroidectomy and 1.75 ± 0.17 mMe/ml after total thyroidectomy, nearing standard values.
Conclusions
Thus, the results after surgery indicate the effectiveness of the treatment, with a significant decrease in clinical manifestations of hypothyroidism in patients after thyroidectomy over the time. Immediate replacement therapy after total thyroidectomy thyroid function earlier reached normal ranges than in subtotal thyroidectomy.

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EP1561

JOINT337

Total thyroidectomy for Graves' disease in a patient with down syndrome and glycogen storage disease type ia

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Introduction
Autoimmune disorders are common in patients with Down syndrome (DS), particularly thyroid diseases. In DS patients, hyperthyroidism occurs less frequently than hypothyroidism, is mostly caused by Graves' disease, typically manifests between late childhood and early adulthood, shows no sex predominance, and often requires definitive treatment. There is a lack of consensus on the role of total thyroidectomy in the treatment of Graves' disease in DS patients due to potential anesthetic and surgical risks associated with craniofacial anomalies and short neck. However, surgery may be necessary when Iodine-131 therapy is contraindicated or refused by the family.
Case Presentation
We report the case of a 19-year-old female patient affected by DS and Graves' disease. Medical history included glycogen storage disease type Ia (GSD Ia), a rare autosomal recessive disorder of carbohydrate metabolism, characterized by fasting hypoglycemia, lactic acidosis, hepatomegaly, and risk of developing hepatocellular adenomas. Hyperthyroidism first manifested at the age of 11, with symptoms of fatigue and weight loss. TSH receptor antibody testing was positive (22 IU/l), while no goiter or exophthalmos were observed. She was started on methimazole therapy, up to 20 mg/day, which was discontinued after 3 years due to biochemical remission, without side effects. After 1 year of euthyroidism, Graves' disease relapsed and methimazole therapy was resumed. Given the recurrence of hyperthyroidism and the need for long-term methimazole therapy, particularly in the context of chronic liver disease, a definitive treatment was considered. Following discussion with the family, nuclear radiologist and endocrine surgeon, total thyroidectomy was preferred over Iodine-131 therapy. Because of GSD Ia-related risk of hypoglycemia and lactic acidosis, perioperative management included infusion of dextrose-containing solution and frequent monitoring of blood glucose and lactate. Total thyroidectomy was performed with a conventional surgical approach. No significant bleeding or recurrent laryngeal nerve paresis occurred, however, the patient developed transient hypocalcemia (down to 7.8 mg/dl), which resolved within 1 month. She was discharged on a liquid levothyroxine formulation due to fasting limitation, requiring frequent high-carbohydrate meals with uncooked corn-starch supplementation. Histological examination documented diffuse hyperplasia with interstitial lymphocytic infiltrates.
Conclusion
To our knowledge, there is limited evidence in the literature regarding the preferred definitive treatment for Graves' disease in individuals with Down syndrome. Our case suggests that total thyroidectomy may be a safe and effective treatment option for these patients. A multidisciplinary discussion—including endocrinologists, pediatricians, endocrine surgeons, nuclear radiologists, as well as the patient's and family's preference—is required.

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EP1562

JOINT1983

Parapharyngeal cystic lymph node metastasis revealing differentiated thyroid microcarcinoma

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Introduction
Later ocervical lymphadenopathies revealing a papillary microcarcinoma of the thyroid are rare (7 to 13% of cases). The parapharyngeal location of these metastatic lymphnodes is exceptional. We report a case of cystic lymph node metastasis of parapharyngeal location which revealed a papillary microcarcinoma of the thyroid.
Observation
A 40-year-old patient with no particular pathological history was admitted for management of an isolated right laterocervical swelling that had been developing for 4 months. The physical examination revealed two high and medium jugulocarotid swellings of 2 and 3 cm respectively, firm, mobile and painless. The rest of the lymph node areas as well as the thyroid lodge were free. On indirect laryngoscopy, the vocal cords were mobile. The cavum was free on nasal endoscopy. Cervical ultrasound showed two right jugulocarotid cystic adenopathies of 45 and 38 mm, the site of microcalcifications with a homogeneous thyroid gland. Cervical CT scan was suggestive of a cystic lymphangioma with the presence of a right parapharyngeal unilocular cystic formation. A complement by cervical MRI revealed right cervical cystic adenopathies, one of which is located in the right parapharyngeal space. A lymph node cytopuncture concluded with the diagnosis of lymph node metastasis of a papillary thyroid carcinoma. The repeated cervical ultrasound showed thyroid micronodules. The patient underwent functional right dissection with extemporaneous histological examination which confirmed the diagnosis of cystic metastasis of papillary thyroid carcinoma. A total thyroidectomy with bilateral recurrent mediastinal dissection was performed. An excision of the parapharyngeal component by the intraoral route after unilateral tonsillectomy was performed. The definitive histology concluded that there was a multifocal and bilateral papillary microcarcinoma of the thyroid (tumor foci between 1 and 5 mm) with central, lateral and parapharyngeal lymph node metastases. Iratherapy was indicated. The evolution was favorable after a 3-year follow-up.
Conclusion
Lymph node dissemination is often reported to the central compartment of the neck followed by the lateral region. Metastasis to the parapharyngeal space seem to be straight forward due to the close anatomical localisation, but a few cases of parapharyngeal involvement have appeared in the literature

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EP1563

JOINT1113

Follicular adenoma with follicular epithelial dysplasia-a care report

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Introduction
Follicular epithelial dysplasia (FED) is suggested to be a pathogenic link between inflammation – related atypia and papillary thyroid carcinoma (PTC) and thus a premalignant percursor of papillary thyroid carcinoma, in Hashimoto – thyroiditis (HT) and in chronic lymphocytic thyroiditis (CLT).
Material and methods
A 66-year-old-woman presented with feeling suffocation, frequent heartbeats, sweating, insomnia, hand tremors. Anamnesis revelead that she was diagnosed with Hyperfunctioning Multinodular Goiter 15 years prior and is on antithyroid medication and antihypertensive medication with moderate success in achieving euthyroidism. On admission, the patient had FT4:0.29 ng/dl (ref 0.34 – 5.6), FT3: 4.44 pg/ml (ref 2.5 – 4.2) TSH:2.65 uUI/ml (0.25 – 5). Cervical ultrasound showed an enlarged thyroid with large nodules. Antithyroid medication was adjusted with Favistan 10 mg/day. At the next visit after 6 weeks the lab results: TSH: 0.344 uUI/ml, FT4: 11.3pg/ml, FT3: 5.82 pg/ml, Anti Tg 26, Anti TPO 6.49, TSH receptors 0.8. Total thyroidectomy was recommended to the patient. The post-surgery biopsy confirmed follicular adenoma with foci of epithelial dysplasia.
Conclusion
Our case demonstrate the presence of atypical microscopic lesions even in follicular adenoma

Keywords
follicular adenoma, follicular epithelial dysplasia, hyperfunxioning multinodular goiter.

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EP1564

JOINT1973

Pazopanib in radioiodine refractory follicular thyroid carcinoma. a case report

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Introduction
Differentiated thyroid carcinoma (DTC), which includes papillary and follicular thyroid cancers, generally has an excellent prognosis. However, a minority of patients (10%) relapse with metastatic disease, and eventually develop radioactive iodine (RAI) refractory disease. Over the last fifteen years the emergence of tyrosine kinase inhibitors (TKIs) has provided important new avenues of treatment for these patients. Currently, Lenvatinib and Sorafenib, multitargeted TKIs, represent the standard first-line systemic treatment options for RAI-refractory thyroid carcinoma, while Cabozantinib is the standard second-line treatment option. There are many phase 2 studies evaluating different multitargeted TKIs with encouraging results, but these drugs do not have FDA or EMA approval.
Case presentation
A 46-year-old male with follicular thyroid carcinoma, diagnosed following pathological fracture of the right femoral neck due to metastatic lesion, for which he underwent total hip replacement, treated with surgery followed by adjuvant RAI (200 mCi) treatment and TSH suppression. The CT scan revealed lung and bone metastases that did not demonstrate any RAI uptake, justifying the initiation of systemic treatment with a 1st-line multitargeted TKI: Sorafenib 800 mg daily. Morphological evaluation at 6 months post-Sorafenib revealed progression of lesion status and appearance of a lytic lesion of the 4th thoracic vertebra with spinal cord compression, for which he underwent laminectomy. Given the progression of lesion status on Sorafenib, a switch to 2nd-line treatment with Pazopanib 400 mg daily was initiated. Response evaluation at 4 months post-Pazopanib showed a progressive disease according to RECIST criteria.
Discussion/Conclusion
Pazopanib is approved for the treatment of advanced renal cell carcinoma and soft tissue sarcoma. It shows unclear efficacy and clinical activity in patients with RAI-refractory DTC, with manageable toxicity profiles. The findings indicate that pazopanib demonstrates clinical activity in RAI-refractory DTC, with the partial response rates ranging from 35.6% to 49% and with a median PFS period of around 11 months. Further large-scale randomized trials are warranted to establish the optimal use of pazopanib in thyroid cancer treatment.

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EP1565

JOINT198

Pemphigus vulgaris and Graves' disease

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Introduction
Bullous dermatoses encompass a range of skin disorders, with pemphigus vulgaris being one of the most severe. Pemphigus is a chronic, recurrent and severe bullous skin disease with acantholysis in the epidermis. In some investigations, thyroid diseases have been found to be a comorbidity of several skin diseases, such as alopecia, vitiligo, chloasma and Sjogren's syndrome. A recent study showed that the relatives of pemphigus patients seemed more prone to thyroid diseases. And about 34% of pemphigus vulgaris patients had hypothyroidism, Graves' disease, toxic multinodular goiter or follicular carcinoma This report presents a case of pemphigus vulgaris associated with thyroid dysfunction, highlighting the potential interplay between autoimmune skin diseases and thyroid pathology.
Case Report
A 25-year-old female patient was admitted in dermatology hospital, where she was diagnosed with pemphigus vulgaris. She was treated with corticosteroids, and the disease course was marked by recurrent flare-ups. After 19 years of disease progression, the patient developed hyperthyroidism, accompanied by a firm goiter and bilateral exophthalmos. Laboratory tests revealed positive antibodies for antithyroid peroxidase (AAT) and anti-TSH receptor antibodies, leading to the diagnosis of Graves' disease. The patient was subsequently treated with a course of radioactive iodine (RAI), which resulted in hypothyroidism 10 months later. She has since been treated with L-thyroxine. HLA typing revealed the haplotype HLA_AB:A1, A white, B17, B40 (BW4, BW6).
Discussion
Some explanations regarding the coexistence of the two conditions are below. First, pemphigus and AITD may have a common susceptibility gene or allele, but show different phenotypes influenced by various genetic and environmental factors. Meanwhile, there may exist a common environment triggering the autoimmune pathogenesis of both. Second, HLA alleles related to the disease may express similar autoantigen epitopes in different tissues. The case underscores the importance of considering thyroid dysfunction in patients with autoimmune skin disorders. A thorough evaluation for thyroid disease is recommended in patients with chronic autoimmune conditions such as pemphigus vulgaris, especially when new symptoms suggest thyroid involvement.
Conclusion
This case illustrates the rare coexistence of pemphigus vulgaris and thyroid dysfunction, specifically Graves' disease. The presence of autoimmune thyroid markers in this patient highlights the potential for autoimmune diseases to be interrelated.

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JOINT1085

Uncommon presentation of thyroid-associated orbitopathy in hypothyroidism: a case report

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Introduction
Thyroid-associated orbitopathy (TAO) is uncommon in patients with Hashimoto's thyroiditis (HT), with a prevalence of 10.36% in those with hypothyroidism. In rare cases, hypothyroidism, orbitopathy, and elevated TSH-receptor autoantibodies (TRAbs) can be associated.
Case Presentation
A 62-year-old male presented with sight-threatening TAO and recently diagnosed hypothyroidism. Three months earlier, he had been started on levothyroxine (75

μg/day) for symptoms of asthenia, myxedema, constipation, and mild exophthalmos without signs of activity. Initial thyroid function tests revealed significantly elevated TSH (34 mIU/l [0.25-4.5]) and low free thyroxine (fT4) (3 pmol/l [12-22]). Upon admission to the ophthalmology department, the patient exhibited severe active orbitopathy, characterized by bilateral visual acuity of 3/10, restricted upward and abduction eye movements, and eyelid swelling. Laboratory investigations showed normal thyroid function (TSH: 4 mIU/l, fT4:11.6 pmol/l) under regular levothyroxine therapy, significantly elevated TRAbs (32 IU/l, normal <2 IU/l), and markedly high anti-thyroid peroxidase antibodies (Anti-TPO) (500 IU/ml, normal <50 IU/ml). Orbital MRI revealed bilateral, symmetrical hypertrophy of the extraocular muscles compressing the optic nerves at the apices and grade 3 exophthalmos. Thyroid ultrasound showed a heterogeneous, pseudonodular gland suggestive of thyroiditis. Treatment involved high-dose intravenous methylprednisolone (1000 mg/day for three consecutive days), achieving partial improvement, followed by a cumulative corticosteroid dose of 4.5 g administered over 12 weekly injections. Selenium supplementation (200 μg/day) was initiated, associated with levothyroxine therapy. At the six-month follow-up, ophthalmological evaluation revealed resolution of oculomotor restriction, absence of disease activity, and improved bilateral visual acuity (5/10). However, persistent TSH suppression, despite adjustments in levothyroxine dosage, led to a six-month interruption of therapy. Subsequent follow-up tests revealed TSH of 0.01 mIU/l[0.25-4.5], fT4 of 16 pmol/l[12-22], undetectable TRAbs levels, and persistently elevated Anti-TPO.

Conclusion

The literature describes different types of TRAbs, including thyroid-stimulating and TSH-blocking autoantibodies, each linked to distinct clinical syndromes. In this case, the predominance of blocking-type TRAbs may explain the presence of hypothyroidism. A multidisciplinary approach is crucial for optimizing outcomes in TAO, particularly in complex cases. Long-term follow-up is essential to monitor both thyroid function and ocular health.

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EP1567

JOINT2889

Primary thyroid lymphoma in hashimoto's thyroiditis: a case report and review of the association and diagnostic approach

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Introduction

Primary thyroid lymphoma (PTL) is a rare cancer, representing 1% to 5% of all thyroid malignancies and 1% to 7% of all extra nodal lymphomas. It predominantly affects females, with the highest incidence occurring in the seventh decade of life. The most common histotypes are diffuse large B-cell lymphoma, which accounts for 50% to 70% of cases. The most significant risk factor for PTL is Hashimoto's thyroiditis, which increases the risk of PTL by 40 to 80 times. However, it remains unclear whether Hashimoto's thyroiditis is a necessary condition for the development of PTL. The aim of this study was to describe a case report of a primary thyroid lymphoma associated with a lesion of Hashimoto's thyroiditis

Materials and Methods

This is a retrospective case report focusing on a patient diagnosed with primary thyroid lymphoma (PTL) associated with Hashimoto's thyroiditis. The study includes a detailed review of the patient's medical history, clinical presentation, imaging results, histopathological examination, and treatment course.

Results

An 84-year-old female patient was admitted for management of dysphagia. On examination, a hard, fixed mass was palpated in the anterior cervical region, adherent to the deep planes. Cervical ultrasound revealed a right-sided thyroid mass measuring 41x28x12 mm, causing mass effect on the trachea. A cervical-thoracic CT scan confirmed the presence of a mass in the right thyroid lobe. An esophagogastroduodenal transit showed deviation of the cervical esophagus to the right, consistent with extrinsic compression. The patient underwent an exploratory cervicotomy, revealing a firm, stone-like mass adherent to the right thyroid lobe, while the left lobe appeared normal. A multiple biopsy of the right mass confirmed a diagnosis of diffuse B-cell lymphoma of germinal center cells, while the left lobe showed lymphocytic thyroiditis. The patient was presented in a multidisciplinary case review (MCR) for chemotherapy consideration.

Conclusion

The strong association between Hashimoto's thyroiditis (HT) and primary thyroid lymphoma (PTL) highlights the significantly increased risk (40- to 80-fold) of developing PTL in patients with HT. PTL should be considered in the differential diagnosis of rapidly enlarging goiter or shortness of breath in patients with thyroiditis. Early recognition and prompt pathological diagnosis are crucial to initiate chemotherapy and improve patient outcomes.

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EP1568

JOINT389

Hypokalemic periodic paralysis in hyperthyroidism: a rare endocrine emergency

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Case Presentation

A 20-year-old male patient, of south american and oriental descent, presented in January 2024 with sudden onset of muscle weakness and flaccid paralysis of the lower limbs, progressing rapidly to upper limb plegia, while respiratory movements remained preserved. Initial examination revealed hypertension (BP $>$ 140/90 mmHg), sinus tachyarrhythmia (ECG), and severe hypokalemia (K: 2.8 mEq/l). The patient was admitted to the Intensive Care Unit for potassium repletion, during which transient hyperkalemia occurred, but was resolved without serious consequences. After normalization of potassium (4.1 mEq/l), the patient was discharged. Approximately 30 days later, the patient experienced another episode of lower limb weakness and hypokalemia, prompting further investigation. Laboratory tests revealed hyperthyroidism (TSH: <0.008 μUI/ml, T4: 5.14 ng/dl, T3: 17.9 ng/dl) and elevated anti-thyroid antibodies. A diagnosis of hyperthyroidism was confirmed, and treatment with methimazole (30 mg/day) was initiated. After 90 days, follow-up tests showed improved thyroid function (TSH: 0.01 μUI/ml, T4: 1.12 ng/dl, TRAB: 1.51 U/l). Thyroid ultrasound showed a normal-sized gland with no solid or cystic lesions. The patient remains asymptomatic with no further episodes of tachycardia, hypokalemia, or paralysis.

Discussion

Hypokalemic periodic paralysis (HPP) is a rare complication of hyperthyroidism characterized by a triad of hypokalemia, thyroid dysfunction, and skeletal muscle paralysis. Episodes of HPP are often transient and can affect the lower limbs, occasionally progressing to the upper limbs. The condition is precipitated by high carbohydrate intake or intense physical activity and often occurs during the night or upon awakening. Thyroid symptoms can be subtle, with diagnosis confirmed through laboratory tests. In the electrocardiogram, signs of HPP include sinus tachycardia, ST-segment alterations, T-wave flattening, prolonged QT intervals, and in severe cases, ventricular fibrillation. Treatment involves controlling hyperthyroidism with antithyroid drugs, iodotherapy, or thyroidectomy. In acute episodes, careful potassium repletion and beta-blockers are essential to prevent recurrence.

Conclusion

Although rare, hypokalemic periodic paralysis (HPP) in the context of hyperthyroidism must be recognized promptly by clinicians. With increasing numbers of individuals of Asian descent in the world, understanding the pathophysiology and epidemiology of this condition is crucial for early diagnosis and treatment, which can prevent severe complications, including respiratory failure and death.

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EP1569

JOINT2577

Thyroid association ophthalmopathy in hashimoto's thyroiditis: a case report

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Introduction

Ophtalmopathy is common in hyperthyroid patients due to Graves' disease. But in Hashimoto's thyroiditis, thyroid associated ophthalmopathy is rarely reported and only few cases have been reported in the literature. Here we report a case of thyroid associated ophthalmopathy in a patient with Hashimoto's thyroiditis.

Observation

A 40-year-old female patient was being followed for Hashimoto hypothyroidism with positive anti-thyroid peroxidase antibodies and thyroiditis on cervical

ultrasound. Two years after the diagnosis, she presented with blurred vision, bilateral exophthalmos and spontaneous ocular pain. On examination, she had bilateral palpebral edema and conjunctival and palpebral redness. clinical activity score (CAS) was 4. CT scan showed bilateral oculomotor muscle infiltration in connection with dysthyroidism and anti-TSH receptor antibodies were negative. The patient was put on corticosteroids: prednisone 1 mg/kg/day with improvement in the signs of ophthalmopathy activity: disappearance of conjunctival and palpebral redness and pain; she gradually tapered off the corticosteroids.

Conculsion

This case highlights the rare association between ophthalmopathy and Hashimoto's thyroiditis, emphasizing that thyroid-related orbitopathy is not exclusive to Graves' disease.

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EP1570

JOINT3528

Surgical treatment of plunging goiters: challenges for ENT specialists

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Introduction

A plunging goiter (PG) is any goiter whose lower limit is not palpable in the surgical position. Its diagnosis is first suspected clinically, then confirmed by imaging. It often requires surgical intervention due to associated life-threatening risks.

Objective

To study the epidemiological aspects of PG, the importance of preoperative imaging and to describe the modalities of surgical management.

Patients and Methods

Retrospective study of 15 cases of PG, operated on at the Department of Head and Neck Surgery and Otorhinolaryngology of the Fattouma Bourguiba University Hospital in Monastir over a period of 5 years from 2020 to 2024.

Results

In 5 years,15 cases of PG representing 1.5% of thyroidectomies performed. The average age was 60 years [33 to 79 years]. The sex ratio was 0.22 with a female predominance (86%). The plunging character was noted on clinical examination and confirmed by imaging. The consultation period was 3 years [4 months - 10 years]. The circumstances of discovery were dominated by the fortuitous discovery of an anterior baservical swelling in 100% of cases and the installation of compressive signs in 73% of cases. A family history of thyroid pathology was reported in 5patients (33%) and a personal history of dysthyroidism was noted in 3patients (20%). All our patients had a chest X-ray, a cervical ultrasound and an indirect laryngoscopy preoperatively. Among the 15 X-rays, an opacity Upper mediastinal goiter was objectified in 8 patients (54%), tracheal deviation in 7 patients (46%), and a normal appearance in 46% of cases. Ultrasound detected the plunging character in 6 patients (40% of cases) and the cervicothoracic CT scan confirmed it in 100% of cases. The goiter plunged to the right in 8 cases (54%), to the left in 6 cases (40%) and bilaterally in 1 case. It also revealed an anterosuperior mediastinal development of the goiter in 13 cases (86%), posterior in 2 cases (13%), and a displacement of the esophagotracheal axis in 9 cases (60%). A loboisthmectomy was performed in 4 cases (33%) and a total thyroidectomy in 11 cases (73%) by the exclusive cervical aaproach. The anatomopathological examination revealed11 benign lesions and 4 malignant ones. Postoperative complications included transient hypoparathyroidism in 2 cases, unilateral transient recurrent paresis in 1 case, and subcutaneous hematoma in another case.

Conclusion

Plunging goiters represent a distinct entity in thyroid pathology due to the complexity of their surgical management. The surgical indication, following a multidisciplinary approach, should be considered prior to the onset of compressive complications.

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EP1571

JOINT1846

Atypical testicular germ cell cancer metastasis in the thyroid: a case report of a very rare clinical presentation

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Introduction

In contrast to primary thyroid cancer, which usually has a good prognosis, thyroid metastases from other primary tumors are associated with a poor prognosis, as they indicate far advanced primary disease [*Zivaljevic V, 2018*]. The most common metastatic sites of testicular cancer are retroperitoneal lymph nodes. In clinical practice, metastases in the thyroid are extremely rare (incidence ranging from 0.006 to 0.3%) [*Battistella E, 2020*].

Case description

A 22-year-old man was referred to the Emergency department due to a painless mass on the left side of his neck that appeared three weeks ago, a decrease in appetite and acute upper respiratory tract infection with negative dynamics that has lasted for three days. The neck ultrasound showed an enlarged left thyroid lobe, with a mixed-structure nodule occupying almost the entire lobe. Enlarged lymph nodes were present in the left supraclavicular and posterior cervical areas. Patient was admitted to the Endocrinology department. Blood tests showed normal thyroid hormone levels, ESR 101 mm/h, increased inflammatory markers. Treatment with NSAIDs was initiated, suspecting a subacute thyroiditis. A biopsy of the neck mass and lymph nodes was performed. The results indicated a mixed germ cell tumor with a high Ki67 proliferation marker. After the CT scan of the chest, abdomen, and pelvic organs, advanced testicular neoplastic process was suspected. After a whole-body PET/CT scan, a metabolically active mass in the right testicle was observed, with the most likely metastases in the liver and in the left supraclavicular, mediastinal, left inguinal region, lungs and neck lymph nodes. Neoadjuvant chemotherapy with BEP (Bleomycin, Etoposide, Cisplatin) was initiated before surgery.

Conclusions

We present an unusual clinical case of advanced testicular germ cell cancer that manifested with thyroid enlargement and metastasis in the neck. Testicular cancer with metastasis of the thyroid is an extremely rare occurrence, only 4 cases in the 40 years period were found in literature [*Mattavelli F, 2009 and Favero D, 2024*].

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EP1572

JOINT1375

Autonomous resolution of a toxic thyroid nodule: a case report

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Introduction/Background

Management of toxic autonomous nodules usually involves antithyroid drugs for temporary control, while definitive treatment options include radioiodine therapy or surgery. However, the natural evolution of these nodules remains an area of interest with uncertain aspects to be explored.

Case Report

A 45-year-old female was sent to the endocrine clinic by her general practitioner with complains of neck discomfort. She was clinically euthyroid, presenting a painless thyroid nodule with about 3 cm on the left lobe. Laboratory tests revealed suppressed TSH levels (0.02 µUI/ml) with normal free T4 levels. Further results showed negative thyroid autoantibodies (antithyroid peroxidase, antithyroglobulin and thyrotropin receptor antibodies), negative C-reactive protein and erythrocyte sedimentation rate. Neck ultrasound revealed heterogeneous thyroid tissue, with a mixed solid and cystic nodule measuring 27 × 20 × 14 mm, in the upper part of the left lobe. Thyroid scintigraphy showed high uptake within the nodule with suppression of the surrounding parenchyma, consistent with an autonomous thyroid nodule. Since the patient was clinical euthyroid no medication was prescribed at the time. At re-evaluation, seven weeks after, TSH raised to 7.8 µUI/ml with free T4 at the lower limit of the reference range. After five weeks, TSH level become normal (2.57 µUI/ml). The patient remained clinically euthyroid and thyroid antibodies were persistently negative. An ultrasound was repeated showing a hypervascular, septated nodule with a cystic component measuring 23x16 mm. At that time scintigraphy also was repeated showing a diffuse increase in radionuclide uptake, with a partially hypoactive area corresponding to the previously detected toxic nodule.

Discussion/Conclusions

This case raises intriguing questions regarding the rare case of a spontaneous involution of the toxic autonomous nodule. Throughout this two-month period, the patient exhibited spontaneous thyroid function fluctuations—from

hyperthyroidism to hypothyroidism and finally to euthyroidism—always with negative thyroid autoantibodies. Possible mechanisms include functional exhaustion, fibrosis or necrosis. While toxic nodules are typically persistent and require treatment, this case highlights an unusual and spontaneous resolution with both biochemical and imaging correlation. The evolution of this patient's nodule from autonomous hyperfunction to apparent inactivation without intervention reenforces that, in selected cases, a conservative approach with close monitoring could justified. Further studies are needed to better understand the mechanisms underlying spontaneous resolution of toxic autonomous nodules and to define predictors of this phenomenon.

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EP1573

JOINT847

Levothyroxine absorption test: practical application. Importance of the clinical laboratory in the diagnosis of refractory hypothyroidism. A case report

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Introduction
Hypothyroidism is a chronic disease with a high prevalence. The treatment of choice in most patients is synthetic levothyroxine (LT4) adjusted for body weight. The objective is to achieve normal levels of thyrotropin (TSH) (0.4-4 µU/ml). Refractory hypothyroidism is defined as persistent hyperthyrotropinemia despite high doses of LT4. Once the usual causes (pharmacological, dietary and/or pathological) that would justify LT4 malabsorption have been ruled out, as well as possible interferences in the measurement of TSH, a dynamic LT4 absorption test (DAT) can be performed. The test allows us to differentiate real malabsorption from pseudomalabsorption or lack of therapeutic adherence. Our purpose is to demonstrate the importance of using DAT in clinical practice.
Case Report
60-year-old woman, under study for difficult-to-control autoimmune primary hypothyroidism (APH), on treatment with Levothyroxine. TSH levels of 166 µU/ml (0.270-4.200) and FT4 of 0.34 ng/dl (0.930-1.700) with significant weight gain (>10 kg), BMI 32.95 (Obesity-Grade-I). Her Primary Care Physician (PCP) increased the dose of Levothyroxine. After a new analytical control, the following were observed: TSH 273.00 µU/ml, FT4 0.221 ng/dl, FT3 1.380 pg/ml (2.00-4.40) and IgG-antiperoxidase-TPO Ac. 187.00 IU/ml (9.00-34.00). The patient began with significant asthenia, hoarseness and dyspnea. Complementary tests were performed to assess intestinal and autoimmune causes, which were negative. There was no analytical interference (macro-TSH and heterophil antibodies). Subsequently, TSH levels were 243.00 µU/ml and FT4 0.308 ng/dl. DAT was performed, which consisted of the administration of 1000 µg of FT4 and monitoring of FT4 levels every 30 min for 4 hours. A baseline ECG and a blood test with TSH and FT4 must be performed beforehand. Absorption is considered normal when FT4 levels are >0.4 ng/dl with respect to the baseline value (absorption >60%). Results: DAT results: 0' TSH 207.00 and FT4 0.277; 30́ FT4 0.293; 60́ FT4: 0.550; 90́ FT4 0.862; 120́ FT4 1.63. 180́ FT4 1.950; 240́ TSH 70.90 and FT4 2.00, in µU/ml and nd/dl, respectively.
Discussion and conclusions
According to the results, everything indicates a pseudomalabsorption of FT4, that is, a lack of therapeutic compliance by the patient. Correct adherence to treatment is insisted upon. After 8 weeks, the thyroid profile is shown to be normalized (TSH 1.080 µU/ml, FT4 1.50 ng/dl, FT3 3.090 pg/ml). DAT is a safe and effective method that allows pseudomalabsorption to be demonstrated after ruling out interferences and underlying gastrointestinal pathology. pseudomalabsorción tras descartar interferencias y patología gastrointestinal subyacente.

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EP1574

JOINT2101

Dual autoimmune thyroid disease: a case of simultaneous Graves' disease and hashimoto's thyroiditis

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Introduction
Autoimmune thyroid diseases (AITDs), including Hashimoto's thyroiditis (HT) and Graves' disease (GD), are distinct yet interrelated conditions. While HT typically causes hypothyroidism and GD results in hyperthyroidism, their coexistence in a single patient is rare. This case highlights the diagnostic and therapeutic complexities of overlapping HT and GD
Case Report
A 26-year-old woman with a positive family history of autoimmune thyroid disease and a personal history of chronic lymphocytic thyroiditis, diagnosed three years prior and managed with 50 µg of L-thyroxine daily, was referred to the endocrinology outpatient clinic for symptoms suggestive of hyperthyroidism. These symptoms persisted despite the progressive reduction and eventual discontinuation of treatment. On initial evaluation, the patient reported diarrhea, palpitations, and increased appetite. Physical examination revealed a non-enlarged thyroid and no exophthalmos. Thyroid function tests showed suppressed TSH levels (<0.001 mIU/l) and elevated free thyroxine (FT4) levels (48 pmol/l; normal range 10–28 pmol/l), persisting despite complete cessation of treatment. Both thyroperoxidase antibodies and TSH receptor antibodies were elevated at 115 IU/l (normal <8 IU/l) and 12.9 IU/l (normal <1.5 IU/l), respectively. Thyroid ultrasound revealed a slightly enlarged gland with irregular edges and increased vascular flow on Doppler, suggestive of thyroiditis. The patient was started on 10 mg of thiamazole and beta-blockers, resulting in significant improvement in clinical symptoms.
Discussion
The coexistence of GD and HT is rare but well-documented in several case reports (1–3). These autoimmune thyroid disorders share pathogenic mechanisms, including genetic and environmental factors, T-cell-mediated autoimmunity, and the presence of autoantibodies (1). Patients with simultaneous GD and HT may exhibit alternating phases of hyperthyroidism and hypothyroidism due to shifting antibody profiles (1). In this patient, hyperthyroidism was suspected when persistently suppressed TSH levels were observed despite reducing and eventually discontinuing L-thyroxine therapy. Diagnosing coexisting GD and HT can be challenging, requiring a thorough evaluation of clinical presentation, thyroid function tests, antibody assays, and imaging studies (3). Notably, our patient lacked classic clinical signs of GD, such as exophthalmos or a homogeneous goiter. Ultrasound findings were indicative of both HT (irregular gland edges, mild enlargement) and GD (increased vascular flow). Coexisting autoimmune thyroid diseases have been associated with other autoimmune conditions, including inflammatory bowel diseases, albeit rarely (4). Long-term monitoring of patients with autoimmune thyroid diseases is essential, even in the absence of clinical manifestations, due to the potential for disease progression (2).

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EP1575

JOINT998

Liquid biopsy in the molecular diagnosis of metastatic medullary thyroid cancer – case report

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Introduction
The medullary thyroid carcinoma (MTC) is one of the most aggressive forms of thyroid malignancy, accounting for up to 10% of all types of this disease. The molecular profile of MTC is well-known. A germline activating mutation of the *RET* proto-oncogene occurs in nearly all patients with hereditary MTC, while a somatic *RET* mutation is found in about 50% of sporadic tumors. In this group of patients, selective tyrosine kinase inhibitors (IKT)are successfully used, particularly in cases of metastatic disease. Management of metastatic disease in patients without RET mutations presents a clinical challenge. The aim of this study is to present the case of a patient with MTC, who 18 years after thyroid surgery, developed liver metastases despite an excellent initial response to treatment. Molecular profile of the primary tumor was not conducted. At the time of liver metastases diagnosis, circulating tumor DNA analysis was performed, allowing determination the molecular profile of the cancer. The driver mutation for MTC was identified as a mutation in the *PIK3CA* gene, which encodes the catalytic subunit of the PI3K protein, playing a key role in the phosphatidyl-inositol-3 kinase /AKT pathways *(*PI3K/Akt) signaling pathway. This mutation is known from other cancers, such as colorectal, ovarian, breast, brain, liver, stomach and lung cancers. The *PIK3CA* mutation is very rare in MTC. Our patient did not have a dynamic progression of MTC (stable disease according to RECIST 1.1 after 12 months of observation). Currently, no decision has been made to

initiate systemic therapy, but knowledge of the molecular profile of the disease may help guide targeted molecular therapy in the future. The alpelisib an α-specific inhibitor of PI3K that targets p110α is currently available. The use of this drug, which has been shown to effectively inhibit tumor progression in patients with the PIK3CA mutation, including those with breast cancer, may be a promising therapeutic option for our patient.
Conclusions
Patients with MTC, even though an excellent response to treatment, require lifelong oncological follow up. Liquid biopsy is a new and valuable tool for molecular diagnostics of cancer, particularly in cases where tumor cells cannot be obtained for analysis.

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EP1576

JOINT26

Diffuse malignancies of the thyroid – clinical cases

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Introduction
Thyroid malignancies usually present as either single or multiple nodules with high-risk ultrasound features. Nevertheless, in some rare cases the thyroid gland can be diffusely and entirely affected by different types of thyroid cancer or a metastasis from another primary site. Clinical case 1: A 34-year-old male presented with a fast-growing lump in the left neck area. The thyroid gland was significantly enlarged, with indistinguishable high-risk zones on ultrasound. Suspicious neck lymphadenopathy was observed in the central and lateral neck compartments. Fine-needle aspiration (FNA) biopsy was performed with a malignant cytological result. The patient was referred for a thyroidectomy with lymph node dissection. The histological analysis of the removed tissue confirmed differentiated thyroid cancer. Clinical case 2: An 84-year-old woman with a history of autoimmune thyroiditis was referred for assessment in regards to a progressive swelling in the neck area. She was successfully treated in the past for non-Hodgkin's lymphoma. The ultrasound examination of the neck area revealed a high-grade diffuse retrosternal compressive goiter and enlarged regional lymph nodes in levels II, III and V on the right. FNA biopsy was performed with a benign cytological result. Due to the high clinical suspicion for malignancy, the patient was referred for a surgical biopsy, which confirmed B-cell lymphoma. Clinical case 3: A 55-year-old female with a progressive goiter presented with dyspnea and palpitations. She was diagnosed recently with advanced colon cancer and treated with polychemotherapy. Laboratory results revealed a hormonal constellation of destructive thyrotoxicosis and negative thyroid autoantibodies. The ultrasound examination revealed a massively enlarged goiter with altered structure and multiple pathological lymph nodes in the neck compartments bilaterally. FNA biopsy of several parts of the diffusely altered thyroid parenchyma was performed with a malignant cytological result. Glucocorticoid therapy was applied with regards to the thyrotoxicosis, with a beneficial effect. The patient was referred for a thyroidectomy, however, due to the abrupt worsening of her condition she was considered inoperable.
Conclusion
Diffuse thyroid gland involvement due to a malignant process is rarely seen. The combination of clinical and ultrasound data, medical history and cytological results from a FNA biopsy provide vital insights into the etiology of the pathological processes, affecting the thyroid in cases of both primary and secondary malignancies.

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EP1577

JOINT635

Non-graves orbitopathy in a patient with hypothyroidism, hashimoto's thyroiditis, and hiv on combined antiretroviral therapy

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Introduction
Hashimoto's thyroiditis, also called chronic autoimmune thyroiditis, is one of the most common autoimmune thyroid diseases. The clinical manifestations can include either hypothyroidism or, in rare cases, hyperthyroidism. Thyroid Eye Disease (TED) occurs when thyroid autoantibodies cause inflammation in the connective tissue of the extraocular muscles and orbital fat, leading to clinical symptoms such as periorbital edema, lid retraction, and proptosis, among others. There is a close relationship between TED and thyroid-stimulating hormone receptor antibodies (TRAb). TED can also occur in patients with chronic autoimmune thyroiditis. HIV infects CD4+ T cells, and approximately 10–40% of patients receiving antiretroviral therapy (ART) may develop immune reconstitution inflammatory syndrome (IRIS).
Case Report
A patient was referred to an endocrinologist by an infectious disease specialist. HIV was diagnosed eight years ago, and the patient has been on combination antiretroviral therapy (Tenofovir, Dolutegravir, and Lamivudine) since then. Approximately two years ago, the patient was diagnosed with autoimmune thyroiditis and primary hypothyroidism but refused consultation with an endocrinologist.
On November 11, 2024, laboratory tests showed:
- TSH: >100 mIU/ml
- Anti-TPO: >600 IU/ml

Levothyroxine 75 mg was prescribed.
On January 8, 2025, follow-up laboratory results showed:
- TSH: 38.81 mIU/ml (reference range: 0.27–4.2)
- FT4: 15.36 pmol/l (reference range: 12–22) Although there was a positive trend in thyroid function, the patient returned for consultation with signs of thyroid orbitopathy, more pronounced in the right eye, as well as spot baldness on the head and brow area—symptoms that were not present during the previous consultation two months prior. Before the endocrinology follow-up, the patient was evaluated by an ophthalmologist and was prescribed steroid eye drops. However, the patient did not notice any improvement in inflammation. On January 10, 2025, an MRI scan of the brain and orbits was performed, revealing:
- No acute focal organic pathology of the brain parenchyma
- Swelling of intraorbital fatty tissue in both eyes
- Exophthalmos in both eyes Levothyroxine dosage was increased to 100 mg, and Selenium 200 mg once daily was introduced for six months. Since Teprotumumab is not available in Georgia, intravenous methylprednisolone pulse therapy is being considered for further treatment.

Conclusion
This case highlights the importance of early ophthalmological evaluation in patients with autoimmune thyroiditis, including thyroid hormone assessment and thyroid autoantibody screening. It also underscores the need for early detection of eye complications, even in patients with autoimmune thyroiditis in the hypothyroid stage and without Graves' disease.

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EP1578

JOINT3123

Metastatic medullary cancer treated with Sorafenib: Service experience

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EP1578

Caractéristiques	Patient 1	Patient 2	Patient 3	Patient 4
Age	64 years	72 years	70 years	32 years
Sex	Male	Male	Male	Male
History of MEN	No	No	No	No
Discovery mode	Cervical lymph-adenopathy.	Cervical lymph-adenopathy.	Cervical lymph-adenopathy	multiple pulmonary metastases.
Surgery	Total thyroidectomy with lymph node dissection.	Total thyroidectomy with central and bilateral jugulocarotid lymph node dissection.	Surgery declined due to multiple metastases.	Surgery declined due to multiple metastases.
Histopathology	PT3N1bM1	PT3aN1bM1	//	//
Metastatic sites	Pulmonary Tracheal	Pulmonary, lumbar	Mediastinal-hilar lymph node, pulmonary, bone, and liver	Pulmonary, cerebellar, bone, and mediastinal
Treatment	Radiotherapy then Sorafenib 800 mg/day, reduced to 600 mg/day	Doxorubicin and Cisplatin then Sorafenib 800 mg/day, reduced to 600 and 400 mg/day	Sorafenib 800 mg/day	Sorafenib 800 mg/day, then Vandetanib 300 mg/day, then Sorafenib 800 mg/day, reduced to 600 mg/day (stopped)
Outcome	Stability of secondary pulmonary lesions.	Stability of pulmonary lesions and 25% reduction of L4 lesion.	18% increase in thyroid mass, leading to a switch to Lenvatinib 24 mg/day.	Disease progression in the brain and bones, regression of pulmonary nodular lesions, and stable mediastinal lymph nodes.
Side effects	Diarrhea, weight loss, hand-foot syndrome	Diarrhea, hair loss.	Hypertension, hand-foot syndrome.	Hand-foot syndrome, vomiting, epigastric pain.

Introduction
Medullary thyroid carcinoma (MTC) accounts for 3–8% of thyroid cancers. In 20% of cases, it is diagnosed at a metastatic stage. Tyrosine kinase inhibitors (TKIs) have revolutionized the management of advanced and metastatic MTC. Among them, Vandetanib and Cabozantinib are the two approved treatments. However, access to these therapies may be limited in certain settings, justifying the exploration of alternatives such as Sorafenib.
Methods
A retrospective analysis of four metastatic MTC patients treated with Sorafenib was conducted. Clinical data, treatment response, and adverse effects were assessed.
Discussion
MTC requires systemic therapy in metastatic cases. Sorafenib, a multikinase inhibitor targeting RET and VEGFR, is used off-label when standard therapies are unavailable. While it stabilizes disease in some cases, efficacy remains modest. Adverse effects may impact adherence, requiring careful monitoring. Further research is needed to define Sorafenib's role and explore combination strategies.
Conclusion
Sorafenib may be an alternative for metastatic MTC when standard treatments are unavailable. Close monitoring is essential to manage adverse effects and optimize outcomes.

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EP1579

JOINT1674

Discordance between clinic, biology and ultrasound in the diagnosis of Graves' disease: contribution of scintigraphy in a case report

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Introduction
Graves' disease, the most common cause of hyperthyroidism, is linked to the presence of anti-TSH receptor antibodies. It is an autoimmune pathology, 5 to 10 times more frequent in women than in men, occurring at any age. Clinical symptoms include thyrotoxicosis and the specific signs of the disease (ophthalmopathy and pretibial myxedema). Biologically, a lowered TSHus concentration and elevated T4 and/or T3 confirm the diagnosis. Ultrasound and scintigraphy are sometimes useful in distinguishing Graves' disease from other causes of hyperthyroidism. When clinical and biological findings are incomplete and/or ultrasound is inconsistent, scintigraphy is of great help. We report on the contribution of scintigraphy to the diagnosis of Graves' disease with clinical, biological and ultrasound discordance.
Case report
A 54-year-old female patient with breast cancer, operated on 7 years ago and currently undergoing hormone therapy, consulted for thyroiditis discovered incidentally by cervical ultrasound, with a reduced thyroid gland, heterogeneous echostructure with hypoechoic areas, discreetly hypervascularized. Clinically, she showed no signs of dysthyroidism. A laboratory workup revealed subclinical hyperthyroidism with TSHus down to 0.05 µUI/ml (0.25-5), T4L and T3L normal. In the immunological work-up, anti-TPO antibodies were positive at 36 and TRAK was slightly elevated at 2.81 (>2.25). In view of this incomplete clinicobiological context and a discordant ultrasound, a Technicium 99m thyroid scintigraphy was requested as a complement, objectifying diffuse and homogeneous hyperfixation of the radiotracer compatible with Graves' disease. The patient was put on low-dose synthetic antithyroid drugs. Biological results were favourable (TSH, T4 and T3 normal at 1-month follow-up).
Discussion/Conclusion
The classic diagnosis of Graves' disease is clinicobiological and secondarily ultrasonographic. However, in the event of discrepancies between the two, and given the operator-dependent nature of ultrasound, scintigraphy can make a considerable contribution.

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EP1580

JOINT2664

Ostéoporose radiale: une complication rare du traitement suppressif du carcinome papillaire de la thyroïde

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Introduction
Hyperthyroidism reduces bone mass and increases fracture risk. These changes are clearly demonstrated in cases of frank thyrotoxicosis in postmenopausal women. Thyroid hormone treatment has a limited effect on bone. Clinical studies show contradictory results. Thyroid hormone treatment should be considered as an additional osteoporotic risk factor in postmenopausal women.
Observation
76-year-old postmenopausal patient, followed for papillary thyroid microcarcinoma operated and irradiated in 2014, initially put on braking treatment with TSH target <0.1 for the first year, given the good biological and morphological response, the TSH target was redefined between 0.5-2 with a dose of 62.5ug levothyroxine. An osteodensitometry was ordered as part of the work-up, and came back in favour of femoral and lumbar osteopenia with radial osteoporosis. The patient was referred to rheumatology for treatment and follow-up.
Discussion
A literature review analyzed 11 significant studies. All provided information on gender, menopause, bone density measured at different sites and a match to control subjects. All patients had received five or more years of hormone-reducing therapy. One limited cross-sectional study found a significant reduction in lumbar density of 2-6% per year since initiation of thyroxine therapy in postmenopausal women, while a single cross-sectional study found a reduction in femoral neck density, with no changes in lumbar or forearm density compared to control subjects. Of nine studies involving postmenopausal women only, six found no difference in bone density between thyroid cancer patients treated with hormone-braking therapy and controls. One study showed only a slight decrease in bone density at the distal end of the radius. In the work by Kung *et al*. thyroxine results in complete TSH suppression in all patients and a decrease in bone density at all sites evaluated in postmenopausal women. These contradictory results do not allow us to confirm or deny the deleterious effect of hormone replacement therapy on bone mass in postmenopausal women It is reasonable to consider hormone replacement therapy as an additional osteoporotic risk factor.
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EP1581

JOINT3552

Unilateral ptosis in a patient with thyroid eye disease: A case report

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Introduction
Thyroid associated orbitopathy (TAO) or graves disease is an autoimmune disorder associated with hyperthyroidism. Most common presentation is eyelid retraction followed by exophthalmos. Although it is associated with myasthenia gravis, it is a relatively uncommon cause of ptosis. We report a case of young adult woman who presented with unilateral ptosis in right eye revealing a graves disease.
Case Report
A 26-year-old female presented with a history of weight loss, panic attacks, palpitations and muscle weakness for 2 months. She had no history of thyroid affection. She complained of dropping of her right eyelid, which was insidious in onset and gradually progressive. Laboratory investigations revealed a hyperthyroidism; the free T3 level was 36.27 pmol/l (reference range: 3.10–6.80), free T4 level was 100 pmol/l (reference range: 12.0–22.0), TSH was 0.008 mIU/l (reference range: 0.27–4.20), and TSH receptor antibody (TRAb) was 6.49IU/l (reference range <1). She was diagnosed with Graves disease and started on intravenous methylprednisolone 120 mg followed by 3 days of 60 mg then 40 mg of Carbimazole.
Discussion
The relationship of muscle size to motility deficit using muscle diameter measurements on CT scans of patients with Thyroid Eye Disease(TED) was studied. There are several mechanisms of ptosis that have been reported in association with TED. Pathologic and radiographic studies revealed that although the inferior rectus is most commonly involved, every extraocular muscle, including the levator palpebrae, can be affected. The immunology of dysthyroid eye disease still complex. This case suggests that TED can significantly affect any muscle in the orbit, causing many unique symptoms and clinical presentations.

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EP1582

JOINT171

Adverse effects of hyperthyroidism therapies: insights from a clinical cohort

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Introduction
The treatment of hyperthyroidism often involves antithyroid drugs (ATDs), radioactive iodine therapy (RIT), and surgery. Although effective, these therapeutic approaches can lead to complications that impact patient outcomes. This study aims to describe and analyze the complications associated with hyperthyroidism treatment in our cohort.
Materials and Methods
We conducted a retrospective analysis of patients treated for hyperthyroidism in our center. Data on treatment-related complications, including their nature, onset, and outcomes, were collected and analyzed.
Results
31 patients were diagnosed with hyperthyroidism. Eleven patients had received treatment with synthetic antithyroid drugs alone. Seventeen patients were treated with radioactive iodine. Of these, 8 were initially treated with RIT and was used after failure of ATDs or intolerance to in 9 patients. A second course of RIT was indicated in 2 patients. Only one patient had a total thyroidectomy. Surgical treatment was indicated in view of resistance to TSA, poor socioeconomic conditions, association with T1DM and the patient's young age. Leukopenia secondary to ATDs was observed in one patient, requiring discontinuation of the therapy and initiation of RIT. Iatrogenic hypothyroidism occurred in 15 patients. Among these, 12 cases were attributed to RIT, with a mean time to onset of 3 years (extremes: 5 months to 6 years). Two cases followed ATD therapy, with a mean onset time of 2.5 years (extremes: 1.5 to 3.5 years). One case resulted from total thyroidectomy. ANCA-associated vasculitis was reported in two patients treated with benzylthiouracil (Basdene). One case resolved favorably, while the other resulted in a fatal outcome.
Conclusion
Treatment-related complications in hyperthyroidism range from manageable conditions, such as hypothyroidism, to severe and potentially fatal outcomes like ANCA-associated vasculitis. These findings underscore the need for careful patient monitoring and the selection of tailored therapeutic strategies to minimize risks and optimize outcomes.

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EP1583

JOINT391

Siblings sharing disorder; familial papillary thyroid carcinoma

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Introduction and Background
Papillary thyroid carcinoma (PTC), a form of well differentiated thyroid cancer, is a slow growing tumor and the commonest form of thyroid cancer in clinical practice, accounting for 80% of all thyroid cancers. Here we describe a case series of a one female sibling being diagnosed with Familial Papillary Thyroid Cancer after being symptomatic for a couple of months. After the surgery, other siblings did investigations and four others were diagnosed and treated for similar condition.
Case discussion
A 42 years old, married female was diagnosed as a case of FPTC. She is the oldest siblings to family of six siblings. The condition started with very delicate, pinpoint nodule in her neck that was associated with an irritating cough interfering with sleep and itching over the nodule. Later, as the mass was increasing in size, the patient started to complain of shortness of breath mainly at night the overall condition was associated with weight gain, heat intolerance, repeated miscarriage, generalized body swelling, palpitation, visual disturbance and double vision, and hair loss. Fine Needle Aspiration Cytology was not possible until 2 years has passed over symptoms. Later on, her siblings where diagnosed with FPTC following that by couple of years. The family has the history of Radiation exposure.

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JOINT199

Immunotherapy-associated thyroid dysfunction during breast cancer treatment

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Background
The discovery of immune checkpoint inhibitors (ICIs), such as anti-PD-1/PD-L1 and anti-CTLA-4 antibodies, has vastly improved survival outcomes among patients diagnosed with triple-negative breast cancer. However, immunotherapy is associated with immune-related adverse effects (irAEs), among which thyroid dysfunction is one of the most common. Understanding the clinical presentation and management of immunotherapy-associated thyroid dysfunction is of utmost importance.
Case Presentation
We report the case of a 50-year-old female with triple-negative breast cancer who developed thyroid dysfunction following treatment with pembrolizumab, an anti-PD-1 inhibitor. Paradoxically, the patient was asymptomatic, except for persistent fatigue which she believed was a frequent side effect of the treatment. Laboratory results revealed an elevated TSH of 195 μIU/ml and suppressed free T4 of 1.30 pmol/l, consistent with severe hypothyroidism, while thyroperoxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) were negative. Thyroid ultrasonography showed diffuse heterogeneity and almost no vascular flow. She was started on levothyroxine therapy with gradual dose escalation. The oncologist decided to continue immunotherapy despite thyroid dysfunction and suggested close monitoring of thyroid function and symptom management.
Discussion
This case highlights the importance of thyroid function evaluation during immunotherapy treatment, even in the absence of clinical manifestations. A multidisciplinary approach is needed in order to optimize patient care and outcomes.
Conclusion
Immunotherapy-related thyroid dysfunction is a manageable irAE than can occur during breast cancer treatment. It is important to implement routine thyroid function monitoring as part of the clinical management of patients undergoing immunotherapy. With appropriate diagnosis and timely intervention, clinicians

can effectively reduce the impact of thyroid dysfunction on the patient's overall treatment protocol and quality of life.

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EP1585

JOINT297

An uncommon cause of hyperthyroidism - gestational trophoblastic neoplasia

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A middle-aged female (gravida 6, para 5) presented at 12 weeks amenorrhoea to the emergency department for persistent nausea and vomiting in pregnancy. Previous pregnancies had been uneventful. She described palpitations, which led to the discovery of hyperthyroidism in pregnancy. A trans-vaginal ultrasound revealed a bulky uterus with complex echogenic endometrial mass containing multiple small cystic areas. Hyperthyroidism was attributed to markedly elevated β-HCG from gestational trophoblastic disease. She underwent urgent dilatation and curettage after medical optimization and under close peri-operative monitoring. Thyroid function normalized within a few short weeks. β-HCG levels showed good early response with sharp decline over the first 2 weeks. However, the figure then plateaued above 10000 IU/l, leading to suspicion of persistent disease and gestational trophoblastic neoplasia. Imaging with computed tomography showed multiple pulmonary nodules and she was commenced on chemotherapy thereafter.

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EP1586

JOINT3926

Evolutive aspects of SUBCLINICAL hypothyroidism

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Subclinical hypothyroidism (SCH) is most often diagnosed incidentally, and raises the question of the treatment indication. The aim of this study was to describe the progressive profile of sch and to identify the factors associated with the absence of spontaneous normalization of the thyroid function.

Methods

Longitudinal study of a retrospective cohort of 69 patients with SCH defined by normal FT4 and TSH $>$ 4mUI/l. Patients were subdivided into two groups according to the spontaneous normalization or non-normalization of thyroid function during follow-up.

Results

The study population was composed of 57 women and 12 men, of mean age of 42.3 $\pm$ 15.8 years. After a mean follow-up time of 19,6 $\pm$ 15.1 months, thyroid function normalized spontaneously in 18 patients (26% of cases). the mean time to normalization of thyroid function was 9,8 $\pm$ 4,2 months. Absence of spontaneous normalization of thyroid function was inversely correlated with FT4 level $P = 0.04$). ATPO positivity was statistically different between groups ($P = 0.01$). ATPO levels were significantly higher in the absence of spontaneous normalization of thyroid function (589.7 $\pm$ 607.7 IU/l vs. 112.1 $\pm$ 54.8 IU/l, $P = 0.01$) and was associated with high prevalence of evolution to an overt hyperthyroidism. TSH level was non-statistically different ($P = 0.2$). Age, gender, presence of symptoms of hypothyroidism and presence of goiter on cervical ultrasonography were not associated with the progression of the SCH in our study

Discussion and Conclusion

Spontaneous normalization of thyroid function was observed in almost a quarter of patients with SCH. A lower FT4 rate, the positivity of ATPO were associated with absence of spontaneous normalization of thyroid function. A Higher rate of ATPO was associated with progression to overt hypothyroidism requiring close monitoring in these patients

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JOINT2632

Would you miss a thyroid storm in acute setting?

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Introduction

Thyrotoxicosis is one of the most common endocrine disorders and in its severe form can manifest as a thyroid storm in an acute setting leading to organ dysfunctions including heart failure.

Case Presentation

A 50-year-old man presented to the emergency department (ED) with a 3-week history of weight loss, palpitations, tremors, breathlessness, and leg swelling. He was initially discharged from the hospital with furosemide as a suspected diagnosis of heart failure. Chest-X-ray on admission demonstrated clear lungs fields. An echocardiogram after admission demonstrated normal left ventricular function (LVEF $>$ 55%), normal right ventricular function, mild MR and Pasp 22-27 mmHg. He was initially discharged with furosemide as a suspected diagnosis of heart failure. Patient remained feeling unwell and his GP performed further blood tests which showed a suppressed TSH and a free T4 $>$ 100, T3 35. ALT 53, Calcium 2.72. He was subsequently referred to the Acute Medicine Department at Queens Hospital. Upon review, there were clear symptoms of thyrotoxicosis. His lower limb swelling had improved with the furosemide prescribed previously. His Burch-Wartofsky Score was 30 suggestive of impending thyroid storm. The case was reviewed by an endocrinologist and the following medications were commenced:

- 4g once daily Cholestyramine 2weeks
- 30 mg Prednisolone 5days (following stat-dose hydrocortisone 100 mg IV in ED)
- 20 mg twice daily Carbimazole
- 20 mg three times a day Propranolol (following stat-dose 40 mg in ED)
- Furosemide 40 mg once daily

He was followed up in the Endocrine clinic and his symptoms had improved

Discussion

Thyrotoxicosis is a life-threatening complication of hyperthyroidism, clinically it is manifested as thyroid storm and triggered by a secondary external event such as infection, myocardial infarction, trauma or surgery. It is crucial to identify the underlying aetiology leading to the severe clinical manifestation of thyroid storm to start appropriate treatment. The consequence of delayed diagnosis and lack of correct treatment can lead to further complication such as delirium, thromboembolic disease, cardiovascular collapse and eventually death. Currently, the Burch Wartfosky point scale is used to diagnose thyroid storm. A score greater than or equal to 45 aligns with a clinical diagnosis of thyroid storm.

Conclusion

Thyroid storm is a medical and an endocrine emergency and appropriate and timely treatment will ensure better patient care and outcomes. In an emergency like acute thyrotoxicosis or thyroid storm, higher doses of antithyroid medications, beta-blockers as well as glucocorticoids can be used to return the patient to a euthyroid state.

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EP1588

JOINT475

Internet searches for thyroid disease and impact of the world thyroid day – a global overview and a local one for Greece

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Introduction

Thyroid diseases are a significant global health concern, affecting millions of people worldwide. Despite their prevalence, public awareness and understanding of these conditions are often limited. World Thyroid Day (WTD), observed annually on May 25th, is a significant event, conceived to raise awareness about thyroid health and the various diseases related to the thyroid gland. The importance of such an awareness day lies in its potential to educate the public, encourage prevention and early detection, and provide a platform for advocacy and support. The rise of the internet and search engines like Google has

transformed the way people seek health information. This study aims to explore the global and Greek Google search trends for thyroid disease, providing insights into public interest and awareness.
Aim
The primary aim of this study is to analyze the volume and patterns of Google searches related to thyroid disease globally and in Greece.
Method
The study used a retrospective observational design, using Google Trends data from 2008 to 2024. The search term "thyroid" (along with its Greek translation) was used for internet searches worldwide and also focused on Greece, as obtained from Google Trends. The results were broken into time periods, which were dictated by changes in Google's algorithms. Analyses of the relevant internet search interest for May (month of the WTD) vs all the other months per year, as well overall over time, were done with the Chi square and Pearson's test, respectively.
Results
Internet searches in months with WTDs were on a par with other months. Worldwide, a negative trend in internet searches (2008-2015) was followed by a positive one (2016-2019), whereas in Greece, trends were positive (2011-2015, for searches in English, 2016-2019, for searches in Greek and 2022-2024 for searches in both languages).
Discussion
An increase in searches related to thyroid health, symptoms, treatments, and related topics could suggest that the awareness campaign has successfully reached a significant number of people and prompted them to seek more information, regardless of the fact that searches were not numerous in months with WTDs. However, while changes in Google searches can provide valuable insights, they should be used in conjunction with other indicators. This is because not all people who become aware of thyroid health issues will turn to Google for more information. Furthermore, an increase in searches does not necessarily translate into changes in health behaviors or improvements in health outcomes.

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EP1589

JOINT126

Asymptomatic riedel's thyroiditis: a case report

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Introduction
Riedel's thyroiditis is a rare form of chronic thyroiditis. It is characterised by extensive infiltrative fibrosis of the thyroid and adjacent organs. The aetiopathogenesis has not yet been elucidated. Diagnosis is anatomopathological.
Case Report
56-year-old female with known diabetis type 2 for 3 months on OAD. Consulted for an anterior basi-cervical swelling, hard, evolving for 1 year without signs of compression. Biologically, she presents with hypothyroidism. Morphologically, a cervical ultrasound showed a lesional process infiltrating the sternohyoid muscle. A thyroid biopsy confirmed the diagnosis of Riedel's thyroiditis. A CTAP scan ruled out other areas of fibrosis outside the thyroid. The patient was put on corticosteroids.
Discussion
Riedel thyroiditis (RT) represents the classic thyroid form of IgG4 disease. It involves the production of autoantibodies, the exact nature of which remains unclear, which activate B lymphocytes, leading to two distinct immunological responses. In the presence of IL-4 and IL-10 factors from a T helper lymphocyte, the B lymphocyte differentiates into an IgG4-secreting plasma cell. This IgG4, which can be measured in plasma circulation, does not appear to have any immunogenic potential and is only an indirect marker of the infiltrative process caused by the second type of immunogenic response mediated by CD4+ cytotoxic T lymphocytes, leading to the proliferative and/or fibrosing process of IgG4 disease, and therefore to the known clinical manifestations, including TR. In this case, impairment of thyroid and/or parathyroid function depends on the extent of infiltration and thyroid comorbidities (1).
Conclusion
As TR is not yet fully understood, the therapeutic approach remains empirical and imperfect. Corticosteroid therapy is effective in the constitutive phase of the disease, but its value beyond this is more controversial. Tamoxifen is a good alternative. Surgery may be indicated in cases of compression.
Références
Thyroidite De Riedel Marie Champagne, Dr Sylvain Prévost — Université de Sherbrooke.

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EP1590

JOINT3978

Feisty hyperplasia - a case of aggressive parathyroid hyperplasia

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Background
Parathyroid adenoma and hyperplasia are common causes of hyperparathyroidism, with solitary adenomas accounting for 85% to 90% of cases, while multiple gland hyperplasia constitutes approximately 10% to 15%. These typically result in moderately elevated PTH levels compared to carcinomas, which can reach significantly higher levels. Here, we present a case of aggressive parathyroid hyperplasia with severely elevated PTH.
Case Summary
An 86-year-old woman presented to the Emergency Department with drowsiness, weakness in her legs, polyuria, and abdominal pain. She had a history of longstanding constipation and unintentional weight loss, which the surgical team had already investigated; a CT scan of the thorax, abdomen, and pelvis ruled out malignancy. Initial investigations revealed severe hypercalcaemia (serum adjusted calcium 4.48 mmol/l, reference range 2.17 – 2.56 mmol/l) and hypokalaemia (serum potassium 2.4 mmol/l, reference range 3.5 – 5.3 mmol/l). The ECG was unremarkable. Work-up for hypercalcaemia indicated raised PTH-191.7 pmol/l (2.0-8.5), with normal inorganic phosphate at 1.02 mmol/l (0.8 – 1.5). Daily serum-adjusted calcium monitoring demonstrated a rising trend, reaching up to 5.11 mmol/l. She was treated with IV fluids, dexamethasone, zoledronic acid, and calcitonin. A CT scan and ultrasound of the neck revealed a 2.8 cm mass at the posterolateral aspect of the left thyroid nodule, with no lymphadenopathy, raising suspicion for parathyroid carcinoma as the primary differential. She was referred to the Parathyroid MDT and underwent an urgent parathyroidectomy. Surgery revealed left-sided superior and right inferior parathyroid lesions. Intraoperative PTH was 49.5 pmol/l and exploration for ectopic parathyroid tissue was undertaken, but none was found; immediate postoperative PTH was 25.3 pmol/l. Histopathology confirmed two glands of parathyroid hyperplasia with no evidence of malignancy. She was alert to time, place, and person post-surgery, achieving a GCS of 15/15. Her serum-adjusted calcium and PTH levels gradually normalised, leading to her discharge.
Conclusion
Such high PTH levels in parathyroid adenomas (PA) are rare and typically associated with parathyroid carcinoma. This case encourages consideration of suspected parathyroid carcinoma; however, it was ultimately determined to be (2-gland) parathyroid hyperplasia (PH). Genetic mutations, particularly MEN1 and cyclin D1, are noted in PH and PA; however, our patient did not have a known family history, so further genetic testing has been deferred.

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EP1591

JOINT1629

Nes-onset diabetes as a potential clue to the early diagnosis of pancreatic cancer

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Introduction
Pancreatic cancer is the fourth leading cause of cancer death in the United States and the fifth leading cause of cancer death in Europe. It has a dismal five-year survival of 5%, primarily related to the fact that disease-specific symptoms occur late in the course of the disease; at the time of diagnosis, 50% have distant metastases, 29% have local and/or regional spread, and only 3% have tumors confined to the pancreas (19% remain unstaged/unknown). By the time of diagnosis $<15\%$ of patients have surgically resectable disease. The median survival of unresectable pancreatic cancer is 4–6 months. While the overall 5-year survival of resected pancreatic cancers (median size 32 mm) is 10–20%, it is 30–60% after resection of small pancreatic cancer (tumor size ≤ 20 mm) and it exceeds 75% when minute pancreatic cancers (≤ 10 mm in size) are resected. While future treatment advances may improve survival, the above noted statistics imply that, in order to substantially impact long-term survival, we will need to detect pancreatic cancer earlier.
Case report
We present a case of a 69-year-old women with strong family history of diabetes. Previous laboratory tests revealed negative anti-pancreatic antibodies and diagnosis of type 2 diabetes was considered. The patient was treated by metformin and gliclazide continued to loose weight. Considering high suspicion for type 1 diabetes patient was switched to basal-bolus insulin therapy. Patient had

unmanaged glucose values and insulin regimen was adjusted according to our recommendations. 2 years after initial diagnosis of diabetes patient was evaluated by internal medicine specialist due to new onset of jaundice. Locally advanced Pancreatic adenocarcinoma was diagnosed and corresponding treatment was initiated.

Conclusion

Patients with pancreatic cancer often have new-onset diabetes which resolves with cancer resection. New-onset diabetes not only defines a high-risk group for pancreatic cancer but is also a marker of early, asymptomatic cancer. Its occurrence in nearly half the patients with pancreatic cancer makes it an attractive screening target for early pancreatic cancer. This observation argues among several mechanisms explaining diabetes in subjects with pancreatic cancer, in favor of tumor-derived diabetogenic substance and suggests that diabetes mellitus could reveal pancreatic cancer even in the presence of conventional risk factors of type 2 diabetes.

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EP1592

JOINT830

A case of newly diagnosed thyroid hormone resistance syndrome in singapore

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A 23 year-old Chinese lady was referred to the Endocrinology clinic by her primary care physician for hyperthyroidism in July 2024. She had reported 1 year history of worsening anterior swelling and palpitations. Her free thyroxine (fT4) was noted to be persistently elevated on different assay platform since 2017, with an inappropriately high-normal Thyroid Stimulating Hormone (TSH) level (see Table 1). Her primary care physician started her on carbimazole 2.5 mg OM in June 2024 prior to the Endocrinology review. On examination, her weight was 41.8kg (stable for the past few years) with a blood pressure of 89/75 mmHg, heart rate 75/min (regular). She had a moderate diffuse goiter, but no tremors and no proptosis. Her carbimazole was stopped and she underwent additional investigations. Of note, a fT4 by equilibirum dialysis was raised at 3.2 ng/dl (RR 0.8 - 2.0) and an alpha subunit /TSH molar ratio was 1.587. An MRI Pituitary showed no pituitary adenoma. A Thyrotropin Releasing Hormone stimulation test demonstrated a large rise in TSH from 2.92 (0 min) to 24.54 (60 min). Her parents (patient is an only child) had their thyroid function tested and were normal. Genetic testing later revealed a heterozygous mutation in the THRB gene (p. Pro453Thr alteration pointing to the diagnosis of Resistance to Thyroid Hormone Beta. The patient was subsequently managed with propranolol 10 mg TDS PRN for control of her palpitations and remains on follow-up with our clinic.

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EP1593

JOINT2024

Elevated calcitonin in the absence of medullary thyroid carcinoma: a diagnostic challenge

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Introduction

Calcitonin (CT) is essential for diagnosing medullary thyroid carcinoma (MTC), with levels >100 pg/ml being highly predictive, though elevated CT is not a pathognomonic factor of MTC. Hypercalcitoninemia has also been linked to conditions like hypercalcemia, hypergastrinemia, renal insufficiency, neuroendocrine tumors, other thyroid carcinomas, prolonged use of certain medications. Chronic autoimmune thyroiditis (AIT) may elevate CT, but its impact on hypercalcitoninemia is unclear. Investigating slightly elevated CT is important for determining treatment, whether monitoring thyroid-related disorders, addressing malignancies or benign conditions like AIT.

Case

A 22-year-old female (BMI 40.9) visited an endocrinologist due to hypercalcitoninemia found after detailed laboratory blood tests performed at the patient's initiative. Family history: thyroid disease, diabetes. In 2023, neck ultrasound showed normal-sized hypoechogenic thyroid with heterogeneous structure, connective tissue degeneration, normal blood flow. No pathological lymph nodes were observed. Both in 2023 and 2025 performed neck ultrasound suggested AIT. In 2025, the patient's thyroid fulfilled EU-TIRADS 2 criteria. Laboratory tests showed fluctuating CT levels from year 2023 to 2025 from 7.02 to 30.07 pg/ml (n. r.<5.89, Table 1). Following tests were within reference ranges: TSH, FT4, FT3, anti-TPO, anti-Tg, anti-TSRH, CEA. Due to low vitamin D (35.5 nmol/l, n. r.125-150), vitamin D3 was taken at 8000 IU/day for 3 months, then reduced to 4000 IU/day permanently. Since anti-TPO and anti-Tg antibodies were within normal limits, elevated CT cannot be linked to AIT. With no clinical signs of thyroid dysfunction, no treatment was prescribed. Blood calcium level, other electrolytes examined were within normal limits. No changes were observed on chest X-ray and abdominal ultrasound. Tests for adrenal conditions detected no pathology. Consequently, other endocrinological causes of hypercalcitoninemia were excluded. Currently, the patient is diagnosed with non-toxic multinodular goiter. Check-up is recommended after 6 months.

Table 1. CT levels

Date	03/2023	08/2023	03/2024	09/2024	01/2025
CT, pg/ml	20.51	7.02	15.00	30.07	20.16

Discussion

This case emphasizes the need to consider both common and rare causes and conduct a thorough evaluation when managing hypercalcitoninemia. Elevated CT levels should be assessed within the full clinical context. An aggressive approach may be unnecessary in patients with marginal increase in CT levels after excluding causes of hypercalcitoninemia demanding specific treatment. Adequate follow-up with serum CT measurement and thyroid ultrasound can prevent missing clinically significant MTC.

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EP1594

JOINT2873

Corticosteroid therapy in dysthyroid orbitopathy: tolerance and therapeutic efficacy

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Introduction

Corticosteroid therapy is a cornerstone in the treatment of active and moderate to severe forms of dysthyroid orbitopathy (DO) due to its powerful anti-inflammatory and immuno-suppressive effect

Materials and methods

This retrospective study included 79 patients managed in the endocrinology, diabetology, metabolic diseases and nutrition department of CHU Ibn Rochd in Casablanca, between 2012 and October 2024.

Results

The mean age of patients was 56.7 ± 14 years, with a male predominance (67%), with an F/H sex ratio of 0.49. Bilateral involvement was found in 80% of cases, with asymmetry in 20%. The average duration of OD was 8 ± 5 months. The onset

EP1592

Table 1. TFT Trend

TFT Assay Platform	31 May 2017	16 June 2017	23 Aug 2017	23 Jan 2019	14 June 2024	5 July 2024
Abbott	27.6 (NR 10.3-25.7) TSH 2.74 (NR 0.5-4.5)	fT4 25 (NR 10.3-25.7) TSH 4.81 (NR 0.5-4.5)	fT4 26.1 (NR 10.3-25.7) TSH 1.99 (NR 0.5-4.5)	T4 24 (NR 10.3-25.7) TSH 2.74 (NR 0.5-4.5		
Roche Cobras E-601					fT4 35.4 (NR 12 - 22) TSH 5.74 (NR 0.27 - 4.20)	
Beckman Coulter						fT4 23 (NR 8-16) TSH 5.00 (NR 0.45 - 4.5) T3 total 2.83 (NR 0.54-2.96)

of DO coincided with Graves' disease in 42 patients, occurred after Graves' disease in 33, and preceded Graves' disease in 3 cases. Oral corticosteroid therapy was initiated in 6 patients with mild DO, at a dose of 20 to 30 mg/day for 3 months, with gradual tapering off. Intravenous corticosteroid therapy was administered in 69 of our patients (87%) with moderate to severe active forms, according to 3 protocols Protocol 1: a bolus of 500 mg/week for 6 weeks, followed by a bolus of 250 mg/week for 6 weeks, with a cumulative dose of 4.5g in 51 patients (74%). Protocol 2: a bolus of 750 mg/week for 6 weeks, followed by a bolus of 500 mg/week for 6 weeks, for a cumulative dose of 7.5g in 12 patients (17%). Protocol 3: a bolus of 1g/day for 3 consecutive days, at weekly intervals, followed by 500 mg/week for a cumulative dose of <8g in 6 patients (9%). With regard to the reasons for discontinuation of intravenous corticosteroid therapy, 7 patients developed keratitis, 2 conjunctivitis, 1 hepatic cytolysis, 4 infections (tuberculosis, syphilis, pulmonary infection), and 4 were lost to follow-up. Clinical improvement was objectified by improvement in functional signs with a reduction in the Mourits score from 4 before treatment to 2 after, with a significant improvement in patients' quality of life.

Conclusion

Corticosteroid therapy, particularly in its intravenous form, is an essential pillar in the management of active forms of DO, offering significant improvement in symptoms when used in an adapted and supervised manner.

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EP1595

JOINT1997

When a hot nodule turns out to be an oncocytic carcinoma

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Introduction

Oncocytic carcinoma is a rare form of thyroid cancer that develops from oncocytic cells, a specialized form of follicular thyroid cells. Representing only 4% of thyroid cancers, it is known for its more aggressive nature, with high potential for lymphatic and distant metastasis, requiring early treatment with regular monitoring to improve prognosis. Its detection as a hot nodule is exceptional, as it is most often considered a benign lesion.

Case report

We report the case of a 69 years old female patient with a medical history of type 2 diabetes treated with metformin, sulfonylurea, and basal insulin, hypertension treated with Ramipril, and dyslipidemia treated with simvastatin, followed for a multinodular goiter. The cervical ultrasound revealed an enlarged thyroid gland (58 ml) with several nodules, the most concerning being in the right upper pole, measuring 10x17 mm, classified as EUTIRADS IV. The biological assessment showed a low-normal TSH, and the additional thyroid scintigraphy with Tc99m revealed a large goiter predominantly on the left, with two hot nodules, one of which was a medium-sized apical nodule on the right. The patient underwent a total thyroidectomy, and the histopathological examination revealed the presence of an oncocytic carcinoma in the right lobe of the thyroid, with vascular emboli, classified as PT2NxMx. A follow-up high-dose radioactive iodine therapy was advised. The patient is currently receiving suppressive hormone therapy with levothyroxine.

Discussion and Conclusion

Thyroid cancers most often present as a cold nodule, and only 3% of cases present as a hot nodule. Fine needle aspiration of the latter is not recommended due to its low malignancy rate. However, it is crucial not to rule out the possibility of thyroid cancer and to inform the patient about the risk of its occurrence. The oncocytic form found in our patient remains even rarer, with few cases reported in the literature. Curative treatment involves total thyroidectomy which decreases the risk of recurrence and allows for postoperative monitoring of thyroglobulin levels, an essential marker for recurrence of oncocytic carcinoma. Additionally, if lymph nodes are clinically positive, a therapeutic neck dissection of the central and lateral compartments is indicated. In contrast to other types of thyroid cancer, oncocytic carcinoma has a reduced capacity for radioactive iodine uptake, making it less suitable for this treatment. However, newer therapies, including tyrosine kinase inhibitors, may be considered.

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EP1596

JOINT3240

Growth challenges in congenital athyreosis: a case report and endocrine insights

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Introduction

Congenital athyreosis is a major cause of neonatal hypothyroidism. Early treatment with L-thyroxine helps prevent severe complications. However, growth disorders may persist despite appropriate management.

Case Report

This is the case of an 11-year-old girl, the eldest of three siblings, born to non-consanguineous parents. The pregnancy was well-monitored and carried to term, with a birth weight of 4.5 kg. A prolonged neonatal jaundice was reported. Congenital hypothyroidism due to athyreosis was diagnosed at 4 months of age. The patient has been on L-thyroxine (62.5 µg/day). The clinical course was marked by growth stagnation over the past two years. Clinical examination revealed a weight of **24 kg (-2 to -3 SD)**, a height of **130.5 cm (-2 SD)**, and an estimated **target height of 161 cm** (1.5 growth channels below the expected range). Pubertal assessment showed **an infantile vulva, Tanner stage 1**. An endocrine and etiological workup was conducted, showing:

- **Karyotype**: Normal
- **8 AM cortisol levels**: Normal
- **Malabsorption screening**: Microcytic anemia, managed with iron supplementation
- **Anti-transglutaminase antibodies**: Negative
- **Liver and kidney function tests**: Normal
- **IGF-1 (Z-score)**: -0.39
- **TSH**: 6.04 mUI/l
- **Bone age**: 10 years and 3 months

Brain MRI revealed a **partial sellar arachnoidocele** with **reduced anterior pituitary volume**. A dynamic insulin-induced hypoglycemia test showed an adequate response, ruling out the need for growth hormone therapy. Under regular follow-up, an improvement in auxological parameters was observed.

Discussion

Congenital athyreosis results from a complete absence of the thyroid gland, confirmed by imaging (ultrasound and scintigraphy). It accounts for approximately **30% of congenital hypothyroidism cases**. Early diagnosis and prompt initiation of replacement therapy help prevent severe complications, particularly **irreversible intellectual disability and growth retardation**. In our case, the diagnosis was made at 4 months, which is late compared to **neonatal screening recommendations**, but still allowed the prevention of major sequelae.

Conclusion

This case highlights the importance of **regular monitoring** in patients with congenital athyreosis. Growth stagnation should prompt a **comprehensive endocrine evaluation** to differentiate between constitutional delay and an underlying pathology requiring specific management.

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EP1597

JOINT3976

Brain metastasis in a patient with oncocytic thyroid carcinoma

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Introduction

Differentiated thyroid cancer has a good prognosis and survival rate. Oncocytic thyroid cancer (formerly known as Hürthle cell carcinoma) is generally considered to be less radioiodine-avid compared to other types of differentiated thyroid cancers. Clinically, oncocytic thyroid cancer is characterized by a higher incidence of locoregional recurrence than follicular thyroid cancer (FTC) and a higher incidence of distant metastases than in papillary thyroid cancer (PTC). Metastases of thyroid cancer to the brain are extremely rare and are usually associated with other typical metastatic locations (lung and bone).

Case Report
We present the case of a patient with a more than 50-year history of thyroid cancer. In 1969, the patient, then 17 years old, underwent a strumectomy for goiter. The documentation contained information about a Hürthle cell adenoma. Seven years later, in 1976, a total thyroidectomy was performed, and in the same year, chemotherapy was started in the Department of Haematology and Oncology. Between 1976 and 1977, the patient received chemotherapy based on 5-fluorouracil, cyclophosphamide, and doxorubicin for 16 months. In 1977, the patient underwent diagnostic scintigraphy with radioiodine I-131—no radioiodine uptake was visualized. Three years later, in 1981, a chest X-ray described multiple lung tumors that persisted for almost 20 years without treatment. In 2023, 54 years after the initial diagnosis, an MRI was performed after the onset of neurological symptoms and showed a lesion in the left occipital region measuring 60×42×52 mm. A craniotomy was performed and the tumor was removed; the course of the operation was complicated by a hematoma, and a reoperation was performed on day 2. A histopathological examination confirmed metastatic thyroid carcinoma from Hurthle cells. This was followed by radiotherapy to the locoregional area, with a total dose of 3000 cGy. Subsequently, treatment with radioiodine I-131 was carried out twice (total activity of 7,4 GBq). Posttherapeutic scintigraphy showed no uptake in the brain region and revealed pathological uptake in numerous diffuse foci in both lungs confirmed in CT scan of the chest. The patient remains in good condition, ECOG 1, without neurological symptoms.
Conclusions
The atypical course of the disease indicates a generally good prognosis in thyroid cancer, a slowly progressive course of lesions, and the possibility of metastasis many years after the initial diagnosis. CNS metastasis is rare, but should always be considered, especially if other lesions coexist.

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EP1599

JOINT265

A challenging etiological diagnosis of hypothyroidism following pazopanib treatment

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Introduction
Hypothyroidism is a common endocrine disorder characterized by a wide range of etiologies, predominantly autoimmune causes in adults. While the etiological diagnosis is often straightforward, it can occasionally pose a challenge, particularly in cases of multiple or complex etiologies. We report the case of a patient presenting with peripheral hypothyroidism associated with pazopanib treatment.
Case Report
A 55-year-old woman, followed for 4 years for renal carcinoma with pulmonary metastases, treated with pazopanib (800 mg/day) for 13 months, presented with fatigue, hoarseness, and memory disturbances. Hormonal evaluation revealed a TSH level of 22 mIU/l and an FT4 level of 4 pmol/l, confirming peripheral hypothyroidism. Physical examination showed no goiter, and thyroid ultrasound revealed an atrophic thyroid gland. Anti-thyroperoxidase antibodies (anti-TPO) were strongly positive. The etiology was debated between atrophic Hashimoto's thyroiditis, a side effect of pazopanib, or a combination of both. Hormone replacement therapy led to clinical and biological improvement.
Discussion and conclusion
Pazopanib, a tyrosine kinase inhibitor targeting tumor growth and pathological angiogenesis, is associated with hypothyroidism in approximately 12% of cases. Proposed mechanisms include thyroid atrophy due to vascular inhibition, drug-induced thyroiditis, interference with iodine uptake, or anti-TPO activity. Paradoxically, cases of pazopanib-induced hyperthyroidism have also been reported, challenging these hypotheses. In this patient, thyroid atrophy and the presence of anti-TPO antibodies, rarely described with pazopanib, suggested Hashimoto's thyroiditis. For other tyrosine kinase inhibitors, such as sunitinib, hypothyroidism has been attributed to drug-induced anti-TPO activity. Regardless of the etiological diagnosis in our patient, the therapeutic approach remains unchanged, given the safety and efficacy of hormone replacement therapy.

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EP1600

JOINT177

Vitiligo and its association with thyroid dysfunction and other autoimmune diseases

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Introduction
Vitiligo is a chronic autoimmune disorder characterized by the loss of skin pigmentation. It is frequently associated with other autoimmune diseases, including thyroid dysfunction. The objective of this study was to examine the clinical characteristics of vitiligo in relation to thyroid pathology and to investigate its association with other autoimmune diseases.
Methods
The study included 16 patients diagnosed with vitiligo, comprising 13 women and 3 men. The mean age of onset was 33.54 years, with a range from 15 to 68 years. We reviewed the clinical histories of the patients, specifically focusing on the chronological relationship between the onset of vitiligo and thyroid dysfunction. HLA typing was performed in one patient who had both hyperthyroidism and vitiligo.
Results
Vitiligo was associated with hypothyroidism in 10 cases, hyperthyroidism in 4 cases, and euthyroid-phase thyreopathy in 2 cases. In 10 patients, vitiligo preceded the onset of thyroid dysfunction, with a mean delay of 131.75 months (ranging from 12 to 480 months). In 4 patients, vitiligo followed thyroid dysfunction, with a mean delay of 111 months (ranging from 24 to 192 months). In only one patient, vitiligo and thyroid dysfunction were diagnosed concurrently, while the chronology of disease onset was unknown in one case. HLA typing in one patient with hyperthyroidism and vitiligo revealed the haplotype A2, A white, B17, B white (BW6). In addition to thyroid dysfunction, other autoimmune diseases were observed in these patients. These included type 1 diabetes in three cases, lichen planus in one case, Biermer's anemia in one case, alopecia universalis in one case, Sjögren's syndrome in one case, and rheumatoid arthritis in one case.
Discussion
This study highlights the frequent association between vitiligo and thyroid dysfunction. The results suggest a potential bidirectional relationship, with vitiligo either preceding or following thyroid pathology in most cases. The presence of other autoimmune diseases in these patients further supports the autoimmune nature of vitiligo. Additionally, the HLA typing results in one patient point to a possible genetic predisposition for both vitiligo and thyroid dysfunction.
Conclusion
The findings of this study reinforce the association between vitiligo, thyroid dysfunction, and other autoimmune diseases. Clinicians should consider conducting comprehensive evaluations for thyroid and other autoimmune disorders in patients with vitiligo. Further research is needed to explore the genetic, immunological, and environmental factors that contribute to these associations.

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EP1601

JOINT197

Exploring the link between universal alopecia and hashimoto's thyroiditis

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Introduction
Universal alopecia is a rare autoimmune disorder often associated with other autoimmune diseases. This study presents two cases of universal alopecia in patients with hypothyroidism, specifically Hashimoto's thyroiditis, highlighting the potential relationship between these autoimmune conditions. **Case 1** The first patient was a 48-year-old man admitted to the endocrinology department of Hedi Chaker University Hospital in Sfax for the management of profound hypothyroidism. The diagnosis of hypothyroidism had been made seven months prior, at the age of 47, following symptoms including psychomotor slowing, hoarseness, fatigue, and a heterogeneous goiter. During hospitalization, the diagnosis of Hashimoto's thyroiditis was confirmed, and the patient was started on levothyroxine therapy. The onset of hypothyroidism occurred 24 years after the development of universal alopecia. **Case 2** The second patient was a 54-year-old woman also hospitalized for the management of hypothyroidism, diagnosed

due to psychomotor slowing and fatigue. She was diagnosed with Hashimoto's thyroiditis and treated with L-thyroxine, showing good clinical and biological improvement. Her hypothyroidism was preceded by two other autoimmune diseases: universal alopecia and vitiligo. HLA typing was performed, revealing haplotype A2, A white, B50, B white (BW6).
Discussion
Both cases suggest a strong autoimmune association between universal alopecia and thyroid dysfunction, particularly Hashimoto's thyroiditis. The presence of other autoimmune diseases such as vitiligo in the second case further emphasizes the autoimmune nature of these conditions. The HLA typing results in the second case suggest a potential genetic predisposition.
Conclusion
This report underscores the need for clinicians to consider the association between universal alopecia, autoimmune thyroid disease, and other autoimmune disorders. Further investigation is needed to better understand the genetic and immunological factors involved in these co-occurring conditions.

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EP1602

JOINT3226

Morphea and papillary thyroid carcinoma

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Introduction
Morphea is a rare chronic fibrosing skin disorder. While typically isolated, its occurrence as a paraneoplastic manifestation is uncommon. Here, we present a unique case of morphea associated with papillary thyroid carcinoma.
Clinical case
A 24-year-old woman, presented with facial skin stiffness, tightness, and discoloration persisting for one year. Examination revealed hypopigmented and indurated plaques with a brownish peripheral halo in the subpalpebral region, the cheek and the upper left lip (**Figure 1**). She denied dysphagia and Raynaud's phenomenon. Physical examination showed no sclerodactyly or abnormalities on nail fold capillaroscopy. A skin biopsy confirmed the diagnosis of morphea. Initial treatment with betamethasone 0.05% and tacrolimus 0.1% ointment showed no improvement after three months, prompting a switch to methotrexate (15 mg/week) and prednisone (30 mg/week), which led to slight improvement. Nine months later, she was diagnosed with papillary thyroid carcinoma. She underwent a total thyroidectomy with right recurrent lymph node dissection, followed by radioactive iodine and hormone therapy achieving curative outcomes. Three months later, morphea plaques softened, leaving residual hyperpigmentation (**Figure 2**).
Discussion
Morphea is a rare condition with a lifetime prevalence of 200 per 100,000 and a female predominance (3:1). It progresses through three stages: inflammatory, fibrotic, atrophic. Although primarily considered a skin-limited disorder, morphea can also affect the musculoskeletal and central nervous systems. Its pathogenesis remains unclear, but is thought to involve genetic susceptibility, vascular dysfunction, autoimmune dysregulation, and environmental factors such as viral infections, trauma, radiation, or medications. While systemic sclerosis is associated with an increased malignancy risk, attributed to shared risk factors, chronic inflammation, premature immunosenescence, impaired DNA repair, and therapy-related immunosuppression, data on morphea's risk remains limited. A recent 2024 cohort study identified non-melanoma skin cancer, cervical cancer, breast cancer, stomach cancer, and lung cancer as the most common malignancies following morphea. However, thyroid carcinoma is very rare, with only one case reported in the literature, specifically in a patient with atrophoderma of Pasini and Pierini. Tumor-derived substances such as hormones, cytokines, proteins, and their precursors may activate dermal fibroblasts causing sclerotic cutaneous lesions. In our patient, thyroid cancer diagnosed 9 months after sclerotic skin changes, without systemic involvement, suggested a probable paraneoplastic manifestation.
Conclusion
This case highlights the need for further research into the link between morphea and cancer. Early detection of malignancies allows timely intervention, prevents metastasis, and reduces the healthcare burden, underscoring the importance of close monitoring in patients with morphea.

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EP1603

JOINT2842

A Case report: acute suppurative thyroiditis presenting with thyroid abscess

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Introduction
Thyroid abscess is a rare condition that constitutes 0.1-0.7% of all thyroid diseases, usually occurring as a result of acute suppurative thyroiditis (AST), which is an infection of the thyroid gland. The rich blood supply of the thyroid gland, extensive lymphatic drainage, high iodine content, have a protective function against infections.
Case
An 18-year-old male patient presented to the emergency service with complaints of gradually increasing swelling, redness, and pain in the neck for approximately 2 weeks. He had no chronic disease and was not using any medication. Upon palpation of the patient's neck, a painful swelling was detected, and an USG was performed, which revealed a hypodense lesion compatible with an abscess, with lobulated contours of 57x50 mm in size in the midline of the neck. A neck CT was requested for additional pathology, which revealed an abscess within the thyroid parenchyma. Purulent fluid was obtained from the lesion in the emergency by fine needle aspiration, which was confirmed, and a sample was sent for culture and direct examination. Later, incision and abscess drainage were performed. Laboratory values were TSH: 10 (0.27-4.2 μIU/ml), CRP: 85 (0-5 mg/l), ALT: 455 (0-40 U/l), AST: 41 (10-41 U/l), WBC: 24.06×10^3/μL (%74 neutrophil), anti-TPO and anti-thyroglobulin antibodies negative, other values were normal. The patient was started on antibiotherapy (ampicillin sulbactam and metronidazole) with drainage. Viral hepatitis markers were negative. Immunoglobulin (IgG, IgA, IgM) values were normal. Gram positive and gram negative bacteria were seen in the abscess culture, but anaerobic bacteria were considered as the possible agent due to the absence of growth in the aerobic culture. The patient, whose symptoms and infection parameters regressed with treatment, was taken under follow-up.
Conclusion
Adult patients with AST usually have evidence of Hashimoto's thyroiditis or thyroid malignancy. Children with congenital anatomical anomalies such as branchial arch anomaly are at increased risk for AST. In our case, anomaly was investigated due to being in late adolescence, but no pathology was detected. Clinically, fever, neck swelling, sore throat, and difficulty swallowing are present as in our case. Rarely, thyrotoxicosis secondary to destruction can occur. In most cases, the predominant cause among bacterial etiology is Staphylococcus aureus. Treatment includes systemic antibiotic therapy with drainage. Recurrence of the abscess, worsening of symptoms, widespread necrosis may require lobectomy. As a result, although rare, AST and thyroid abscess are possible even in immunocompetent patients without congenital anomaly and thyroid disorder

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EP1604

JOINT155

Parotid metastasis as the first presentation of papillary thyroid carcinoma: a case report

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Papillary thyroid carcinoma (PTC) is the most common histological type of thyroid cancer. Its spread is mainly lymphatic. Distant metastases are rare and most often affect the lungs, liver and bones. Despite the anatomical proximity of the parotid gland, metastases at its level are extremely rare. The revelation of a PTC by a metastasis of this region remains exceptional.
Observation
57-year-old patient, with no significant history, presenting with a latero-cervical swelling that had been developing for 3 years. Cervical CT scan revealed a right subparotid mass originating from the right sternocleidomastoid muscle, infiltrating the lower pole of the homolateral parotid. The patient underwent resection of the tumor mass and adenopathy of territory IIa, in addition to a right exofacial parotidectomy. The anatomical-pathological and immunohistochemical analysis was in favor of a parotid and lymph node localization of a CPT. The

patient was subsequently referred to our training for further management. The cervical examination was normal, without nodules or adenopathies. The cervical ultrasound revealed a small thyroid. Given the anatomopathological result of the initial surgery, a total thyroidectomy with bilateral recurrent and jugulo-carotid lymph node dissection was indicated and performed. The anatomo-pathological study showed two foci of invasive papillary carcinoma of 2 mm and 7 mm in long axis with the presence of 37N-/37N reactive lymph nodes. The CPT was classified as: pT1aN1bM1.

Discussion

Papillary thyroid carcinoma is the most common type of well-differentiated thyroid cancer. It is usually revealed by a thyroid nodule. Local and distant metastases of classic papillary thyroid carcinoma occur mainly in regional lymph nodes, lungs, and bones. Parotid involvement in PTC is unusual, and especially as the first presentation of the disease and rarely reported in the literature. Treatment is mainly based on surgery and radiation therapy, with recourse to chemo-radiotherapy in certain situations

Conclusions

The revelation of papillary thyroid carcinoma by a parotid metastasis constitutes the particularity of our case. Metastasis to parotid gland from thyroid origin, seems to be an indication of aggressive disease. Therapeutic management in this type of situation is based on surgery with the addition of adjuvant iratherapy and then hormone therapy at a restraining dose.

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EP1605

JOINT156

A vesicular carcinoma of the thyroid on Graves' disease: a rare association

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Thyroid carcinoma coexisting with hyperthyroidism is an uncommon occurrence, as low thyroid-stimulating hormone (TSH) levels can suppress the development and growth of differentiated thyroid carcinoma cells. The majority of nodules in patients with low TSH levels are considered to be benign; however, an increasing number of thyroid carcinoma cases are diagnosed in patients with Graves' disease, toxic goiter and functioning thyroid adenoma We report the case of a vesicular carcinoma discovered on anatomopathological study of a total thyroidectomy in a patient with **Grave's disease** The patient was 60 years old on hemodialysis for hypertensive renal failure. Consulted for a cervical swelling with thyrotoxicosis. The biological assessment showed suppressed TSH, elevated T4 and T3 levels, negative anti-TPO antibodies and elevated TSH receptor antibodies. Cervical ultrasonography revealed a multinodular goiter, the most significant nodule was left inferior polar measuring 31x19 mm classified eutirads3. Fine needle aspiration (FNA) of this nodule was non-contributory The patient received synthetic antithyroid drugs until euthyroidism was obtained, then she underwent a total thyroidectomy. Histology concluded to a vesicular micro carcinoma of the thyroid measuring 8 mm in diameter without vascular emboli. The patient did not receive iodine 131, simple monitoring with L-thyroxine inhibitor treatment were indicated. Hyperthyroidism does not exclude the possibility of associated thyroid cancer. The prevalence of this association varies according to recent series, from 0.2% to 8.3%. The association of Graves' disease and vesicular carcinoma remains rare.

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EP1606

JOINT3433

Graves disease after radioactive iodine treated toxic adenoma

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Background

The most frequent causes of hyperthyroidism are Graves disease (GD) and toxic thyroid adenomas. The development of postradioiodine immunogenic hyperthyroidism/GD after radioiodine therapy (RAI) for toxic adenomas occurs in approximately 1.4% of the patients and seems to be more common in patients with increased anti-TPO levels pre-treatment. This effect occurs on average 4.6 months after RAI.

Case Report

A 49 years-old women was evaluated for thyroid nodular disease and hyperthyroidism on our endocrinology clinic in May 2021. She denied compressive symptoms, excessive sweating, loss of weight, or altered intestinal pattern, but confirmed occasional palpitations. No relevant personal or family history. Clinical exam was normal and exophthalmia not present. Cervical palpation unveiled bilateral goitre with palpable nodules bilaterally, 3 cm each, mobile on swallowing and absent cervical adenopathies. Biochemical evaluation reported TSH 0.02, FT4 1.07 (0.8-1.76), FT3 3.84 (1.88-3.18), ATG 499 (<4.11), ATPO 96.3 (<5.61), TRAb 1.2 (<1.8). Cervical ultrasonography (US) showed a multinodular goitre, EU-TIRADS 3 nodules, 33 mm and 13 mm on right lobe, 33 mm and 14 mm on left lobe, and 20 mm and 14 mm on isthmus. Thyroid scintigraphy revealed a hot nodule in the inferior right lobe. Patient initiated methimazole and performed fine needle aspiration biopsy of the cold nodules, revealing a benign cytology. The toxic nodule of the right lobe was treated with 10mCi of RAI I-131 achieving clinical and biochemical euthyroidism (TSH 1.54, FT4 1.05, FT3 3.02). One year later she presented with sinus tachycardia on clinical exam, but otherwise without hyperthyroidism signs or symptoms, and analysis reported TSH 0.09, FT4 1.27. Thyroid scintigraphy was repeated and revealed hypofixation of radiocontrast in the lower half of right lobe, and hyperfixation bilaterally in the remaining parenchyma. Laboratory workup reported TSH 0.011, FT4 1.44, FT3 5.37, TRAb 2.5. After discussion with the patient and in multidisciplinary reunion, total thyroidectomy was performed for definitive treatment of Graves disease.

Conclusion

This patient presented with GD 12 months after RAI therapy for toxic adenoma. This rare case highlights the importance of maintaining vigilance of patients after RAI, especially those with elevated anti-TPO.

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EP1607

JOINT2042

Challenges in managing severe T3 thyrotoxicosis: a complex case of Graves' disease with multidisciplinary intervention and surgical resolution

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We present a case of severe T3 thyrotoxicosis in a 23-year-old female with Graves' disease. The patient presented in August 2023 with weight loss despite increased appetite, tachycardia (up to 130/min), and peripheral tremors. Laboratory tests confirmed thyrotoxicosis. Ultrasonographic examination revealed a homogenous goiter, with a volume exceeding 50 ml, with marked vascularization, consistent with the typical features of Graves' disease. The diagnosis was confirmed by high TRAB levels (36.94 UI/l) Initial treatment with Thiamazole (20 mg/day) triggered a mild allergic reaction (dermatitis) and was switched to propylthiouracil (PTU) 75 mg/day but this led to severe hepatotoxic reaction (liver enzymes elevated to 7xUNL). Despite switching to cholestyramine (20 mg/day), thyroid function remained poorly controlled, with persistently elevated T3 (on many occasions found to be over 600 ng/dl, reference range 35-193 ng/dl) and ongoing symptoms of thyrotoxicosis and Graves' ophthalmopathy. Intravenous methylprednisolone (MTP) was initiated, reaching a total dose of 1750 mg along 3 months, which led to a reduction in T3 levels and allowed to resume thiamazole treatment. Despite this, thyroid function remained unstable with suppressed TSH and high T3. Heart rate remained poorly controlled despite 120 mg daily propranolol. Given the severity of her thyrotoxicosis, surgical treatment was considered but it was declined by two surgeons due to the increased bleeding risk associated with uncontrolled disease, the cardiac risks of severe T3 thyrotoxicosis and the possibility of postoperative tracheotomy. The patient continued with 40 mg Thiamazole daily and 120 mg propranolol, but thyroid function remained inadequately controlled for T3 while fT4 reached target. In November 2024 she had an uneventful total thyroidectomy after preoperative treatment (10 days) with Lugol's iodine (15 drops/day), methylprednisolone (16 mg/day) and Thiamazole (40 mg /day). The gland was symmetrically enlarged

(max diameter 9 cm (right) and 10 cm (left)). Both recurrent laryngeal nerves showed normal parameters on intraoperative nerve monitoring and postoperative voice was unaffected. One month later, the patient achieved euthyroidism, with normal T3/TSH while on replacement therapy with Levothyroxine 100 µg/day. In conclusion, this case highlights the aggressive nature of T3 thyrotoxicosis, its resistance to conventional treatments, and the challenges posed by multiple medication allergies. It underscores the importance of a multidisciplinary approach in managing severe, refractory hyperthyroidism.

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EP1608

JOINT3604

Hypoparathyroidism after total thyroidectomy: an epidemiological study

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Introduction

Hypoparathyroidism is a recognized complication following total thyroidectomy

Aim

to investigate the epidemiological aspects of post-thyroidectomy hypoparathyroidism, including its incidence, risk factors, and duration.

Methods

Retrospective study for over a two-year period (2022-2023) including 100 patients who underwent total thyroidectomy. Data were collected from medical records, including patient demographics (age, sex), surgical indication, postoperative parathyroid hormone (PTH) and calcium levels (day 3 and 1 month post-operatively), hypocalcemia symptoms, and symptom duration.

Results

The study revealed a clear female predominance (female:male ratio of 16:1). The median age was 37 years (range 10-69). The incidence of hypoparathyroidism on postoperative day 3 was 17%, with a median PTH level of 6.2. Only 2 (11.8%) of the 17 patients with hypoparathyroidism exhibited symptomatic hypocalcemia, presenting with paresthesia and calcium levels < 1.8 mg/dl requiring parenteral calcium correction. The remaining 15 patients (88.2%) had mild hypocalcemia and remained asymptomatic. Hypoparathyroidism was most frequently observed in patients operated for papillary thyroid carcinoma (52.9%), followed by multinodular goiter (29.4%). Graves' disease, benign cysts, and lymphocytic thyroiditis each accounted for 5.9% of cases. At the one-month follow-up, all patients had normal PTH levels, with a median of 33.4. No patients exhibited signs of permanent hypoparathyroidism.

Conclusions

This study provides data on the incidence and risk factors of hypoparathyroidism after total thyroidectomy in our population. The high rate of transient hypoparathyroidism, particularly in patients with papillary thyroid carcinoma, highlights the importance of close postoperative monitoring and surveillance.

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EP1609

JOINT1160

Recurrence of subacute thyroiditis 20 years after the first attack in two female patients

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Heterogenous clinical picture, variety of non-specific symptoms and atypical presentation may pose a diagnostic challenge in some patients with subacute thyroiditis (SAT). SAT occurs most often in young and middle-aged women. It is a self-limited inflammatory disease, but in many cases the resolution of symptoms can be achieved only by a medical treatment, and relapses are possible. The diagnosis of SAT in hyperthyroid phase was established in two 77 and 68-year-old female patients, due to self-referral to endocrinologist 10-20 days after the first symptoms had appeared. Both had a history of SAT 20,5 - 20 years ago, at the age of 56 and 48 years, respectively. Both received corticosteroids and stayed euthyroid after the end of treatment. Diagnostic delay in the first episode was more than 2 months. One patient was followed with a diagnosis of upper respiratory tract infection (treated with antibiotics) and mild anemia. In another woman clinical manifestations of SAT were initially regarded as symptoms of menopause. These cases demonstrate late recurrences of SAT two decades after complete recovery in two female patients of advanced age. Primary care physicians need to be better aware of SAT symptoms. At the same time, patients with medical history of SAT should be informed about potential repeated episodes at any age during lifetime. Prompt self-referral in case of resumption of suspicious manifestations, resembling those during the first attack, can reduce diagnostic delay, help to establish correct diagnosis, avoid unnecessary investigations and treatment.

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EP1610

JOINT3819

The plunging goiter: a report of 18 cases

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Introduction

The plunging goiter is a rare and atypical form of goiter that extends into the chest, compressing the trachea and esophagus. This results in a variety of symptoms, including respiratory issues (dyspnea, cough) and digestive disturbances (dysphagia). Diagnosis is primarily based on imaging techniques, and treatment options range from medication to surgical intervention. This study aims to investigate the clinical features and therapeutic strategies for plunging goiter.

Objective

To evaluate the clinical presentation, diagnostic procedures, and treatment outcomes of plunging goiter, assessing the effectiveness of medical and surgical interventions in alleviating symptoms and reducing complications.

Patients and Methods

A descriptive study was conducted on 18 patients with plunging goiter admitted to the Endocrinology and Metabolic Diseases Department of Ibn Rochd University Hospital between 01/01/2022 and 20/01/2025.

Results

The study included 18 patients, with a predominance of females ($n = 12$) and an average age of 58.3 years. Eight patients were from endemic regions. The main presenting symptoms were dysphagia (4 patients), dyspnea (5 patients), dysphonia (1 patient), and signs of thyroid dysfunction (3 patients). Upon physical examination, 5 patients had grade 1 goiter, 6 had grade 2, and 7 had grade 3 goiter. Cervical ultrasound revealed multi-nodular goiters, and signs suggestive of malignancy were found in 4 patients. Chest CT scans performed on all patients confirmed the presence of plunging goiter. Management involved total thyroidectomy in 16 cases, with 2 patients undergoing ultrasound surveillance. Histopathological analysis showed papillary carcinoma in 3 patients and follicular carcinoma in 1. Immediate postoperative complications included cervical hematoma in 1 patient and dysphonia in 2 patients. Monitoring of calcium and phosphate levels post-surgery revealed hypocalcemia in 7 patients, requiring oral calcium supplementation. All patients were placed on thyroid hormone replacement therapy following surgery.

Conclusions

This study supports total thyroidectomy as the treatment of choice for plunging goiter. Continuous follow-up with thyroid hormone replacement therapy is essential for optimal long-term outcomes. Early diagnosis and timely surgical intervention are crucial for preventing complications and improving prognosis.

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EP1611

JOINT3787

Out of service: late-onset hypoparathyroidism

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Introduction
Post-thyroidectomy hypoparathyroidism is a well-documented complication, typically presenting within 48 hours of surgery. While most cases are transient, permanent hypoparathyroidism occurs in approximately 1.5% of patients. A rare and underrecognized form, delayed hypoparathyroidism, manifests years after surgery, likely due to progressive ischemia or atrophy of preserved parathyroid glands. This report discusses a case of severe hypocalcemia occurring 15 years after total thyroidectomy.
Case Presentation
A 50-year-old postmenopausal woman was admitted for the management of severe hypocalcemia (54 mg/l). Her medical history revealed a total thyroidectomy performed 15 years earlier for a retrosternal goiter with no immediate postoperative complications. Clinical examination showed a positive Chvostek sign, but the patient was hemodynamically and neurologically stable. Non-parathyroid causes of hypocalcemia were excluded, leading to a diagnosis of delayed post-surgical hypoparathyroidism.
Discussion
This case highlights potential mechanisms for delayed hypoparathyroidism, including progressive hypovascularization and scar tissue formation. Similar cases in the literature underline risk factors such as female gender, advanced age at surgery, and underlying thyroid pathology. Management included intravenous calcium correction followed by long-term oral supplementation with calcitriol and calcium, resulting in significant symptom improvement.
Conclusion
Although rare, delayed hypoparathyroidism should be considered in patients presenting with unexplained hypocalcemia and a history of thyroidectomy, regardless of the time elapsed since surgery. Prompt recognition and appropriate management can prevent severe complications and improve patient outcomes.

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EP1612

JOINT639

Endocrine follow-up during pregnancy for surgically treated medullary thyroid microcarcinoma

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Introduction
The impact of pregnancy on medullary thyroid microcarcinoma (MTmC) has not been extensively studied to date. Its management during pregnancy remains challenging. According to WHO grading criteria, the presence of at least one of the following criteria: mitotic index $\geq 5/mm^2$, Ki67 $\geq 5\%$, or tumor necrosis, qualifies MTmC as high grade, whereas MTmC lacking all three criteria is considered low-grade.
The case report
A pregnant woman, 31 years old, visits the outpatient Endocrine unit in the 6th week of pregnancy to check the quality of levothyroxine (LT4) substitution therapy. Her medical history revealed total thyroidectomy due to nodular thyroid disease and incidental histological finding of MTmC four months before pregnancy. Histological findings pointed out MTmC classical histological type, presented with low mitotic index, minimal amount of amyloid, and tumor-clear resection margins on the slide. Furthermore, lympho-vascular invasion and in-tumor necrosis were not detected. Biochemistry showed insufficient LT4 substitution in the first trimester of pregnancy (TSH 2.72), along with negative markers of MTmC recurrence or progression, and MEN syndrome presence (Calcitonin <0.5, CEA 0.8, PTH 17, Ca 2.45). The quality of LT4 substitution is improved during pregnancy and serial biochemistry follow-up on calcitonin levels were stationary (Calcitonin <0.5 at the 11th, 23rd, and 33th week of gestation). Genetic testing to rule out an inherited form of MTmC (RET gene, Thyroid carcinoma (HP:0002890, Neoplasm (HP:0002664 by *Exome 2.0 Illumina* panel) was negative.
Conclusion
Pregnancy did not increase the risk of a non-inherited MTmC recurrence in this 31-year-old patient with low-grade tumor characteristics. Based on the consistency of biochemical markers during pregnancy, there was no MTmC progression. The mainstay of thyroidectomized patients' surveillance for MTmC is a careful monitoring and individualized management throughout pregnancy.

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EP1613

JOINT3991

Screening for dysthyroidism in pregnant women with diabetes

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Introduction
Pregnancy is accompanied by physiological changes that affect the functioning of the thyroid gland. These changes put pregnant women at increased risk of dysthyroidism. The objective of this study was to screen for dysthyroidism in pregnant diabetic women.
Methods
This is a descriptive study carried out on 50 diabetic pregnant women. The diagnosis of hypothyroidism is made at a TSH level greater than 2.5 µmol/l in the first trimester, and 3 µmol/l in the second and third trimesters.
Results
The average age of the patients was 33 years. Pregnancy was planned in 38% of cases, 84% of whom had controlled diabetes during hospitalization (average HBA1c of 6.33%). The average duration of progression of diabetes was 9 years. Forty-eight percent of pregnant women had type 1 diabetes. The average cholesterol level was 4.84 mmol/l. The mean FT4 level was 9.45 pmol/l and the mean TSH level was 2.1 µmol/l. The diagnosis of hypothyroidism was made in 22% of the population studied at an average term of 9 weeks of amenorrhea. All of these patients had type 1 diabetes. The patients were placed on a dose of 25 mg/day. Only two of them required an increase in the dose to 50 mg/day. No cases of hyperthyroidism were found.
Conclusion
Pregnancy planning in diabetic women is imperative. It is essential to systematically include a thyroid assessment in order to detect dysthyroidism and its fetal complications early.

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EP1614

JOINT3996

New-onset diabetes associated with severe hyperthyroidism: a case report.

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Background
The association between diabetes mellitus and thyroid abnormalities is well established. However, a new-onset case of diabetes mellitus associated with severe hyperthyroidism poses a number of diagnostic and pathophysiological questions. We thus attempt to use this case to highlight the need to seek for an underlying autoimmune origin.
Case summary
A 52-year-old man, an active smoker with a family history of type 1 diabetes (T1DM) in both father and son, presented to the emergency department with a one month history of polyuria, polydipsia, polyphagia and significant weight loss. Physical examination revealed a fatigued patient with tachycardia at 120 beats/min, with no marked signs of thyrotoxicosis (exophthalmos, goitre). Finger glucose was 4.60 g/l. Urine examination showed two-cross glycosuria and one-cross ketonuria. Initial laboratory data revealed normal natraemia and kaliemia, alkaline reserves of 21 mmol/l, and creatinemia of 67 µmol/l. Glycated haemoglobin was 7.4%. New-onset diabetes with ketotic decompensation was diagnosed and the patient was admitted to emergency. An electrocardiogram confirmed the tachycardia. In parallel, thyroid function tests were performed. Decreased thyroid-stimulating hormone (0.005 µUI/l) and increased free thyroxine (84.4 pmol/l) confirmed the diagnosis of hyperthyroidism and anti–thyroid peroxidase autoantibodies were found to be markedly positive. In order to determine both the type of diabetes and the cause of the hyperthyroidism, we carried out an assay of antibodies (anti-glutamic acid

decarboxylase (anti-GAD65), anti-TSH receptor), and a cervical ultrasound scan, which showed signs of hyperthyroidism. The patient was treated with insulin, synthetic antithyroid drugs (Thyrozol 3 tablets/day) and a beta-blocker to control the tachycardia.
Discussion
The coexistence of new onset diabetes and severe hyperthyroidism suggests a common autoimmune cause. The diagnosis of Latent autoimmune diabetes in adults (LADA) associated with basedow's disease is the most likely in this family context of T1DM. Hyperthyroidism increases insulin resistance and exacerbates diabetes, requiring adjustment of insulin therapy. Early identification of anti-GAD and anti-TSH receptor antibodies is extremely important in order to adjust treatment and prevent complications.
Conclusion
This case highlights the importance of a rigorous assessment of associated endocrine disorders in a patient with newly diagnosed diabetes. Screening for associated autoimmune diseases allows more appropriate management and better prediction of complications.

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EP1615

JOINT581

Failure of a contraception in graves' disease woman, a case report

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Introduction
Clinical hyperthyroidism in the first trimester of pregnancy secondary to Graves' disease can lead to maternal, obstetric and fetal complications requiring appropriate treatment to restore euthyroidism. Because of fetal malformations reported after treatment with carbimazole/methimazole during gestation, treatment of Graves' hyperthyroidism in pregnancy should be based on propylthio-uracil (PTU) during the first trimester, followed by carbimazole/-methimazole during the second and third trimesters of pregnancy.
Observation
A 40-year-old female patient with no previous medical history, consulted for management of clinically and biologically confirmed Graves' disease -already on treatment-, in the third month of pregnancy. Given that PTU was not available, and the hyperthyroidism was well tolerated, simple clinical and biological monitoring was decided for her. The pregnancy progressed correctly and the delivery was normal and uneventful. The child was male, in good general condition and without any malformations. After delivery, the patient was put back on antithyroid treatment and underwent total thyroidectomy.
Discussion
Subclinical or moderate thyrotoxicosis may improve during pregnancy (increase in TBG, decrease iodine pool, immune tolerance status) and does not require treatment in pregnant women. In this patient with Graves' disease treated with synthetic antithyroid drugs before pregnancy, euthyroidism was maintained without treatment during pregnancy, but a recurrence of the disease occurred after delivery, requiring radical treatment, illustrating the immune tolerance favoured by the pregnant state.

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EP1616

JOINT3754

Anaplastic thyroid carcinoma with thoracic metastases: a case report

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Introduction
Anaplastic thyroid carcinoma (ATC) is among the rarest and most aggressive tumors, often diagnosed in late, advanced stages, showing local invasion and distant metastases. The most common site for metastases is the lungs, generally detected through imaging examinations of the thorax.
Case Presentation
We present the case of a 46-year-old male who has been diagnosed with anaplastic papillary thyroid carcinoma, managed with thyroidectomy. Three months later, the patient showed signs of progressive dyspnea along with discomfort in the chest. CT scan of the thorax revealed multiple bilateral pulmonary metastatic lesions associated with mediastinal lymphadenopathy and pleural effusion suggestive of advanced states of disease. Histopathological examination confirmed the presence of anaplastic thyroid carcinoma with capsular invasion and embolic dissemination. Aggressive treatment was rendered: total thyroidectomy with selective lymph node dissection and external beam radiation therapy. The patient's clinical condition rapidly deteriorated.
Discussion
This case demonstrates the rapidly progressing nature of anaplastic thyroid carcinoma, often diagnosed late with distant metastases, particularly in the thorax. Imaging studies such as CT scans of the thorax play a decisive role in assessment of the extent of possible metastatic spread and help inform treatment decisions. The clinical condition has a very grave prognosis, thus requiring early and multidisciplinary management of such cases for better patient outcomes.

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EP1617

JOINT3906

Investigating the role of selenium and inositol supplementation in managing hashimoto's thyroiditis: a preliminary observational study

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Hashimoto's thyroiditis (HT) is an autoimmune disorder of the thyroid marked by increased levels of anti-thyroid antibodies and a gradual decline in thyroid function. This observational study investigates the effects of supplementing selenium and inositol three times a week on antibody levels in five patients diagnosed with HT. Throughout the treatment period, there was a notable decrease in the levels of anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TG) antibodies. After two years of follow-up, four patients showed complete remission of HT, particularly those who maintained good mental health and engaged in regular exercise. These results indicate that selenium and inositol supplementation may have a positive impact on autoimmune activity in HT, potentially enhancing thyroid function and overall patient outcomes. However, further controlled studies are necessary to validate these initial findings and develop standardized treatment guidelines.

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EP1618

JOINT3645

Discrepancy between cytological findings and histopathological results in thyroid nodules

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Introduction
Advancements in imaging techniques, particularly ultrasonography, have significantly improved the detection and characterization of thyroid nodules. The implementation of the EU-TIRADS classification system has standardized clinical practices, providing clear guidelines for fine-needle aspiration cytology (FNAC). Interpretation of FNAC using the Bethesda categories enables clinicians to decide between ultrasound surveillance and therapeutic intervention. However, discrepancies between imaging findings, cytological and histopathological results can pose diagnostic challenges, necessitating a multidisciplinary approach to ensure accurate diagnosis and appropriate management.
Case Presentations
Case 1: A 59-year-old female undergoing evaluation for chronic cough was found to have a heterogeneous macronodule in the left thyroid lobe on thoracic CT-scan, along with multiple nodules and micronodules present in both lung fields, osteolytic lesion affecting the body and right pedicle of the D3 vertebra with right paramedian and foraminal tumor-related epiduritis, likely of secondary origin.

Cervical ultrasound confirmed the 56×34×40 mm EU-TIRADS IV nodule where fine-needle aspiration (FNA) classified it as Bethesda II. Calcitonin level was normal. Despite normal calcitonin level, the clinical context and suspicious imaging findings prompted total thyroidectomy. Histopathology revealed a conventional subtype papillary carcinoma (pT3aN1M1). Case 2: A 20-year-old female presented with dysphagia and a cervical swelling. Ultrasound identified a 15×8×14 mm right loboisthmic nodule (EU-TIRADS III) and a 5×3 mm left mediolobar nodule (EU-TIRADS III). FNA of the right nodule indicated a benign lesion (Bethesda II). Due to compressive symptoms, a right lobectomy was performed, revealing a 20 mm encapsulated variant of papillary carcinoma (pT1bN0). Subsequent left lobectomy identified a 3 mm follicular variant of papillary carcinoma with capsular invasion (pT1bNxMx). Initial thyroglobulin level was 7 ng/ml.

Discussion

The diagnostic evaluation of thyroid nodules aims to accurately identify malignancy while avoiding unnecessary interventions. However, discordance between imaging and cytological findings should prompt clinicians to pursue further investigations and engage in specialized multidisciplinary discussions to reach an appropriate therapeutic decision, ensuring thyroid neoplasms are not overlooked. Our study highlights the limitations of FNA in certain clinical scenarios and the potential of multifocal disease despite benign cytology.

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EP1619

JOINT3619

Rare recurrence of de quervain's thyroiditis

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Introduction

Subacute thyroiditis of Quervain is an acute inflammatory condition of the thyroid, most likely triggered by a viral infection. Its prevalence is estimated to be around 0.1% to 0.5% of the general population, making it relatively rare compared to other types of thyroiditis.

Case report

A 55-year-old female patient with no significant medical history who presented with a cervical swelling. Ultrasound examination revealed a thyroid nodule classified as EUTIRADS 4, with a Bethesda II on fine-needle aspiration cytology. In June 2024, the patient developed flu-like symptoms followed by the onset of a painful, vascular goiter in the context of a febrile illness. Laboratory investigations showed an inflammatory syndrome with a CRP of 179, and hyperthyroidism (TSH 0.02 mIU/l, FT4 36 pmol/l). The patient was treated with anti-inflammatory drugs for one month, resulting in significant improvement of the pain. Subsequent tests two months after the first episode revealed a hypothyroidism with a TSH of 87 mIU/l and FT4 of 3.6 pmol/l. Ultrasound imaging confirmed the presence of a goiter with features suggestive of acute thyroiditis. Levothyroxine therapy was initiated. Six months after this episode, the patient re-presented with the same plaints: bilateral neck pain and odynophagia. Examination revealed a tender goiter, with a CRP of 92 and an elevated erythrocyte sedimentation rate (ESR) of 91 mm/h and a TSH level at 13 mUI/l, confirming the recurrence of the Subacute thyroiditis.

Conclusion

The Quervain's thyroiditis typically follows a course of three phases: an initial hyperthyroid phase, followed by a hypothyroid phase, and eventual spontaneous recovery within two to three months, with recurrence being rare, occurring in only 1.4% to 10% of cases. These recurrences are mainly due to the inflammatory origin of this pathology, the underlying inflammation may persist or reactivate, potentially causing a recurrence of the disease. Additionally, factors such as genetics, the immune system, and recurrent viral infections could contribute to this reactivation.

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EP1620

JOINT98

De Quervain thyroiditis mimicking an aggressive thyroid malignancy

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We report on a patient with likely de Quervain thyroiditis who presented with clinical features of an aggressive thyroid malignancy. A 46-year-old female was referred from the ENT department with a 4-week history of weight loss, feeling hot, and fullness of her neck which was becoming increasingly painful. There was no family history of thyroid disorders. The patient did not mention any clear predating symptoms of any viral catarrh or relevant history. Initial biochemistry through her doctor showed thyrotoxicosis with elevated T4, and T3 and suppressing TSH. Examination revealed a large irregular tender mass over the left lobe of the thyroid and multiple tender palpable lymph nodes in the neck. The patient was clinically thyrotoxic with tachycardia of 110 beats per minute and fine tremors over her outstretched hands but no clinical signs of any thyroid eye disease. An ultrasound of the thyroid revealed a poorly defined hypoechoic mass over the left lobe with a possible extension through the thyroid capsule and several level 3 and level 5 cervical lymph nodes. Thyroid antibodies were negative. She was initially commenced on carbimazole and propranolol for symptomatic control of her thyrotoxicosis while choosing simple analgesia over steroids for her neck soreness. An ultrasound-guided FNAC was carried out 2 weeks later. This revealed only scant follicular epithelial cells and hence labelled as Thy1. The patient made good progress with the carbimazole with good symptom control of her thyrotoxicosis and biochemical improvement. A repeat ultrasound-guided FNAC was carried out 2 weeks later which however showed very scant cells and hence relabelled as Thy1. The ultrasound at this stage however confirmed a sizeable reduction in the left lobe thyroid mass and now insignificant cervical lymphadenopathy. The patient was monitored for her thyroid biochemistry every 3 to 4 weeks with a titrating regime of carbimazole. The initial ENT opinion and a further review after 4 weeks concurred with the clinical diagnosis of likely thyroiditis. Further monitoring was deemed to be under endocrinology, and a further thyroid ultrasound in 3 to 6 months was agreed upon. The patient had come off her carbimazole after 6 weeks and remained euthyroid without any intervening hypothyroid phase. This case serves to highlight the need for clinical assessment and pertinent investigations to avoid overdiagnosis and potentially unhelpful surgical intervention. Hyperthyroidism can very rarely be a manifestation of metastatic follicular thyroid cancer which however was not the case in our patient.

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EP1621

JOINT3818

The impact of nighttime liothyronine and selenium supplementation on hypothyroid patient well-being and thyroid function

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Many patients with hypothyroidism who are taking levothyroxine (LT4) continue to experience ongoing symptoms and a general sense of unwellness, alongside issues like a slow metabolism and obesity. This observational study investigates the impact of adding low-dose liothyronine (LT3) taken at night, along with selenium supplements and foods rich in selenium, e. g. mushrooms, three times a week, for these patients. The study included seven participants of both genders, aged between 21 and 49 years, with TSH levels reaching as high as 6.4. By monitoring T3 levels and ensuring that both T3 and T4 remained within the upper normal range, adjustments were made to their TSH levels, targeting a range of 0.8-2 based on age. This treatment approach resulted in enhanced well-being, improved weight management through diet and exercise, and even a decrease in the size of thyroid nodules. Regular thyroid function tests every three months, including serum T3 assessments, along with thyroid ultrasounds every six months, proved crucial for these patients. These results emphasize the necessity for further research into the combined therapy of LT4, LT3, and selenium in a larger population.

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EP1622

JOINT748

A rare presentation of hypothyreosis complicated by rhabdomyolysis and acute renal injury

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Hypothyroidism is a common endocrine disorder characterized by the impaired function of the thyroid gland and reduced production of thyroid hormones. The clinical manifestations of hypothyroidism can vary significantly, ranging from asymptomatic presentations to those that are life-threatening. We present a unique case of acute renal failure attributed to rhabdomyolysis in conjunction with a severe form of hypothyroidism. Remarkably, the patient's condition improved completely following the administration of levothyroxine, resulting in the induction of a euthyroid state. This case underscores the importance of evaluating thyroid function in patients presenting with acute kidney failure, as it may play a critical role in clinical decision-making and management.

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EP1623

JOINT136

Unveiling the causes of hyperthyroidism: a retrospective analysis

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Introduction
Hyperthyroidism is a frequent endocrine condition resulting from an over-production of thyroid hormones. The disorder is caused by diverse underlying etiologies, each with distinct clinical and immunological profiles. This study aimed to analyze the etiological distribution of hyperthyroidism in a cohort of patients followed in our center.
Materials and Methods
We conducted a retrospective analysis of patients diagnosed with hyperthyroidism in our institution. The diagnosis was based on clinical presentation, laboratory findings, and immunological markers. Specific antibodies, including anti-TSH receptor (anti-RTSH), anti-thyroperoxidase (anti-TPO), and anti-thyroglobulin (anti-Tg), were systematically assessed.
Results
31 patients were diagnosed with hyperthyroidism. Graves' disease was identified in 19 patients, including 10 men and 9 women, with a mean age of onset of 35.52 years. All patients presented with a goiter, and exophthalmos was observed in 11 cases. Anti-TSH receptor antibodies were positive in all patients, confirming the autoimmune nature of the disease. Hashitoxicosis was diagnosed in 12 patients, including 10 women and 2 men, with a mean age of onset of 36.83 years. Goiter was present in 9 cases. Immunological testing revealed positivity for anti-TPO and/or anti-Tg antibodies in all patients, while anti-TSH receptor antibodies were negative.
Discussion
Graves' disease emerged as the leading cause of hyperthyroidism in our cohort, consistent with global epidemiological data. Its hallmark clinical features, including diffuse goiter and the frequent occurrence of exophthalmos, underline the importance of clinical examination and antibody testing. Hashitoxicosis, often considered a transient phase of autoimmune thyroiditis, represented the second most common etiology. Its diagnosis relies on the presence of specific thyroid antibodies and the exclusion of anti-TSH receptor positivity.
Conclusion
This study emphasizes the predominance of Graves' disease and Hashitoxicosis as etiologies of hyperthyroidism. The distinct clinical and immunological profiles observed highlight the necessity for a comprehensive diagnostic approach to guide appropriate management strategies.

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EP1624

JOINT1923

Echographic features of nodular hashimoto's thyroiditis

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Objective
The aim of the study is to analyze the sonographic features of nodular Hashimoto thyroiditis (HT).
Methods and materials
In a retrospective study, the clinicohistopathologic and echographic (number, diameter, shape, margins, vascularity, halo) data of patients who underwent total or partial thyroidectomy and had a HT in the histopathological specimen, from the 1st of January 2018 to the 31st july 2023 were analyzed.
Results
Our serie includes 73 patients and 155 thyroid nodules. All the patients are female and the mean age is 47 years. 16 patients have a thyroid dysfunction. No patient have a personal history of neck irradiation. 12 patients have family history of thyroidectomy. The mean nodule diameter is 35,5 mm(4-68 mm). 59.3%of nodules are located in the right lobe while 40.6% are located in the left lobe. 43.2% are completely solid,10.3% are kystic and 46.4% have a mixed structure. 83.8% have an oval shape and 16.2% have a round shape. Nodules margins were sharp in 78.06% and indistinct in 21.9%. 16.12% are hyperechoic,54.19% are isoechoic,20.6% are moderately hypoechoic and 9.03% are very hypoechoic. 55.48% of nodules are surrounded by a thin halo and 44.5% does not. On color doppler,18..6% of nodules showed peripheral hypervascularity,32.9% were diffusely hypervascular and 49.03% were isovascular. 7.06% of nodules have microcalcification while 9.67% have macrocalcification.
Conclusion
The sonographic appearance is variable but the most common aspect is an isoechoiec, isovascular and oval shaped nodule with sharp margins.

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Author Index